Approval Sheet

William Bruce Tuemmler, Ph.D., 1953

Title of Thesis: "The Synthesis of an Open-Chain Analogue of Podophyllotoxin"

Thesis and Abstract approved:

Professor in charge of thesis
Head, Department of Chemistry

July 11, 1953

THE SYNTHESIS OF AN OPEN-CHAIN ANALOGUE OF PODOPHYLLOTOXIN

by

William Bruce Tuemmler

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

1953

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

ACKNOWLEDGMENTS

The author gratefully acknowledges the continuing interest and guidance of Professor Nathan L. Drake during the course of this research.

The author would also like to express his gratitude for generous financial support provided by the Cancer Institute, National Institutes of Health, Bethesda, Maryland, and also by E. I. duPont de Nemours and Co., Wilmington, Delaware.

TABLE OF CONTENTS

	Page
INTRODUCTION	1
DISCUSSION	2
SECTION I. Diethyl 3,4,5-Trimethoxybenzylmalonate (VII)	2
SECTION II. 3,4-Methylenedioxyphenacyl Bromide (XIX)	11
SECTION III. Diethyl 3,4,5-Trimethoxybenzyl-3',4'-methylenedioxyphenacylmalonate (XX)	15
SECTION IV. 3,4,5-Trimethoxybenzyl-3',4'-methylenedioxyphenacylacetic Acid (XXVIII)	21
SECTION V. The Attempted Synthesis of 1-(3,4-Methylenedioxyphenyl)-1-keto-2-hydroxymethylene-3-carbethoxy-4-(3',4',5'-trimethoxyphenyl)-butane (XXIV)	23
SECTION VI. 4-Phenyl-3-carbethoxy-2-hydroxymethylene-tetralone-1 (XLII)	28
SECTION VII. The Synthesis of an Unsubstituted Analogue of Podophyllotoxin	34
SECTION VIII. 2-Benzyl-3-(α-hydroxybenzyl)-butyrolactone (LVI)	38
SECTION IX. 2-(3,4,5-Trimethoxybenzyl)-3-(α-hydroxy-3',4'-methylenedioxybenzyl)-butyrolactone (II)	42
EXPERIMENTAL	50
Ethyl 3,4,5-Trimethoxybenzoate (IV)	50
3,4,5-Trimethoxybenzyl Alcohol (V). Method A	51
3,4,5-Trimethoxybenzyl Alcohol (v). Method B	52
3,4,5-Trimethoxybenzyl Chloride (VI)	52
Direct Conversion of Ethyl 3,4,5-Trimethoxybenzoate (IV) to 3,4,5-Trimethoxybenzyl Chloride (VI)	53
Diethyl 3,4,5-Trimethoxybenzylmalonate (VII). Method A	54
Diethyl 3,4,5-Trimethoxybenzalmalonate (XI)	55

Page

Diethyl 3,4,5-Trimethoxybenzylmalonate (VII). Method B 56

Diethyl 3,4,5-Trimethoxybenzoylmalonate (IX)..... 57

Hydrogenation of Diethyl 3,4,5-Trimethoxybenzoylmalonate (IX) Using Palladium Charcoal..... 58

Hydrogenation of Diethyl 3,4,5-Trimethoxybenzoylmalonate (IX) Using Platinum..... 59

1,2,3,5,6,7-Hexamethoxy-9,10-dihydroanthracene (XIII)..... 59

Piperonoyl Chloride (XVI)..... 59

Diethyl Piperonoylmalonate (XVII)..... 60

3,4-Methylenedioxyacetophenone (XVIII). Method A 60

3,4-Methylenedioxyacetophenone (XVIII). Method B 61

3,4-Methylenedioxyphenacyl Bromide (XIX)..... 62

Phenacylation of Diethyl Malonate 63

Diethyl Benzylphenacylmalonate (XXII)..... 63

Benzylphenacylmalonic Acid 64

Methyl Benzylphenacylacetate 65

Diethyl 3,4,5-Trimethoxybenzyl-3',4'-methylenedioxyphenacylmalonate (XX)..... 65

2-(3,4,5-Trimethoxybenzyl)-2-carbethoxy-4-(3,4-methylenedioxyphenyl)-butyrolactone (XXI)..... 66

3,4,5-Trimethoxybenzyl-3',4'-methylenedioxyphenacylmalonic Acid (XXVII)..... 67

3,4,5-Trimethoxybenzyl-3',4'-methylenedioxyphenacylacetic Acid (XXVIII)..... 68

Methyl 3,4,5-Trimethoxybenzyl-3',4'-methylenedioxyphenacylacetate (XXXII)..... 69

Ethyl 3,4,5-Trimethoxybenzyl-3',4'-methylenedioxyphenacylacetate (XXIX)..... 69

2-(3,4,5-Trimethoxybenzyl)-4-(3',4'-methylenedioxyphenyl)-butyrolactone (XXXI)..... 69

Benzhydrylsuccinic Acid (XXXVIII)..... 70

4-Phenyl-3-carboxytetralone-1 (XL)..... 71

Page

4-Phenyl-3-carbethoxytetralone-1 (XLI)..... 72

4-Phenyl-3-carboxy-2-hydroxymethylenetetralone-1 (XLIII)..... 73

4-Phenyl-3-carboxy-2-hydroxymethyl-1-hydroxytetralin (XLVIII) Method A 74

Lactone of 4-Phenyl-3-carboxy-2-hydroxymethyl-1-hydroxy-tetralin (XLIX)..... 74

4-Phenyl-3-carbethoxy-2-hydroxymethylenetetralone-1 (XLII)... 75

4-Phenyl-3-carboxy-2-hydroxymethyl-1-hydroxytetralin (XLVIII). Method B 76

4-Phenyl-3-carbethoxy-2-hydroxymethyl-1-hydroxytetralin (XLVII)..... 77

4-Phenyl-3-carbethoxy-1-hydroxytetralin (LI) 77

Lactone of cis-1-Hydroxy-3-carboxy-4-phenyltetralin (LII).... 78

trans-1-Hydroxy-3-carboxy-4-phenyltetralin (LIV)..... 79

cis-1-Hydroxy-3-carboxy-4-phenyltetralin (LIII)..... 79

Ethyl α-Methyl-β-benzoylpropionate (LV)..... 79

Reaction of Formaldehyde with Benzylphenacylacetic Acid. 2-Benzyl-3-benzoylbutyrolactone (LXIV) and 2-Benzyl-3-hydroxy-methyl-3-benzoylbutyrolactone (LXV)..... 80

2-Benzyl-3-benzoylbutyrolactone (LXIV)..... 81

2-Benzyl-3-(α-hydroxybenzyl)-butyrolactone (LXVIa)..... 82

2-Benzyl-3-(α-hydroxybenzyl)-butyrolactone (LXVIb)..... 82

2-(3,4,5-Trimethoxybenzyl)-3-(3',4'-methylenedioxybenzoyl)-4-hydroxybutyric Acid (LXVII)..... 83

2-(3,4,5-Trimethoxybenzyl)-3-(3',4'-methylenedioxybenzoyl)-butyrolactone (LXVIIIa)..... 83

2-(3,4,5-Trimethoxybenzyl)-3-(α-hydroxy-3',4'-methylene-dioxybenzyl)-butyrolactone (II)..... 84

2-(3,4,5-Trimethoxybenzyl)-3-(3',4'-methylenedioxybenzoyl)-butyric Acid (LXXIII)..... 85

Infrared Spectra 86

LITERATURE CITED 88

LIST OF CHARTS

	Page
Chart 1	2
Chart 2	2
Chart 3	5
Chart 4	5
Chart 5	12
Chart 6	12
Chart 7	16
Chart 8	24
Chart 9	24
Chart 10	30
Chart 11	36
Chart 12	39
Chart 13	44
Chart 14	87

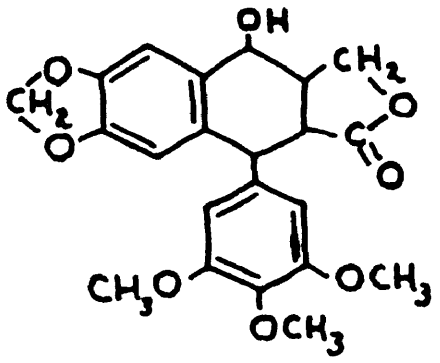
INTRODUCTION

The discovery that podophyllotoxin causes regression of mouse Sarcoma 37 has renewed interest in this substance and in compounds related to it (1). Hartwell and Schrecker (2) have recently revised the original formula proposed by Borsche (3) and Späth (4), so that I (Chart 1) represents the presently accepted structure. The high toxicity of podophyllotoxin has prevented its use in cancer therapy. This has prompted a search for analogues which might retain the desirable properties of podophyllotoxin, but have lower toxicities.

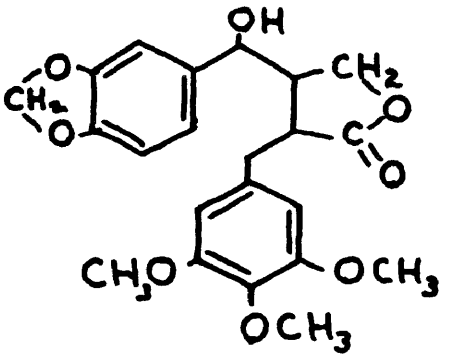
This thesis describes the synthesis of II, the open-chain analogue of podophyllotoxin. The Discussion is divided into Sections, each describing the research done on the preparation of a key intermediate as well as on related compounds which are not intermediates in the main synthesis. Each Section is accompanied by a chart which depicts the synthetic route under discussion. A solid arrow indicates a completed reaction for which an experimental procedure is given in the Experimental Section. Unsuccessful reactions are indicated by a broken arrow and are briefly described in the Discussion.

Many of the compounds prepared in this work have been submitted to the Cancer Institute, U. S. Public Health Service, Bethesda, Maryland, for evaluation of their effects on mouse Sarcoma 37. The results of these tests are not yet known.

Chart 1

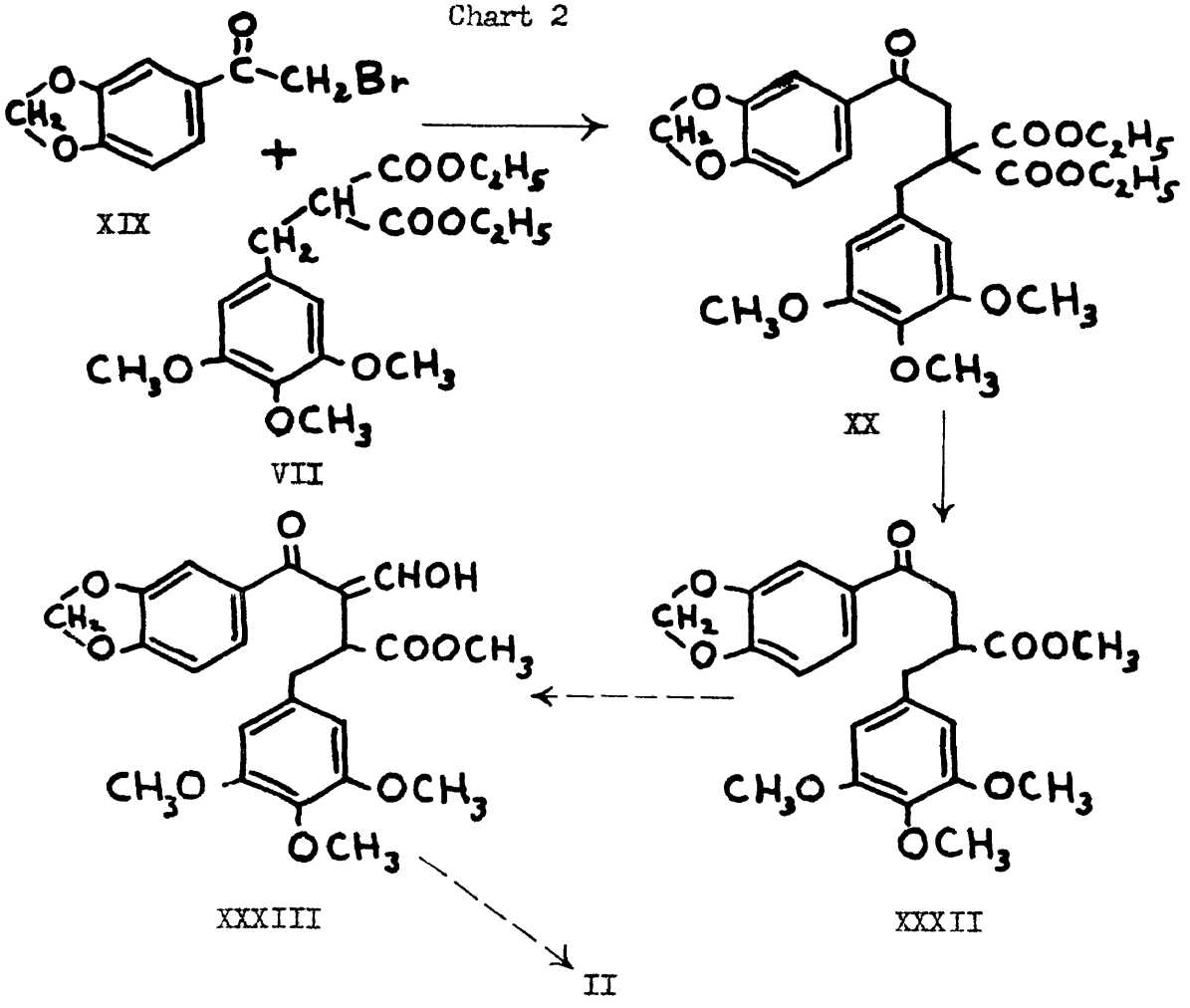


I



II

Chart 2



DISCUSSION

The originally proposed synthetic route to II is outlined in Chart 2.

SECTION I

Diethyl 3,4,5-Trimethoxybenzylmalonate (VII). Cook and co-workers (5) have described a synthesis of diethyl 3,4,5-trimethoxybenzylmalonate (VII) in which 3,4,5-trimethoxybenzanilide was converted to 3,4,5-trimethoxybenzaldehyde which was then hydrogenated to 3,4,5-trimethoxybenzyl alcohol. The reported yield of the alcohol based on 3,4,5-trimethoxybenzanilide was sixty-three percent. Conversion of the alcohol to 3,4,5-trimethoxybenzyl chloride followed by reaction with diethyl sodiomalonate afforded diethyl 3,4,5-trimethoxybenzylmalonate in unspecified yield.

The reduction of 3,4,5-trimethoxybenzoic acid (III) by lithium aluminum hydride (Chart 3) appeared to be a more satisfactory route to 3,4,5-trimethoxybenzyl alcohol (V) which would avoid the troublesome preparation of 3,4,5-trimethoxybenzaldehyde and its subsequent hydrogenation. The reduction of 3,5-dimethoxybenzoic acid by lithium aluminum hydride in ether is reported to proceed in ninety-three percent yield (6). Because of the limited solubility of 3,4,5-trimethoxybenzoic acid in ether, the technique of continuous extraction was employed to introduce the acid into the reaction mixture. The acid proved to be extremely resistant to reduction, probably because of the insolubility of the initially formed salt in the reaction medium.

Since the direct reduction of 3,4,5-trimethoxybenzoic acid was unpromising, attention was directed to the reduction of the corresponding

ethyl ester IV. Ethyl 3,4,5-trimethoxybenzoate was prepared by heating a mixture of 3,4,5-trimethoxybenzoic acid, absolute ethanol, and benzene with p-toluenesulfonic acid and slowly removing the benzene-alcohol-water azeotrope by fractional distillation.

Reduction of the ester by lithium aluminum hydride in ether afforded a fifty percent yield of a product which proved to be a mixture of starting material and 3,4,5-trimethoxybenzyl alcohol. In another experiment in which the reaction mixture was treated with aqueous alkali instead of acid to decompose the complex, the product resinified to a red glass upon attempted distillation.

Because of the ease of reduction of acid chlorides, 3,4,5-trimethoxybenzoyl chloride (VIII) was prepared (7) and subjected to reduction by lithium aluminum hydride in ether. A fifty percent yield of 3,4,5-trimethoxybenzyl alcohol was obtained.

The conversion of 3,4,5-trimethoxybenzyl alcohol to the chloride VI was reported to proceed in sixty-eight percent yield, while the yield in the subsequent alkylation step was not indicated (5). Repetition of the published directions resulted in only a forty-three percent yield of the chloride, and from this only a small amount of diethyl 3,4,5-trimethoxybenzylmalonate could be obtained upon reaction with diethyl sodiomalonate.

Since this synthetic route to the desired product VII appeared unattractive, the possibility of reducing diethyl 3,4,5-trimethoxybenzoylmalonate (IX) was considered (Chart 4). It was found possible to duplicate the reported preparation of IX in eighty-five percent yield by reacting a suspension of diethyl sodiomalonate in benzene with 3,4,5-

Chart 3

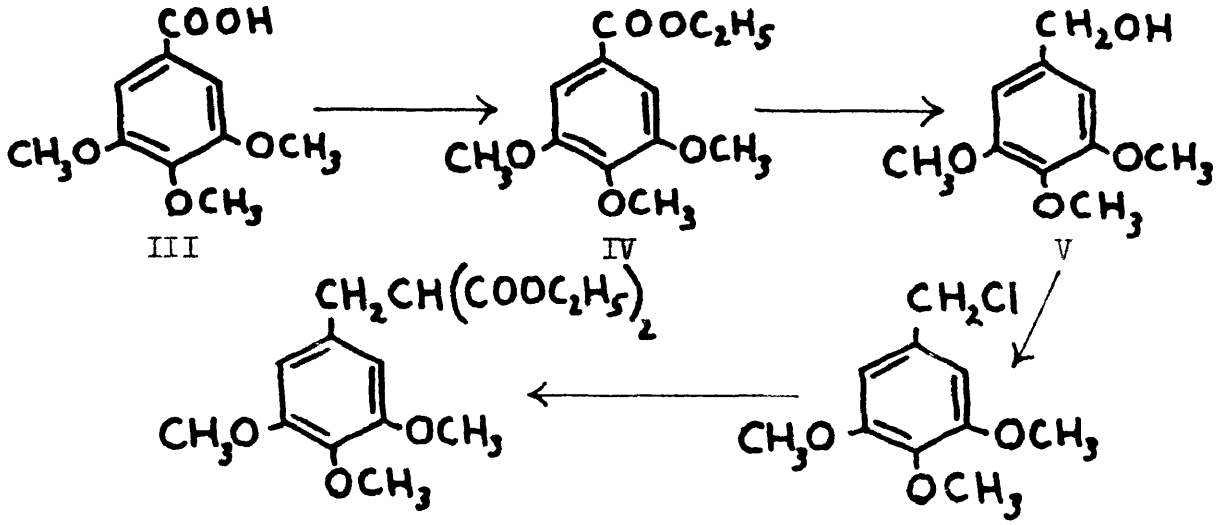
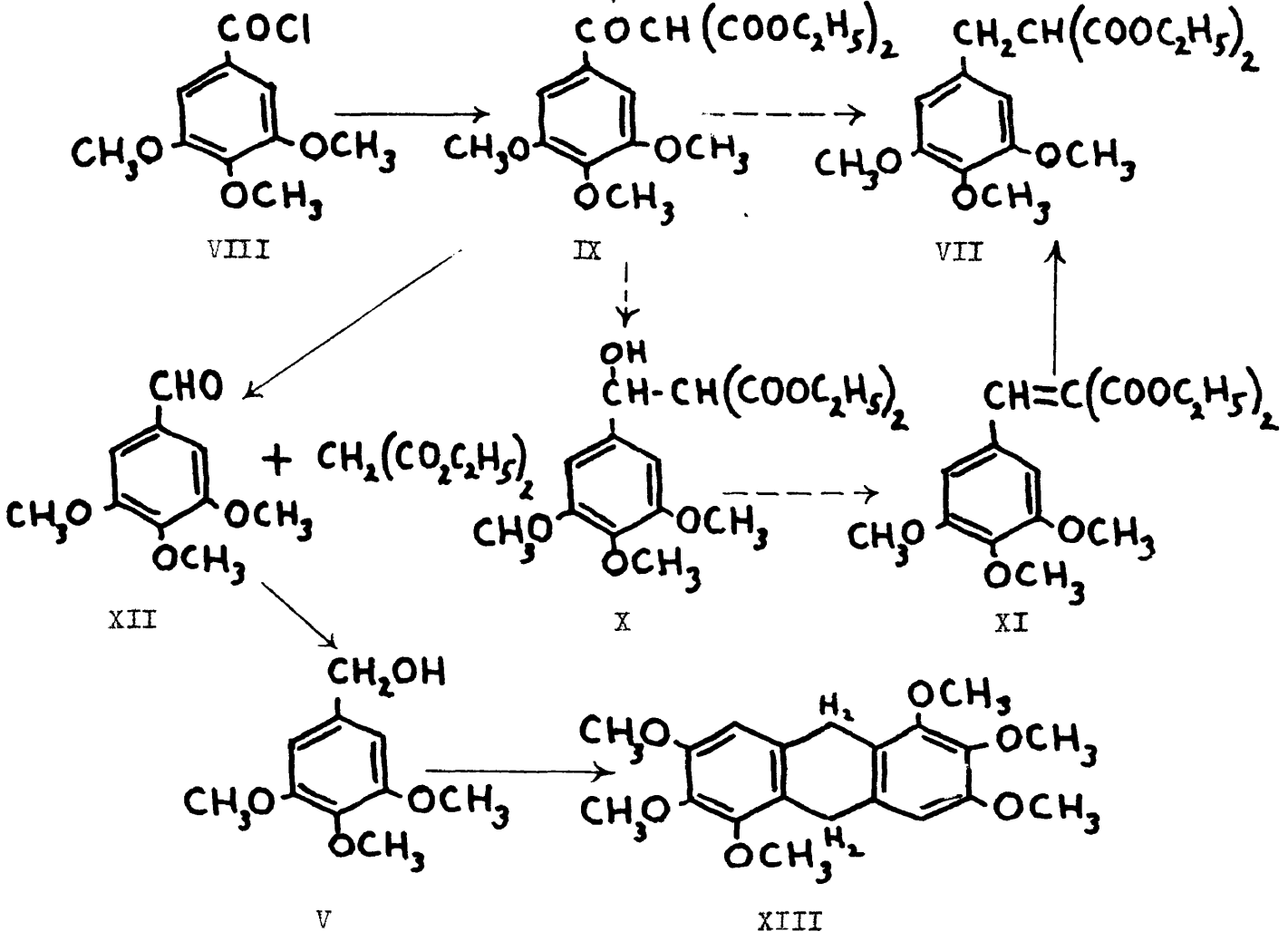


Chart 4



trimethoxybenzoyl chloride over a period of twenty hours (8). The application of the procedure originally described by Lund (9) for the acylation of malonic esters increased the yield to ninety-one percent and shortened the reaction time to a few hours.

Of the various methods (10)(11) for accomplishing the conversion of a keto group to a methylene group, the technique of catalytic hydrogenolysis seemed most applicable to the case at hand. However, the desired reaction failed to take place even though a variety of procedures was employed (12)(13). The compound readily absorbed hydrogen, but attempts to isolate diethyl 3,4,5-trimethoxybenzylmalonate were unsuccessful except in one instance. When palladium on charcoal was used as the catalyst, there was a rapid absorption of one mole of hydrogen, and it was possible to isolate 3,4,5-trimethoxybenzaldehyde (XII) and diethyl malonate. This aldehyde is only slowly reduced by palladium, in agreement with the fact that in its preparation by the Rosenmund procedure, no catalytic poison is required (14).

When platinum was employed as the catalyst, the reaction proceeded with the absorption of two moles of hydrogen, and the products isolated were diethyl malonate and 3,4,5-trimethoxybenzyl alcohol. Interruption of the hydrogenation after the absorption of one mole of hydrogen resulted in the isolation of starting material and the alcohol, but no intermediate aldehyde. Thus it appears that the aldehyde, which must be generated by hydrogenolysis, is immediately reduced to the alcohol in the presence of platinum.

In one early experiment, a twenty percent yield of diethyl 3,4,5-trimethoxybenzylmalonate was obtained. This encouraged the belief

that the proposed reduction was feasible. The failure of the material to absorb more than one mole of hydrogen when palladium was the catalyst was interpreted as being due to a resistance of the presumed hydroxy intermediate X to hydrogenolysis. Accordingly, it was felt that if the hydroxy compound was dehydrated to diethyl 3,4,5-trimethoxybenzalmalonate (XI), hydrogenation of the double bond would proceed readily to afford the desired product. Upon heating the partially hydrogenated material with a two percent solution of p-toluenesulfonic acid in benzene, no water was evolved. However, subsequent hydrogenation proceeded with the absorption of one mole of hydrogen, and a twenty percent yield of diethyl 3,4,5-trimethoxybenzylmalonate was obtained.

Despite the failure to observe the formation of water, the possibility remained that the isolation of diethyl 3,4,5-trimethoxybenzylmalonate in this instance resulted from a Knoevenagel condensation between the initially formed 3,4,5-trimethoxybenzaldehyde and diethyl malonate followed by hydrogenation of the resulting diethyl 3,4,5-trimethoxybenzalmalonate. The condensation of benzaldehyde with diethyl malonate in the presence of p-toluenesulfonic acid in benzene is reported to proceed in sixty percent yield (15). However, an attempted condensation under these conditions failed to afford any diethyl 3,4,5-trimethoxybenzalmalonate; only tarry material and starting compound were obtained. This indicates that VII was obtained by a different route.

Huang, Tarbell and Arnstein (8) attempted to prepare β—(3,4,5-trimethoxy phenyl) —propionic acid by the hydrogenolysis of diethyl 3,4,5-trimethoxybenzoylmalonate followed by acid hydrolysis. They isolated only 3,4,5-trimethoxybenzoic acid and a small amount of a white

solid of unknown structure, melting at 201-202°, which had a carbon and hydrogen content of 66.6 percent and 6.7 percent respectively. Cook and co-workers (5) obtained a similar material, melting at 201°, as a by-product from the preparation of 3,4,5-trimethoxybenzyl alcohol by the methylation of syringic alcohol using methyl p-toluenesulfonate and potassium hydroxide. They characterized the material as 1,2,3,5,6,7-hexamethoxy-9,10-dihydroanthracene (XIII) (For $C_{20}H_{24}O_6$: C, 66.7; H, 6.7; OCH_3, 51.7; Found: C, 67.1; H, 6.7; OCH_3, 52.0).

It seemed likely that the material isolated by Huang, Tarbell and Arnstein was the same as that obtained by Cook. If the initial hydrogenation afforded 3,4,5-trimethoxybenzyl alcohol, it was not unlikely that the subsequent boiling of the material with ten percent sulfuric acid afforded some of the dihydroanthracene derivative.

In order to test this hypothesis, 3,4,5-trimethoxybenzyl alcohol was boiled with ten percent sulfuric acid. A small amount of ether insoluble product melting at 201.5-203° was isolated. The analytical data were in agreement with theory for XIII, and it is concluded that Tarbell's compound is the same as that isolated by Cook.

The ready hydrogenolysis of the carbon-carbon bond in diethyl 3,4,5-trimethoxybenzoylmalonate is consistent with some other observations. When an attempt was made to hydrogenate the ketone using copper-chromium-barium oxide in ethanol, the only product isolated was ethyl 3,4,5-trimethoxybenzoate (IV), indicating that the molecule had undergone alcoholysis. In the determination of the saponification equivalent using 0.1 N alcoholic potassium hydroxide, it was found that the molecule rapidly consumed three equivalents of alkali, and trimethoxybenzoic

acid was isolated from the reaction.

The renewed availability of 3,4,5-trimethoxybenzyl alcohol from the platinum catalyzed hydrogenolysis of diethyl 3,4,5-trimethoxybenzoylmalonate prompted a reinvestigation of the approach first considered (Chart 3). In Cook's procedure for converting 3,4,5-trimethoxybenzyl alcohol to the chloride VI, a mixture of the alcohol and dimethylaniline at 0° was treated with thionyl chloride to afford a sixty-eight percent yield of the chloride. Repetition of this procedure afforded a forty-three percent yield of product. Considerable difficulty was experienced in stirring the viscous reaction mixture efficiently. It was found that by diluting the reaction mixture with benzene, efficient stirring was possible, and the yield was increased to seventy-six percent.

Since the alkylation of diethyl sodiomalonate by 3,4,5-trimethoxybenzyl chloride in ethanol gave a poor yield of impure product, the alkylation of diethyl sodiomalonate in excess diethyl malonate was investigated. This technique has been employed with success in the preparation of diethyl benzylmalonate (16). The reaction was found to proceed in seventy-five to eighty-five percent yield to afford diethyl 3,4,5-trimethoxybenzylmalonate.

The demonstration of the feasibility of converting 3,4,5-trimethoxybenzyl alcohol to the malonic ester VII renewed interest in devising an attractive synthesis of the alcohol. While this work was in progress, a report appeared describing the lithium aluminum hydride reduction in ether of methyl 3,4,5-trimethoxybenzoate to 3,4,5-trimethoxybenzyl alcohol in seventy-three percent yield (17). The reduction of ethyl 3,4,5-trimethoxybenzoate in boiling tetrahydrofuran was found to proceed

in seventy-nine percent yield. The use of tetrahydrofuran, in addition to permitting a higher reaction temperature, had the perhaps more significant advantage that no complex separated from the reaction mixture as had been observed when ether was employed as the solvent. The superiority of tetrahydrofuran over ether was further demonstrated when it was shown that 3,4,5-trimethoxybenzoic acid could be reduced to the alcohol in fifty-eight percent yield in boiling tetrahydrofuran. In ether, starting material was recovered in good yield. Again, this difference may be ascribed to solubility differences. While the reaction mixture in tetrahydrofuran was homogeneous, the salt of the acid precipitated from ether, thus inhibiting further reaction.

Since there was little by-product formation in the reduction of the ester, it appeared feasible to convert the crude alcohol to the chloride. When this was done, the overall yield of the chloride was seventy-six percent based on the ester.

The Knoevenagel condensation of 3,4,5-trimethoxybenzaldehyde with diethyl malonate followed by hydrogenation of the resulting benzalmalonic ester XI appeared to be an attractive alternative synthesis of the benzylmalonic ester VII (Chart 5). However, initial experiments in which the condensation was conducted in ethanol using piperidine benzoate as the catalyst afforded yields of approximately thirty-five percent of XI, and this approach was abandoned. Subsequently however, the use of the procedure of Pratt and Werble (18), afforded a seventy-four percent yield of XI. This material was readily hydrogenated in the presence of platinum to afford an eighty-five percent yield of VII.

When a sample of the originally prepared diethyl 3,4,5-trimethoxybenzalmalonate which had stood for twenty months was repurified for analysis, it was somewhat surprising to find that the material, although originally recrystallized from petroleum ether, was no longer completely soluble in this solvent. The insoluble material, which constituted nearly half of the sample, was high melting, but gave a carbon and hydrogen analysis identical with that obtained on the soluble portion. It is believed that dimerization occurred to afford the cyclobutane derivative XIV. The dimerization of cinnamic acid to form truxillic acid is well known, as is the dimerization of methylenemalonic ester to form 1,1,3,3-tetracarbethoxycyclobutane (19). In view of the formation of a symmetrical product in the case of methylenemalonic ester, it is believed that the product XIV is also symmetrical.

The two successful routes to diethyl 3,4,5-trimethoxybenzylmalonate described in this Section represent satisfactory syntheses of the compound. The scheme shown in Chart 3 has been employed as the primary synthesis of VII in an overall yield of sixty-one percent, based on the optimum yields obtained in this work. An alternative synthesis of VII, outlined in Chart 5, has been conducted on a small scale to afford VII in sixty-four percent yield, based on 3,4,5-trimethoxybenzaldehyde.

SECTION II

3,4-Methylenedioxyphenacyl Bromide (XIX). Späth and Lederer (20) have described a synthesis of 3,4-methylenedioxyphenacyl bromide (XIX) by the ultraviolet catalyzed bromination of 3,4-methylenedioxyacetophenone (XVIII) in acetic acid. Several syntheses of XVIII have been reported,

Chart 5

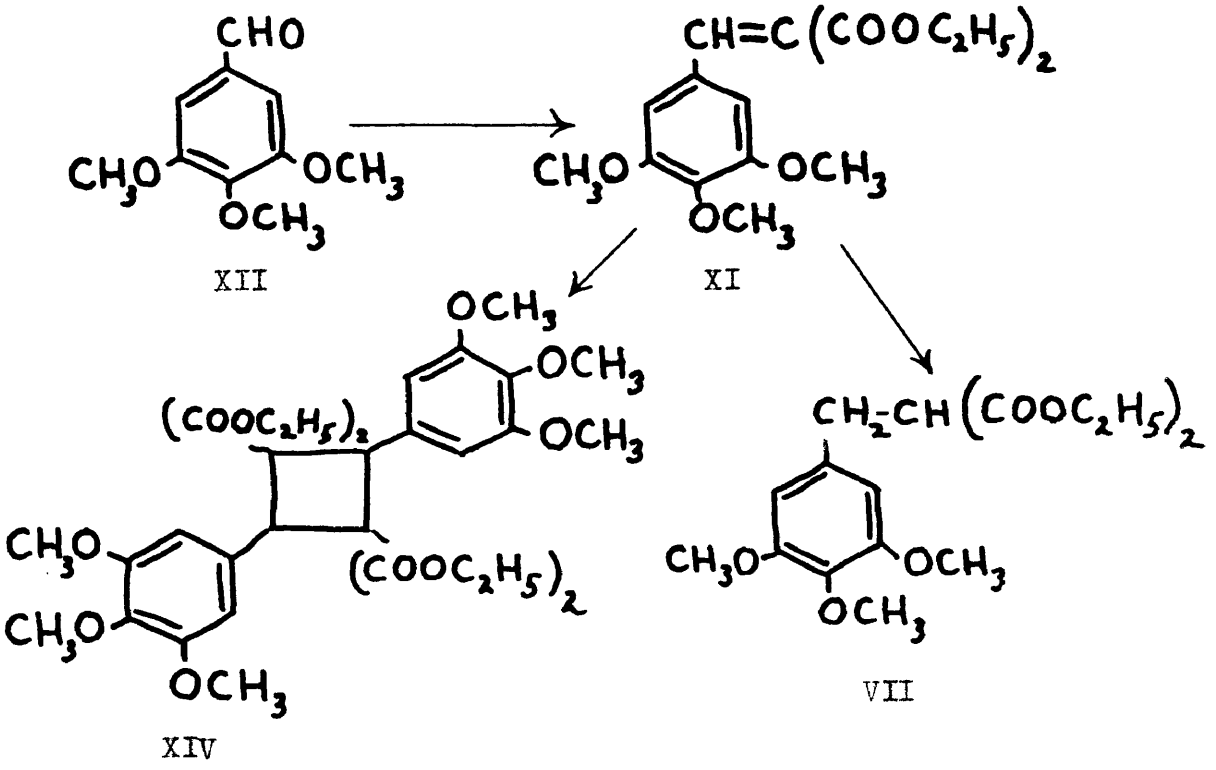
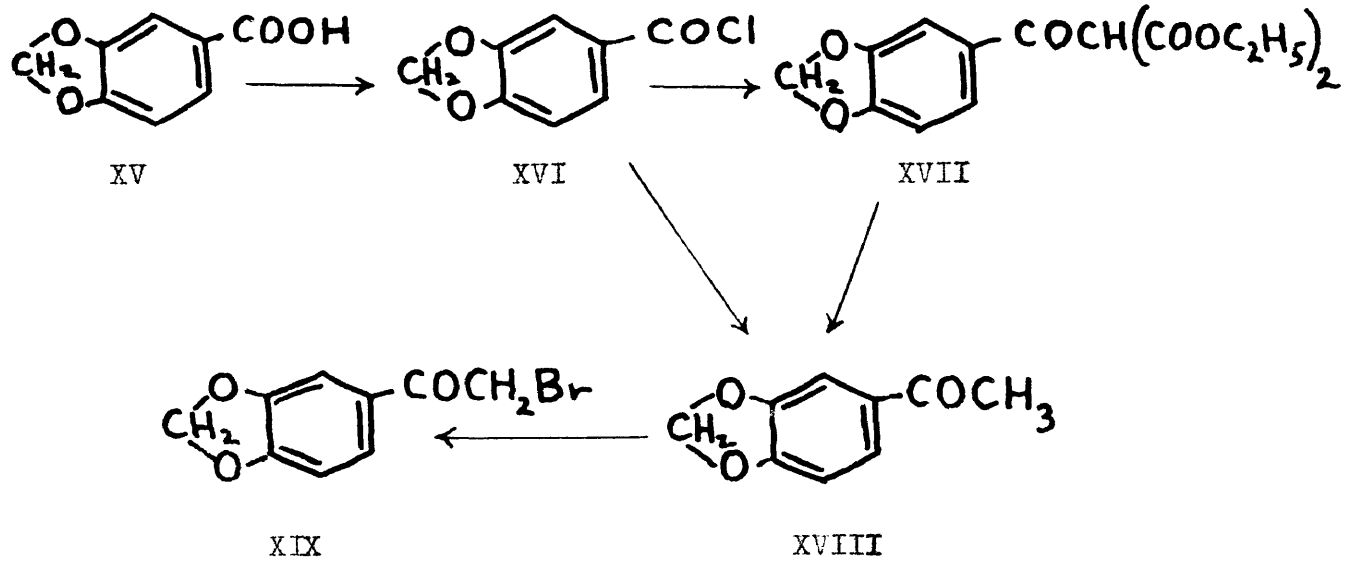


Chart 6



among them being the reaction of piperonal with methylmagnesium iodide followed by dichromate oxidation of the resulting 3,4-methylenedioxyphenylmethylcarbinol (21), the condensation of methyl piperonylate with ethyl acetate followed by hydrolysis and decarboxylation of the resulting ethyl piperonoylacetate (22), and the direct Friedel-Crafts acylation of methylenedioxybenzene (23).

Of these methods, the first seemed the most promising. The original work of Klages (21) indicated that the carbinol was obtained when a fourfold excess of the Grignard reagent was employed, and the insoluble complex was isolated directly and carefully decomposed. Otherwise, the dehydration product was obtained. Subsequent work of Böttcher (24) indicated that the carbinol could be obtained in over ninety percent yield in the usual manner if the complex was decomposed with a freezing mixture of ammoniacal ammonium chloride. Repetition of this procedure afforded 3,4-methylenedioxystyrene in sixty-four percent yield. Since it was thought that dehydration might have taken place during distillation, the crude product was subjected to direct oxidation using potassium dichromate and sulfuric acid. A ten percent yield of XVIII was obtained from the crude product of the Grignard reaction.

Because of the unpromising aspect of this approach and the difficulties inherent in the alternative methods described in the literature, a different approach was sought.

Methods of synthesizing methyl ketones have been the subject of several recent publications (25)(26)(27). In the procedure described by Walker and Hauser (25), acyl malonic esters are hydrolyzed by aqueous

acetic acid and sulfuric acid and undergo simultaneous decarboxylation to the methyl ketones. Although the method is not applicable to aliphatic ketones, it affords good yields of acetophenone derivatives and is manipulatively simple. The application of this method to the synthesis of XVIII was tried next (Chart 6).

The conversion of piperonylic acid (XV) to piperonoyl chloride (XVI) according to Bruchhausen and Gerhard (28) is accomplished by heating a suspension of the acid in benzene containing a small excess of thionyl chloride. Although good yields are reported, this procedure resulted in the formation of large amounts of a by-product identified as piperonylic anhydride. Anhydride formation under these conditions is due to a loss of hydrogen chloride from the reaction medium (29), and this is facilitated by operating in boiling benzene. Omission of the benzene and the use of a threefold excess of thionyl chloride resulted in a nearly quantitative yield of the acid chloride.

The acylation of diethyl ethoxymagnesiummalonate with piperonoyl chloride followed by hydrolysis and decarboxylation of the resulting diethyl piperonoylmalonate (XVII) afforded an eighty-one percent yield of XVIII based on piperonylic acid and corrected for a small amount of recovered piperonylic acid.

The preparation of XVIII by the reaction of piperonoyl chloride with dimethylcadmium was also investigated. The yield obtained by this method was comparable to that obtained from the malonic ester procedure. However, the product was contaminated with a persistent, yellow impurity which could only be removed by chromatography on alumina, and since the

procedure was somewhat tedious, the method was abandoned in favor of the malonic ester approach.

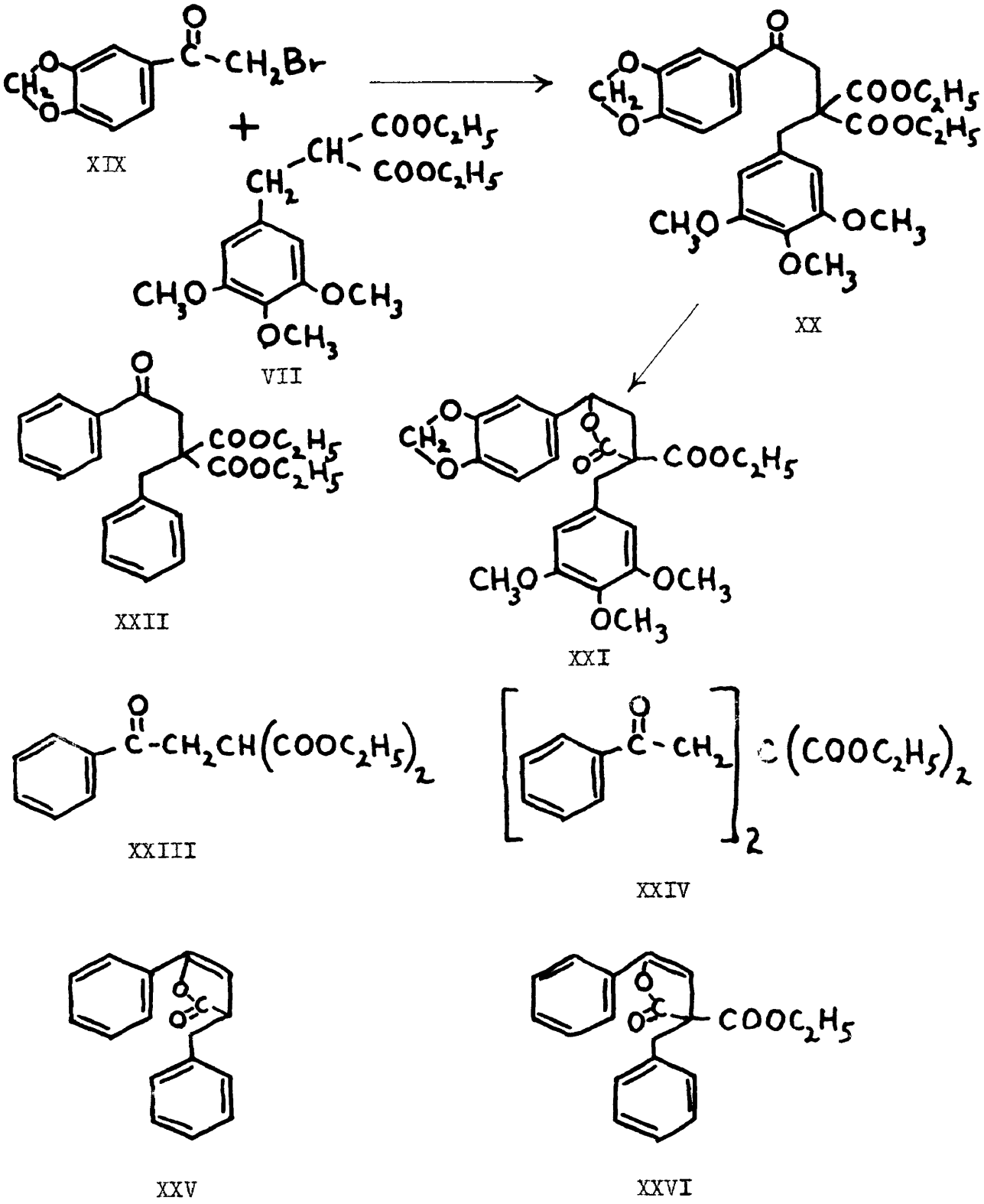
The bromination of XVIII according to Späth and Lederer (20) was accomplished by irradiating a solution of the ketone and bromine in acetic acid with ultraviolet light from a quartz lamp for ten minutes. Upon irradiation of such a mixture with short ultraviolet light, the expected rapid decolorization did not take place. After one hour, the mixture was lighter in color, but continued exposure resulted in darkening. A forty percent yield of 3,4-methylenedioxyphenacyl bromide was isolated from this procedure. Subsequently, the bromination of a suspension of XVIII in ice-cold, anhydrous ether was found to afford yields of seventy-three to seventy-seven percent. The use of a catalytic amount of aluminum chloride was unnecessary and lowered the yield to sixty-seven percent.

The synthesis of 3,4-methylenedioxyphenacyl bromide (XIX) from piperonylic acid (XV) was thus accomplished in an overall yield of sixty-three percent based on the optimum yields obtained in this work.

SECTION III

Diethyl 3,4,5-Trimethoxybenzyl-3',4'-methylenedioxyphenacylmalonate (XX). Previous work in this Laboratory (16) indicated that the preparation of the unsubstituted analogue, diethyl benzylphenacylmalonate (XXII), was best accomplished by adding phenacyl bromide to a boiling solution of the sodium salt of diethyl benzylmalonate in benzene containing an excess of diethyl benzylmalonate. The excess of diethyl benzylmalonate

Chart 7



resulted in a solution of the salt, and under these conditions the product was obtained in fifty-five percent yield. The application of this procedure to the preparation of the substituted compound XX had the objection that an excess of diethyl 3,4,5-trimethoxybenzylmalonate (VII) could not be employed since it could not be removed by distillation as was the case with diethyl benzylmalonate. Furthermore, a more economical use of VII was desirable in view of the value of the material. Resort to fractional crystallisation seemed questionable. As a result of these considerations, the use of equimolar quantities of VII and XIX was indicated (Chart 7).

The reaction of diethyl 3,4,5-trimethoxybenzylmalonate in benzene with sodium hydride was slow, and the mixture was heated under reflux overnight. At the end of this time no hydrogen evolution could be detected, although a small amount of undissolved solid remained. This was assumed to be extraneous material, probably an impurity in the sodium hydride. Otherwise, the solution was clear, and consequently, it was felt that the sodium salt was soluble in benzene. After adding 3,4-methylenedioxyphenacyl bromide, the mixture was heated for thirty-six hours. Removal of the solvent afforded an orange oil which could not be crystallized directly, but which, after chromatography on alumina, afforded a twenty-five percent yield of diethyl 3,4,5-trimethoxybenzyl-3',4'-methylenedioxyphenacylmalonate (XX). Upon repetition of the reaction it was thought that the uncertainty regarding the completeness of reaction of sodium hydride with VII in benzene could be avoided by conducting the salt formation using sodium ethoxide in absolute ethanol.

The ethanol could then be azeotropically displaced with benzene, and since the sodium derivative was believed to be soluble in benzene, this procedure should afford a homogeneous mixture. However, when this procedure was employed, an orange, benzene-insoluble oil was obtained which was apparently the sodium salt. Upon treatment with XIX, it dissolved forming a neutral solution. The failure to detect any benzene-insoluble material from the sodium hydride reaction may have been due to incomplete conversion of VII to the salt in view of the solubility of diethyl benzylsodiomalonate in benzene containing an excess of diethyl benzylmalonate.

Saponification experiments with the keto diester XX indicated that decarboxylation took place under the alkaline conditions employed to afford the corresponding keto acid, 3,4,5-trimethoxybenzyl-3',4'-methylenedioxyphenacylacetic acid (XXVIII)(Chart 8). It was hoped that direct saponification of the crude phenacylation product would permit separation of the tarry material by extraction of the alkaline saponification mixture. The desired keto acid XXVIII could then be separated from non-ketonic impurities using Girard's reagent (30).

However, the tarry material proved to be acidic and could not be extracted from the alkaline mixture. Upon acidification of the alkaline solution, a brown, gummy precipitate formed. Most of this dissolved in benzene, but a small amount resisted solution. This was also insoluble in ether. It was collected and proved to be the ketomalonic acid XXVII (Chart 8), showing that decarboxylation was incomplete. Treatment of the remaining acidic material with Girard's reagent T afforded

a twelve percent yield of XXVIII. The combined yield of XXVII and XXVIII obtained in this way was not appreciably different from that to be expected from saponification of the keto diester XX obtained in the earlier experiment.

The unsatisfactory nature of these experiments prompted the investigation of another approach. According to Lund (9), allyl-type halides react with ethoxymagnesium malonic esters to afford the substituted malonic esters. However, the use of phenacyl halides in the reaction has not been reported.

The reaction of phenacyl bromide with a ten percent excess of diethyl ethoxymagnesiummalonate in boiling ether afforded a thirty-five percent yield of diethyl phenacylmalonate (XXIII) and a twenty percent yield of diethyl diphenacylmalonate (XXIV), along with recovered diethyl malonate and phenacyl bromide. Disubstitution apparently resulted from a failure of the initially formed diethyl phenacylmalonate to precipitate from solution as a magnesium complex as is observed in the acylation of ethoxymagnesium malonic esters. The slowness of the reaction compared to acylation undoubtedly favored this.

While this was of interest from the standpoint of the monophenacylation of diethyl malonate, it posed no problem for the phenacylation of monosubstituted malonic esters. The application of the procedure to the system studied by Brown (16) was sought.

Diethyl benzylmalonate reacted with magnesium and ethanol to form the ethoxymagnesium derivative which was soluble in ether and benzene. Reaction of the salt with phenacyl bromide was first attempted in

refluxing ether over a period of 4-5 hours. A twenty-five percent yield of diethyl benzylphenacylmalonate (XXII) was obtained along with approximately sixty percent recovery of both starting materials.

The reaction was repeated in boiling, alcohol-free benzene over a period of nine hours. Direct crystallization of the crude material afforded a fifty-three percent yield of XXII.

A third procedure was employed in which an alcohol-free benzene solution of the reactants was stirred at room temperature for twenty-four hours, followed by a sixteen hour reflux period. The dark, crude material afforded only a thirty percent yield of impure product upon direct crystallization. Distillation of the remaining material at 0.1 micron afforded a little starting material and a considerable quantity of an oil which resisted crystallization. Saponification of a sample of the oil afforded a solid which appeared to be a mixture of benzylphenacylmalonic acid and benzylphenacylacetic acid. Thermal decarboxylation of this mixture afforded benzylphenacylacetic acid. The remainder of the oil was dissolved in ethanol and deposited a small amount of diethyl benzylphenacylmalonate. The identity of the balance of the material is unknown. Brown (16) reported the isolation of the enol lactone XXV from the treatment of XXII with base in refluxing benzene. Since basic conditions existed in the reaction mixture, it was not unlikely that the enol lactone was formed.

The isolation of the enol lactone ester XXVI has also been reported from the phenacylation conducted in the usual manner in ethanolic solution (31). This product may also have been formed. Both structures are plausible in light of the result of the saponification.

Since prolonged treatment at elevated temperatures appeared to have a deleterious effect on the yield, the reaction was repeated in benzene at room temperature and allowed to stand seven days. An eighty-one percent yield of diethyl benzylphenacylmalonate was obtained. Application of this procedure to the preparation of the substituted keto diester XX afforded yields of seventy-six to eighty-one percent of purified product.

Attempts to determine the saponification equivalent of the keto diester XX gave variable results, as had been observed by Brown (15) in the case of the unsubstituted keto diester XXII. The carbonyl activity of XX was likewise feeble, although it was eventually possible to isolate a 2,4-dinitrophenylhydrazone. Attempted hydrogenation of XX using platinum in ethanol failed. However, when palladium-charcoal in ethanol was employed, a very slow absorption of one mole of hydrogen took place. A low yield of crystalline material was isolated whose analysis indicated that it was the lactone ester XXI. Brown found that catalytic hydrogenation of XXII always afforded the corresponding methylene derivative.

SECTION IV

3,4,5-Trimethoxybenzyl-3',4'-methylenedioxyphenacylacetic Acid (XXVIII). Although the hydrolysis of the keto diester XX to the ketomalonic acid XXVII followed by thermal decarboxylation (Chart 8) appeared to be straightforward, considerable difficulty was experienced in obtaining good yields. The initial attempts to hydrolyze the keto diester XX with alcoholic potassium hydroxide or aqueous alcoholic potassium hydroxide afforded poor yields of crude material which upon purification proved to

be the decarboxylated product XXVIII. An attempt to conduct the hydrolysis under acidic conditions afforded only starting material in an impure condition. In one experiment, the keto diester was warmed for several hours at 50° with a three percent solution of potassium hydroxide in fifty percent aqueous alcohol, then stirred overnight at room temperature. The product obtained melted with decomposition over a twenty degree range. It was thought that this was the ketomalonic acid XXVII in an impure condition, and consequently, the material was subjected to thermal decarboxylation. The product obtained was not the expected keto acid XXVIII but a neutral material which analysis showed to be the keto ester XXIX. Evidently half-saponification occurred under the mild conditions employed, and the acid ester XXX underwent subsequent decarboxylation to the ester. Since the ester was ultimately desired, this suggested the possibility of utilizing the half-saponification as a preparative method, and attention was turned to the conditions which might be expected to favor half-saponification. It was hoped that by operating at room temperature in concentrated alcoholic potassium hydroxide, the potassium salt of the acid ester would precipitate before complete saponification took place. The reaction was conducted using a large excess of saturated alcoholic potassium hydroxide so that the dilution effect of adding an alcoholic solution of the keto diester was minimized. It was found that a precipitate formed rapidly. The salt obtained was readily soluble in water. Acidification of the aqueous solution of the salt produced a white solid which proved to be the ketomalonic acid XXVII instead of the hoped for acid ester XXX. However, the process was so superior to

the previous saponification procedure in point of time, purity of product, and yield that no further time was expended on the half-saponification. The yield was eighty-two percent of material pure enough to use directly. Thermal decarboxylation of XXVII at 150° afforded a ninety-four percent yield of XXVIII. In subsequent experiments on a larger scale, overall yields of eighty-three to eighty-five percent of XXVIII were realized, based on the keto diester XX.

During the thermal decarboxylation of the dried ketomalonic acid XXVII, the condensation of water vapor on the cool upper surfaces of the flask indicated that the material was a hydrate. The neutralization equivalent was in good agreement with that to be expected for the ketomalonic acid dihydrate although the carbon and hydrogen analyses were not in satisfactory agreement with theory. This poor agreement is not regarded as serious in view of the difficulties inherent in purifying malonic acids. Brown (16) was unable to obtain satisfactory carbon and hydrogen analyses on benzylphenacylmalonic acid. The analytical data obtained on the keto acid provide ample confirmation that the proposed structure is correct .

Reduction of the sodium salt of the keto acid XXVIII in aqueous alkali using sodium borohydride afforded a low yield of the lactone(XXXI).

SECTION V

The Attempted Synthesis of 1-(3,4-Methylenedioxyphenyl)-1-keto-2-hydroxymethylene-3-carbethoxy-4-(3',4',5'-trimethoxyphenyl)-butane (XXXIV). The condensation of formic acid esters with active methylene compounds has been a widely used preparative method. However, there has

Chart 8

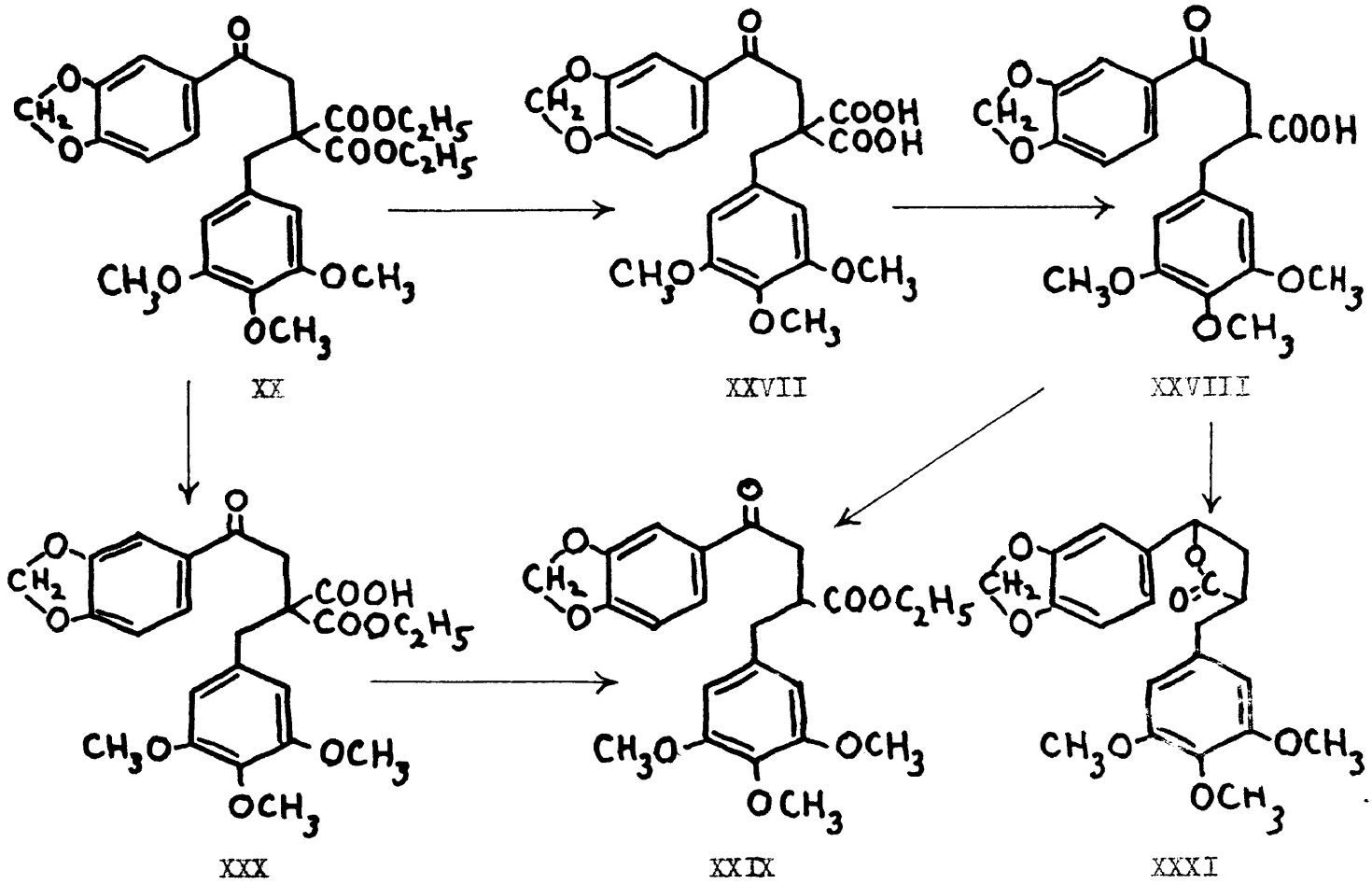
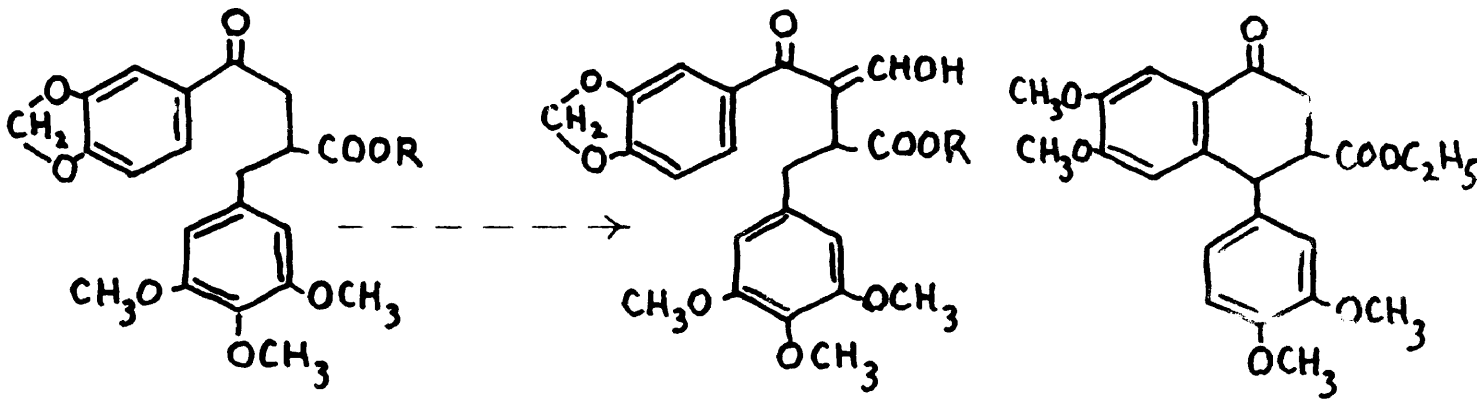


Chart 9



been no systematic study made of the scope and limitations of the reaction, and the reported yields vary widely. Johnson has described the formylation of a large number of cyclic ketones in uniformly good yield (32)(33)(34)(35). The optimum conditions reported are the use of two moles of ethyl formate and sodium methoxide for each mole of ketone in benzene at temperatures around 25°. Applications of the formylation reaction to acyclic ketones, with the exception of methyl ketones, have been rare and have not given very satisfactory results (36). Brown (16) studied the reaction of diethyl benzylphenacylmalonate with ethyl formate using essentially the procedure described by Johnson (32). Although the alkali-soluble material obtained was believed to be a hydroxymethylene derivative, no crystalline material could be isolated. The presumed hydroxymethylene ketone could not be alkylated by the method of Claisen (37) to afford a crystalline product nor reduced by aluminum isopropoxide in isopropyl alcohol. The principal evidence for the existence of the formylated material was the formation of a copper derivative whose solubility characteristics indicated that it was a chelate compound. However, the analytical data were not in agreement with the proposed structure.

It appeared likely that the difficulty experienced by Brown in formylating XXII was in part due to the presence of a quaternary carbon adjacent to the position of the desired reaction. Consequently, the reaction of the less hindered keto ester XXXII was investigated. Although there is a hydrogen alpha to the ester group in this structure, it was felt that this would not cause any interference because

of the well known difficulty of ester condensations at tertiary carbon atoms (38). The formylation of ethyl isobutyrate requires the use of sodium triphenylmethyl and proceeds in only sixteen percent yield (39). Furthermore, Haworth and Sheldrick (40) were able to formylate the similarly constituted keto ester (XXXV) alpha to the keto group in good yield. In any event, the inability of a formyl group alpha to the ester group to enolize would permit separation of the possible isomers.

Treatment of the keto acid with diazomethane afforded a colorless oil which failed to crystallize. Nevertheless, the presumed methyl ester XXXII was used directly in subsequent formylation experiments.

Formylation according to the directions of Johnson (32) afforded a small amount of alkali-soluble material which gave a deep brown color with ferric chloride. This was subjected to direct reduction by sodium borohydride. The product obtained from the reduction failed to give a color with ferric chloride but resisted attempts at crystallization. Chromatography on silicic acid failed to give any separation.

Since it was known that the ethyl ester XXIX was a crystalline material, it seemed likely that the methyl ester XXXII should also be a solid, although the product obtained from the diazomethane treatment was an oil. Esterification of XXVIII with methanolic hydrogen chloride afforded a sixty-eight percent yield of XXXII which, although a solid, crystallized with some difficulty. A question was raised concerning the purity of the presumed methyl ester employed in the formylation experiments. The preparation of the ethyl ester using ethanolic hydrogen chloride afforded a ninety-four percent yield of easily crystallized

product. For this reason, it was decided to use the ethyl ester in future experiments.

Attempted formylations of the ethyl ester using sodium methoxide and sodium hydride afforded no detectable enolic material.

Although the results of the initial experiments indicated that the formylation was feasible, the low yields of enolic material obtained prompted a study of the reaction on the more available, unsubstituted keto ester LXII (Chart 12).

Ethyl benzylphenacylacetate was prepared according to the procedure described by Brown (16) with the application of modified procedures for conducting the phenacylation of diethyl benzylmalonate and for the saponification of the ketomalonic ester.

An attempt was made to formylate LXII using sodium powder in benzene overnight at room temperature. There was obtained a thirty-three percent yield of a neutral fraction, a fifty-seven percent yield of material soluble in sodium bicarbonate solution, and a five percent yield of sodium hydroxide soluble material. No enol tests were obtained. The neutral fraction was a sweet-smelling, yellow oil. Saponification of a sample of the oil afforded benzylphenacylacetic acid, but the oil resisted crystallization when seeded with starting material. A small quantity of solid obtained upon recrystallization from petroleum ether proved to be the enol lactone XXV originally isolated by Brown. The identity of the acidic fraction is unknown.

In a later experiment in which sodium methoxide in benzene was used at 0° for seventy minutes, a ninety percent yield of a similar

fragrant, yellow oil was obtained. Its saponfication equivalent was intermediate in value between those to be expected for the starting material LXII and the corresponding enol lactone XXV. Again, benzylphenacylacetic acid was isolated from the saponification, and a small amount of the enol lactone was isolated directly from the oil.

The results of this experiment indicate that the preferred reaction under the conditions employed is enol lactone formation. Apparently, the enolate ion undergoes an intramolecular transesterification to afford the enol lactone.

In order to test this hypothesis, the keto ester was subjected to the same conditions as previously, except that the ethyl formate was omitted. The neutral oil obtained from this procedure also had a lowered saponification equivalent.

Since these experiments showed that the formylation was not feasible, it was of interest to determine some of the factors which contributed to the failure of the reaction. Comparison of the reaction with the cyclic analogue, 4-phenyl-3-carbethoxytetralone-1 (XLI), was sought since the formylation of cyclic ketones usually occurs readily. In addition, subsequent operations on this material would afford an unsubstituted analogue of podophyllotoxin.

SECTION VI

4-Phenyl-3-carbethoxy-2-hydroxymethylenetetralone-1 (XLII). The reaction sequence employed is outlined in Chart 10.

The Stobbe condensation of benzophenone with diethyl succinate in the presence of sodium hydride afforded the benzhydrylidenesuccinic acid ester XXXVI in eighty-eight percent yield (41). Although the

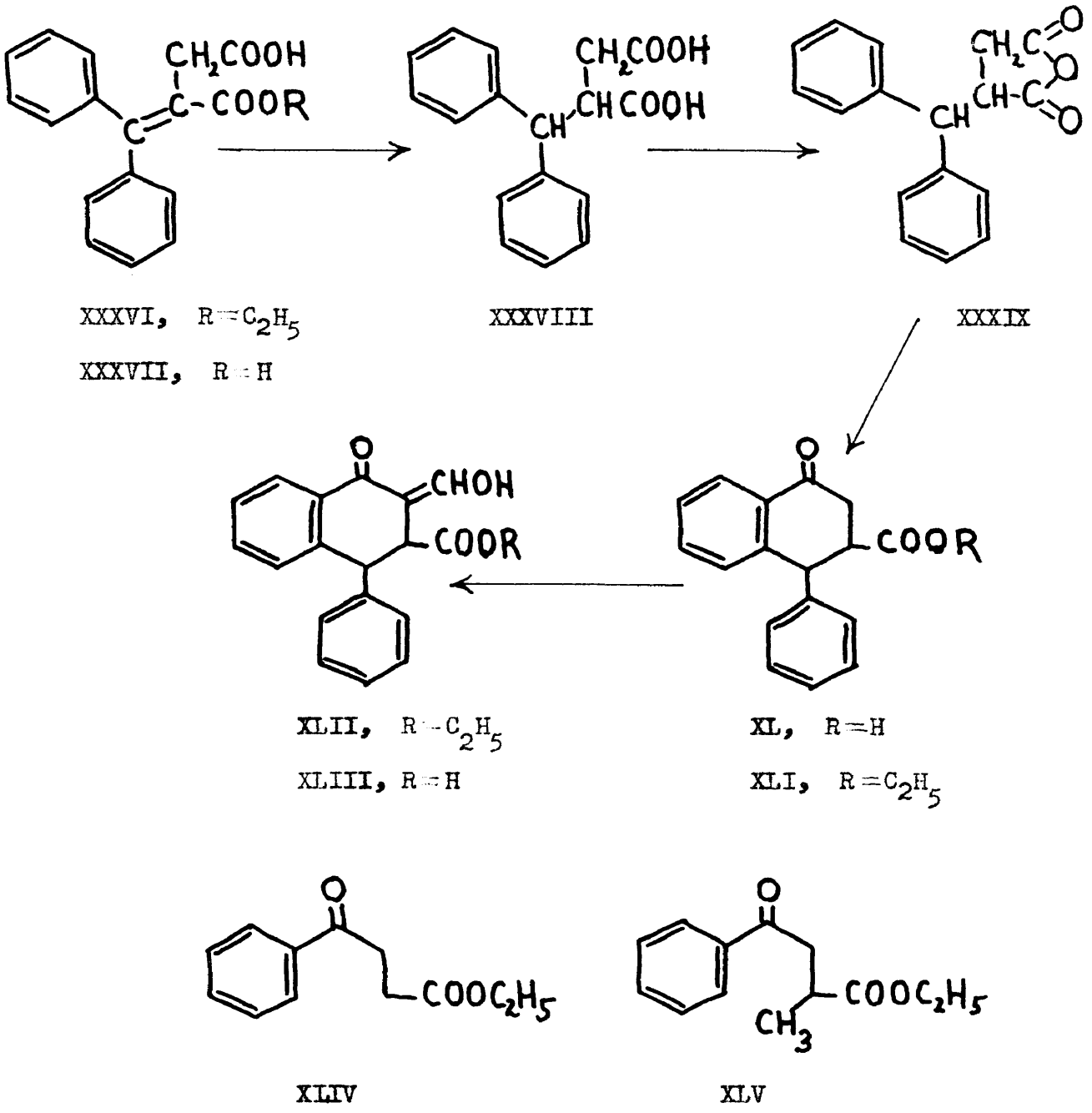
reduction of benzhydrylidenesuccinic acid (XXXVII) to benzhydrylsuccinic acid (XXXVIII) using sodium amalgam is reported, few experimental details and no yields are given, and the procedure appears tedious (42). The catalytic hydrogenation of the double bond was investigated. Despite the use of a variety of catalysts and solvents including palladium-charcoal in ethanol and in hot acetic acid, platinum in ethanol and in hot acetic acid, and Raney nickel in ethanol at 150°, no satisfactory procedure for the reduction could be devised. An attempt to reduce the sodium salt of XXXVI using platinum also met with failure.

The catalytic hydrogenation of benzhydrylidenesuccinic acid likewise was unsuccessful using platinum in ethanol and in hot acetic acid.

The difficulty in hydrogenating a highly substituted carbon-carbon double bond of this type is referred to by Johnson (43). He was able to overcome the difficulty by employing the method of Schwenk and Papa (44) in which the acid is treated with excess aqueous alkali and Raney nickel alloy. Application of this procedure to XXXVI afforded an eighty-six percent yield of XXXVIII, isolated as the hemibenzeneate.

Published directions for the preparation of 4-phenyl-3-carboxy-tetralone-1 (XL) from benzhydrylsuccinic acid call for formation of the anhydride XXXIX followed by Friedel-Crafts cyclisation of the anhydride using aluminum chloride in ice-cold nitrobenzene (45). Repetition of this procedure afforded the cyclized product in forty percent yield. The reported yield of seventy-five percent could not be duplicated despite repeated attempts.

Chart 10



XXXVI, R = C_2H_5

XXXVII, R = H

XXXVIII

XXXIX

XLII, R = C_2H_5

XLIII, R = H

XL, R = H

XLI, R = C_2H_5

XLIV

XLV

Cyclization of benzhydrylsuccinic acid using polyphosphoric acid was tried (46), but the insolubility of the material in the reagent prevented the reaction from taking the desired course.

Cyclization using ninety-two percent sulfuric acid at 90-100° afforded a thirty-seven percent yield of the keto acid. When eighty-four percent sulfuric acid was employed, starting material was recovered in an impure condition.

The use of hydrogen fluoride as a cyclizing agent afforded approximately twenty-five percent of impure product.

Although none of these methods was satisfactory, it was decided to employ the Friedel-Crafts method on larger scale preparations.

Esterification of the keto acid XL using ethanolic hydrogen chloride afforded a ninety-five percent yield of the ester XLI.

The formylation of the keto ester was conducted according to the directions of Johnson (32). After standing overnight at 5°, there was obtained approximately fifty-five percent of the hydroxymethylene carboxylic acid XLIII which could be recrystallized and which gave analytical data in agreement with the proposed structure. The balance of the material was enolic and was thought to be the hydroxymethylene carboxylic ester XLII.

The appearance of the formylation mixture was interesting. Upon addition of the keto ester to a suspension of sodium methoxide in benzene containing ethyl formate, a deep red color developed rapidly. After approximately one-half hour, all the solid dissolved affording a clear, deep red solution. In all other examples of this reaction, a precipitate

of the salt of the hydroxymethylene compound forms. The failure of the salt to precipitate in this case is not understood.

When the formylation reaction was stopped soon after the sodium methoxide dissolved, the hydroxymethylene carboxylic ester XLII was obtained in eighty-seven percent crude yield.

Both the hydroxymethylene ester and the hydroxymethylene acid could be titrated in aqueous alcohol using phenolphthalein as the indicator.

An attempt to prepare the O-methyl ether of the hydroxymethylene carboxylic ester by treatment of the enol with methyl iodide and potassium carbonate afforded a product which could not be purified satisfactorily, possibly because of contamination with the C-alkylated isomer (34). Other attempts to obtain the O-methyl ether by treatment of the enol with diazomethane were unsuccessful, in agreement with the results of Campbell, Schrage and Campbell (47) who were unable to form the enol methyl ethers of a series of hydroxymethylene ketones.

The great difference in the behavior of the open-chain keto ester LXII compared to the cyclic keto ester XLI indicates that a steric factor constitutes the important difference in the molecules under consideration. Molecular models show that the methylene group of the cyclic compound is much less sterically hindered than that of the acyclic compound. It is possible that because of this, the desired condensation in the case of the acyclic keto ester takes place so slowly that competitive reactions such as enol lactone formation can occur. It is evident that in the case of the acyclic material, the flexible nature of the molecule permits the enol lactone to form, whereas with the cyclic compound, the rigid nature

of the molecule prevents this.

Since a steric factor appeared to be preventing the desired condensation from taking place with ethyl benzylphenacylacetate, the reaction was examined with acyclic keto esters in which steric hindrance might be absent or minimized.

Ethyl β-benzoylpropionate (XLIV) upon treatment with ethyl formate and sodium methoxide reacted rapidly to afford a mixture from which approximately fifty percent of enolic material was isolated. Although no indication of the position of the hydroxymethylene group was obtained, from the greater activating influence of the keto group compared to the ester group, it is assumed that condensation alpha to the keto group predominated. Borsche (48) reported the condensation of benzaldehyde with XLIV occurs alpha to the keto group.

A fragrant, neutral oil was also isolated from the formylation of XLIV. Again, the lowered saponification equivalent and the isolation of β-benzoylpropionic acid from the saponification indicated that the oil was a mixture of starting material and enol lactone.

Because of the ambiguity arising from the possibility of condensation at either of the two methylene groups in ethyl β-benzoylpropionate, the reaction of ethyl α-methyl-β-benzoylpropionate (XLV) with ethyl formate was investigated. Although the appearance of the reaction mixture was similar to that observed previously with the cyclic keto ester XLI, there was obtained only eight percent of crude enolic material. The balance of the material was obtained as a neutral oil having a sweet odor unlike that of the starting material. Distillation of the neutral

oil afforded a mixture of lowered saponification equivalent. The residue from the distillation crystallized, but attempts to purify the solid were unsuccessful, and its identity was not established.

The failure of XLV to undergo the formylation to any large extent is interpreted as being due to steric hindrance. Apparently the existence of branching adjacent to the activated methylene group in the acyclic series results in sufficient hindrance to prevent the desired condensation from taking place, and side reactions predominate. The failure of ethyl isovalerate to undergo self condensation in the presence of sodium ethoxide represents a similar situation. In this case, the use of a very strong base such as sodium hydride causes the reaction to take place (49).

An attempt to conduct the formylation of ethyl benzylphenacylacetate using sodium hydride met with failure. The use of potassium tertiary-butoxide resulted in rapid decomposition of the ethyl formate to carbon monoxide and ethanol, and no enolic material was isolated.

The results of these experiments demonstrated that the introduction of the desired carbon by condensation with ethyl formate was not feasible, and alternative methods of accomplishing this objective were, therefore, considered.

SECTION VII

The Synthesis of an Unsubstituted Analogue of Podophyllotoxin. The successful introduction of the hydroxymethylene group into the cyclic keto ester prompted an attempt to reduce the hydroxymethylene ketone system to the 1,3-diol, a procedure which would afford a structure analogous

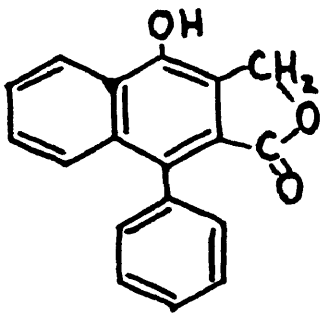
to that of podophyllotoxin (Chart 11).

The problem of synthesizing an unsubstituted analogue of podophyllotoxin was first undertaken by Borsche (50). The essential details of the present synthesis were outlined by Borsche, but the reported experimental work followed a somewhat different approach through the napthol derivative. Attempted reduction of the lactone of 4-phenyl-3-carboxy-2-hydroxymethyl-1-napthol (XLVI) afforded an inseparable mixture. No attempt to investigate the approach used in this work was reported.

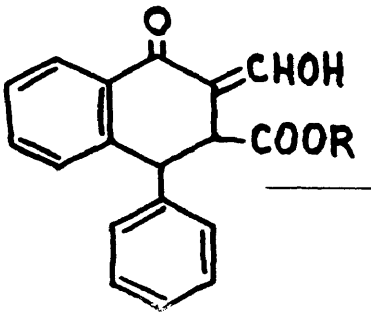
The reduction of hydroxymethylene ketones and β-ketoesters by lithium aluminum hydride is reported to be a complex reaction from which unsaturated alcohols are obtained in addition to the diols (51). The use of lithium aluminum hydride was prohibited in this case by the presence of the carboxyl or carbethoxy group. The reduction of enolic compounds by aluminum isopropoxide is reported to fail because of the formation of insoluble enolate salts (52). The use of sodium borohydride in aqueous alkali appeared to be a promising procedure.

When a solution of the hydroxymethylene carboxylic acid XLIII in aqueous alkali was treated with sodium borohydride, an acidic, crystalline product was obtained in forty percent yield which was not enolic and which melted with decomposition to afford another higher melting, neutral solid. The carbon and hydrogen analyses of the acidic material were in agreement with theory for the dihydroxy acid XLVIII. Upon heating, the material lost weight equivalent to one molecule of water per molecule of dihydroxy acid to afford a neutral substance whose carbon and hydrogen analyses and saponification equivalent were in agreement

Chart 11

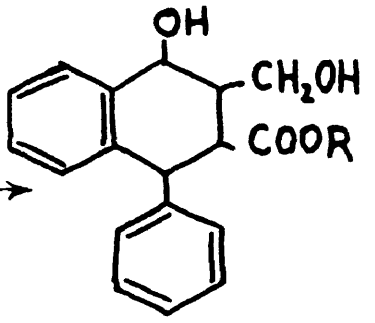


XLVI



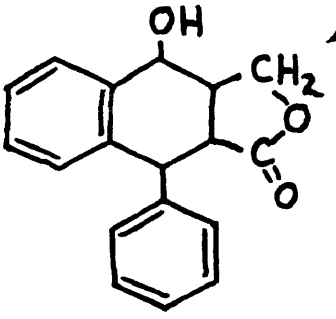
XLII, R = C_2H_5

XLIII, R = H

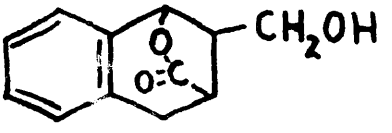


XLVII, R = C_2H_5

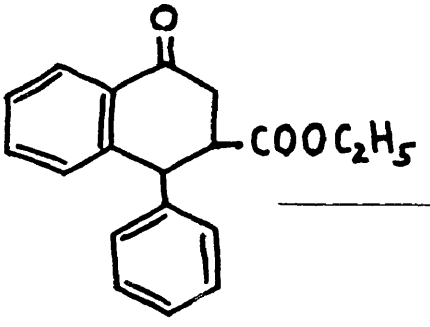
XLVIII, R = H



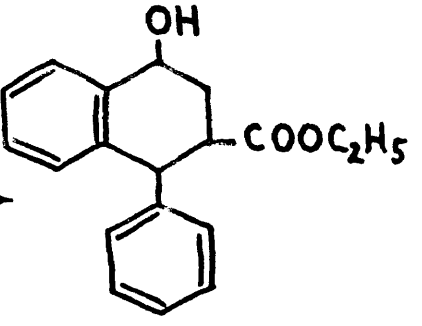
XLIX



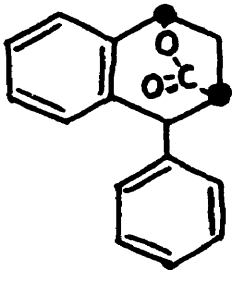
L



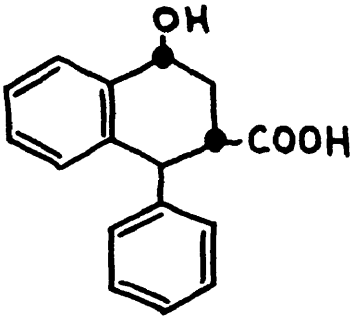
XLI



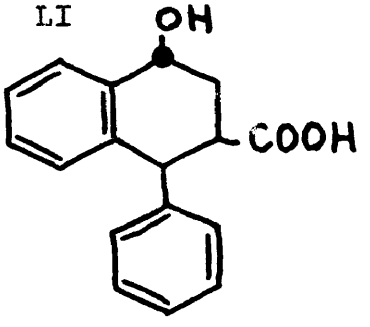
LI



LII



LIII



LIV

with the hydroxy lactone structure XLIX.

The position of lactonization is speculative. Although it might be assumed that the less strained lactone XLIX involving the methylol group would form preferentially, infrared studies on the analogous lactone formed from 1-hydroxy-2-hydroxymethyl-3-carboxytetralin indicate that the secondary hydroxyl participates in lactonization (L)(53). It was also found possible to form the lactone LII of cis-1-hydroxy-3-carboxy-4-phenyltetralin by thermal treatment of the hydroxy acid LIII, although the yield of pure product was much lower than in the case of the dihydroxy acid XLVIII. This demonstrates that the bicyclic lactone type of structure LII cannot be excluded on the basis of strain.

Attempts to dehydrate the hydroxy lactone using p-toluenesulfonic acid in benzene and sulfuric acid in acetic anhydride afforded only tarry products.

Reduction of the hydroxymethylene carboxylic ester in aqueous alkali using sodium borohydride also afforded the dihydroxy acid, although in only twenty-five percent yield. When the reduction was conducted in absolute ethanol, a low yield of the dihydroxy ester XLVII was obtained. A small amount of this material was also isolated from the reduction conducted on the hydroxymethylene carboxylic ester in aqueous alkali.

In connection with another study in progress in this Laboratory (53), it was of interest to prepare the lactone LII. Reduction of 4-phenyl-3-carbethoxytetralone-1 (XLI) by aluminum isopropoxide in isopropyl alcohol, followed by direct saponification of the crude hydroxy esters afforded a mixture of LIII and LIV. Separation was accomplished by subjecting the

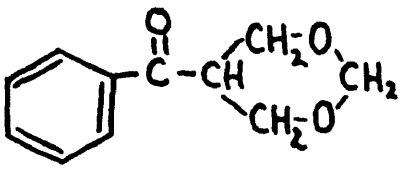
mixture to thermal lactonization, then removing the trans-hydroxy acid LIV by washing with sodium bicarbonate.

SECTION VIII

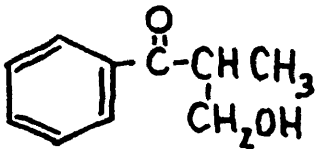
2-Benzyl-3-(α-hydroxybenzyl)-butyrolactone (LXVI). Since the results of the formylation experiments showed this approach to be fruitless in the acyclic series, the possibility of the direct introduction of the methylol group using formaldehyde was considered. The condensation of alkyl aryl ketones with formaldehyde has received relatively little study. The reaction of acetophenone with paraformaldehyde in methanol using potassium carbonate as the base affords the formal of dimethylolacetophenone LV in moderate yield while under the same conditions, propiophenone affords the monomethylol derivative LVI (54). On the other hand, acetomesitylene affords the monomethylol derivative LVII while propiomesitylene is converted to the methylene derivative LVIII (55). Haworth and Sheldrick (56) obtained the methylol lactone LX in excellent yield by treating the keto acid LIX with excess formaldehyde in the presence of aqueous sodium hydroxide. Saponification of LX produced the methylene derivative LXI. Brown (16) attempted the condensation of paraformaldehyde with diethyl benzylphenacylmalonate in methanol using potassium carbonate as well as the reaction of formaldehyde with benzylphenacylmalonic acid in aqueous alkali. Both procedures resulted in the recovery of starting material in good yield. This provides evidence of the hindered nature of the methylene group in this system.

The reaction of formaldehyde with benzylphenacylacetic acid (LXIII) in aqueous alkali was also attempted by Brown. A glassy material was

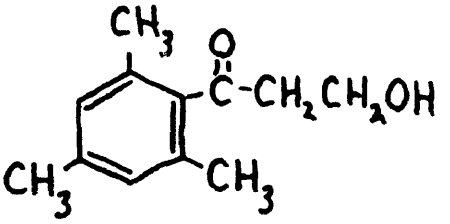
Chart 12



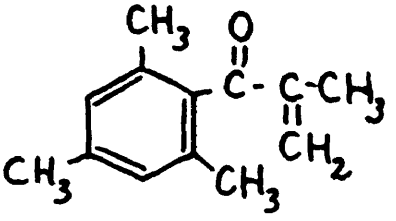
LV



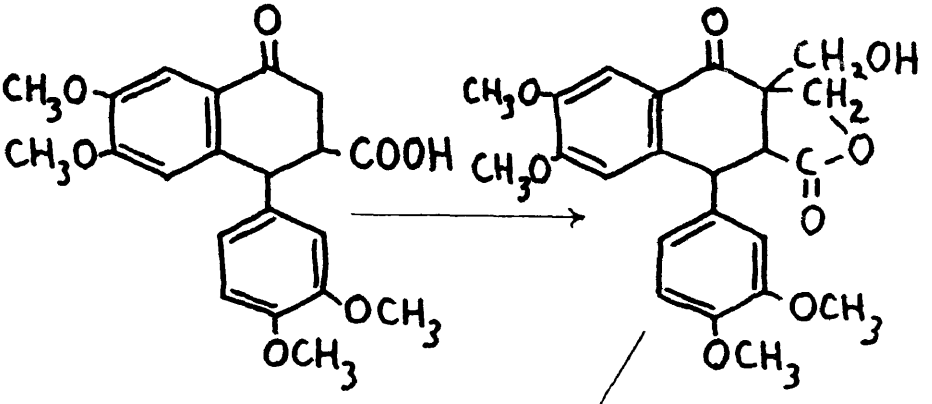
LVI



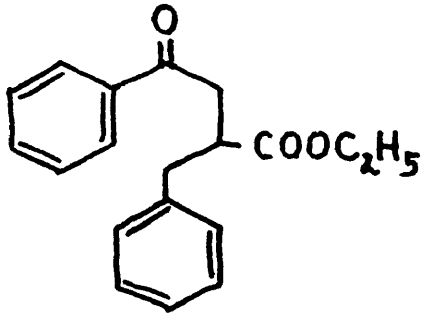
LVII



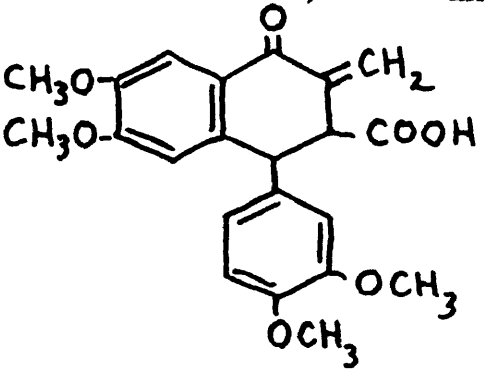
LVIII



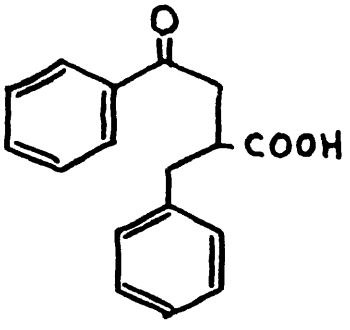
LIX LX



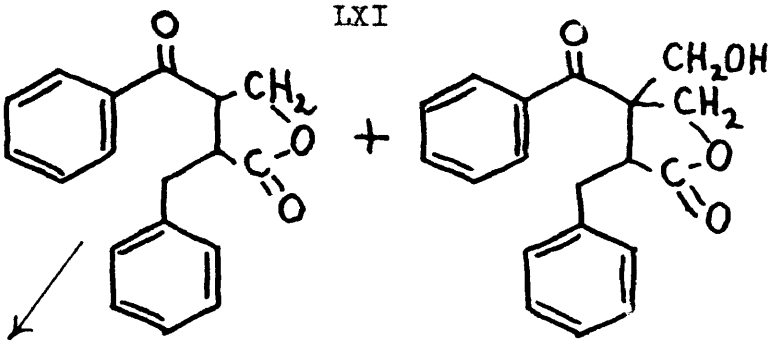
LXII



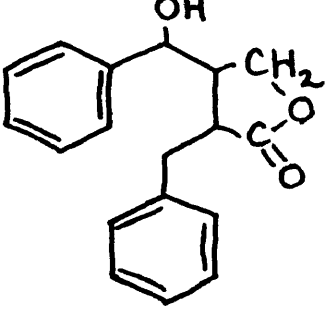
LXI



LXIII



LXIVa LXV



LXIVb

LXVIa

LXVIb

isolated which resisted purification and which was assumed to be starting material.

The condensation of the keto ester LXII with formaldehyde, both in the presence of potassium carbonate in methanol and also using sodium methoxide in methanol, afforded starting material. The failure of these procedures prompted a reinvestigation of the reaction of formaldehyde with the keto acid LXIII in aqueous alkali. The glassy material obtained by Brown was the result of a prolonged reaction time. Although it was believed to be starting material, no evidence was advanced in support of this.

The reaction of LXIII with a tenfold excess of formaldehyde in aqueous alkali afforded a mobile oil which was only partially soluble in sodium bicarbonate. Acidification of the bicarbonate extract precipitated an oil which subsequently could not be titrated directly with aqueous sodium hydroxide. This behavior can be rationalized if it is assumed that the material is a lactone which failed to undergo complete lactonization before the extraction with sodium bicarbonate, or which was partially hydrolyzed during the bicarbonate wash.

The procedure was repeated, except that the oil obtained was chromatographed on silicic acid. The material was separated into two approximately equal, noncrystalline fractions. The less strongly adsorbed fraction gave analytical data consistent with the keto lactone LXIV, and the more strongly adsorbed fraction gave analytical data in agreement with the keto methylol lactone LXV. The keto lactone LXIV readily formed a 2,4-dinitrophenylhydrazone, while the keto methylol lactone LXV failed

to form such a derivative, in agreement with the feeble carbonyl activity observed by Haworth and Sheldrick (56) in their keto methylol lactone LX. When saponification equivalents were determined using an excess of boiling standard alkali, low values were obtained. If the lactones were allowed to stand at room temperature with excess alkali, the values obtained were in agreement with theory. This behavior can be explained by assuming that the original condensation was reversed by boiling alkali, and the formaldehyde regenerated underwent a Cannizzaro reaction, thus consuming alkali.

The high proportion of LXV formed when a large excess of formaldehyde was employed prompted an experiment in which only a small excess of formaldehyde was used. After chromatography, an eighty-six percent yield of crude LXIV was obtained. From this a crystalline isomer (LXIVa) was obtained in thirty-two percent yield, based on the keto acid LXIII.

Because the position of lactonization in the keto lactone LXIV was known unequivocally and corresponded to that in podophyllotoxin (2), the conditions of reduction of the carbonyl group had to be such that translactonization of the product was rendered improbable. Thus, the use of basic reagents such as aluminum isopropoxide or lithium borohydride was prohibited. Likewise, it seemed desirable to avoid acidic conditions, since the presence of acid might catalyze translactonization. These limitations excluded most of the common techniques for reducing ketones except catalytic hydrogenation in neutral solvents.

It was found that the hydrogenation of the crystalline keto lactone LXIVa using palladium-charcoal in cyclohexane at room temperature proceeded quite readily with the absorption of one mole of hydrogen. The

crystalline product LXVIa isolated from this in forty percent yield proved to be very difficult to purify and persisted in melting over a ten degree range.

Hydrogenation of LXIVa using palladium-charcoal in ethanol proceeded very rapidly. The product isolated proved to be identical to that obtained when cyclohexane was the solvent, indicating that the ethanol did not promote translactonization. Again, the product failed to exhibit a sharp melting point, even though crystallization from different solvents was employed. The slightly high carbon analyses indicate that the compound may undergo partial dehydration.

Hydrogenation of the noncrystalline keto lactone LXIVb using palladium-charcoal in ethanol afforded a twenty-eight percent yield of crystalline material which gave analytical data in agreement with the hydroxy lactone structure LXVIb.

Thus, two of the possible four racemates corresponding to 2-benzyl-3-(α-hydroxybenzyl)-butyrolactone (LXVI) have been obtained in a crystalline condition. It seems unlikely that translactonization occurred under the conditions employed, although one of the products appeared to be contaminated with a material of higher carbon content which was not removed by repeated recrystallization.

SECTION IX

2-(3,4,5-Trimethoxybenzyl)-3-(α-hydroxy-3',4'-methylenedioxybenzyl)-butyrolactone (II). The reaction of 3,4,5-trimethoxybenzyl-3',4'-methylenedioxyphenacylacetic acid (XXVIII) with formaldehyde in aqueous alkali was conducted using a fifty percent excess of formaldehyde at room temperature

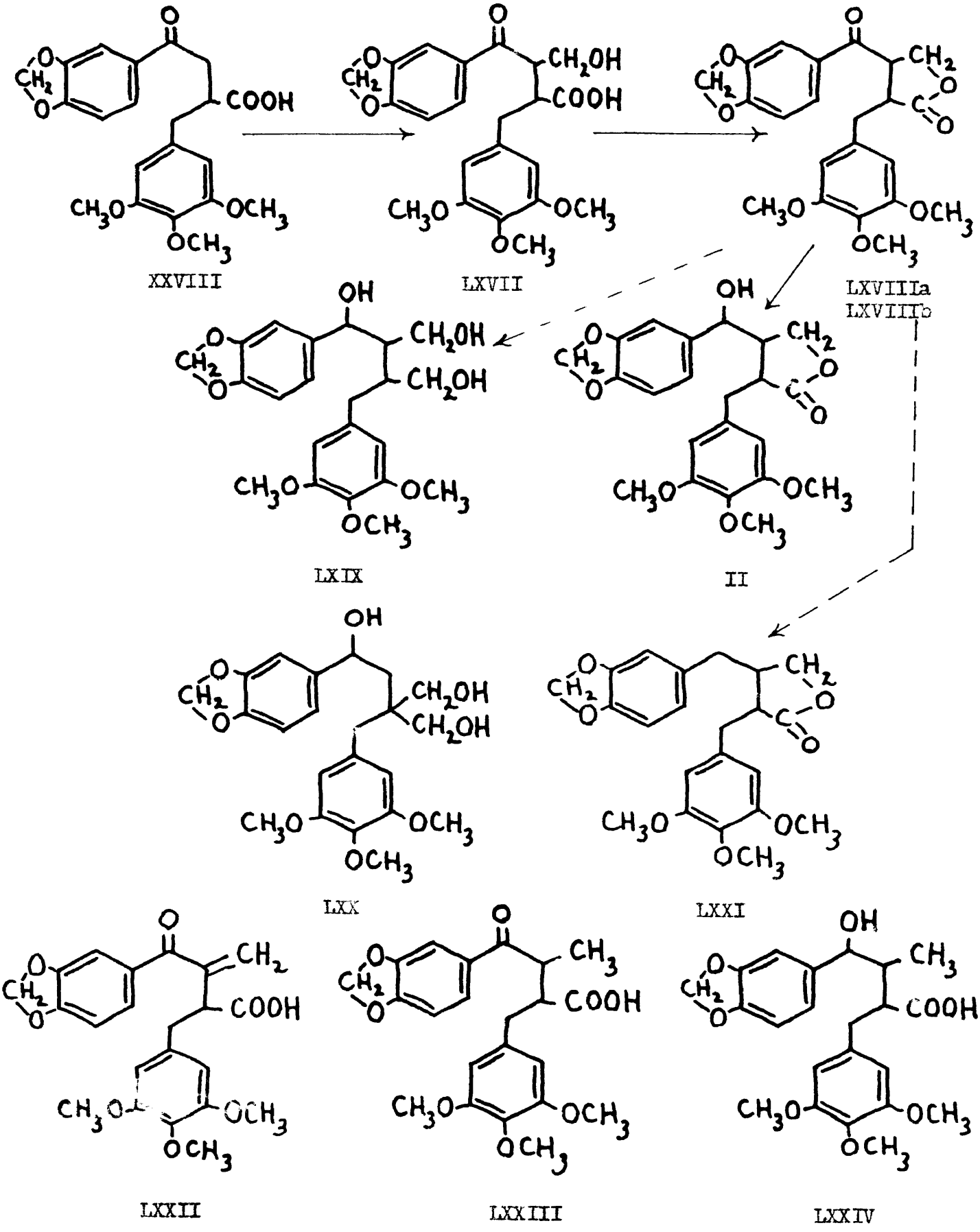
for two days (Chart 13). Acidification of the reaction mixture afforded a semi-solid precipitate which proved to be only partially soluble in ether. The ether-insoluble solid was obtained in sixty-three percent yield and was shown to be the methylol acid LXVII by analysis and neutralization equivalent. The use of a five percent excess of formaldehyde lowered the yield to forty-four percent. The failure of LXVII to lactonize as was observed with the unsubstituted compounds may be attributed to the extreme insolubility of the material in the aqueous mixture. On one occasion, acidification of a solution of the sodium salt of LXVII in aqueous alcohol failed to produce an immediate precipitate. Upon standing in the cold a precipitate was deposited which proved to be the corresponding lactone LXVIIIa, showing that lactonization would take place under mild conditions if a homogeneous mixture existed.

Upon melting, the methylol acid LXVII lactonized spontaneously. The conversion of the crude methylol acid to the purified lactone LXVIIIa by thermal lactonization was accomplished in ninety percent yield.

The noncrystalline, ether-soluble material from the formaldehyde condensation was believed to be the isomeric keto lactone LXVIIIb, possibly contaminated with the keto methylol lactone. Chromatography on silicic acid failed to achieve any separation, although a small amount of the crystalline keto lactone LXVIIIa was isolated from one of the fractions.

Attempts to gain direct evidence concerning the location of the methylol group by oxidation with potassium permanganate failed to afford any crystalline products except starting material.

Chart 13


XXVIII
LXVII
LXVIIIa
LXVIIIb
LXIX
II
LXX
LXXI
LXXII
LXXIII
LXXIV

Although it appeared quite unlikely, it was thought that the possibility that the methylol group had entered the molecule alpha to the carboxyl group instead of alpha to the keto group could be eliminated by comparing the product LXIX of lithium aluminum hydride reduction of the keto lactone with LXX, obtained by reduction of the keto diester XX. The extreme insolubility of LXVIIIa in ether prompted the use of tetrahydrofuran as the solvent for both reductions. Although reduction evidently took place, no crystalline products could be isolated, and attempts to prepare crystalline benzoates of the crude products likewise met with failure.

When a determination of the saponification equivalent of LXVIIIa was made using excess, boiling alkali, a low saponification equivalent was obtained, as had also been the case with the unsubstituted keto lactone LXIV. Furthermore, continued boiling with alkali resulted in an increased consumption of alkali. When the saponification equivalent was determined in aqueous alcohol at room temperature, the value obtained was in agreement with theory.

The lowered value of the saponification equivalent when boiling alkali was employed is interpreted as being due to reversal of the original condensation followed by a Cannizzaro reaction of the formaldehyde. The reversal of the condensation by alkali is evidence that the methylol group is alpha to either the keto group or the carboxyl group. Since the methylol acid readily formed a lactone, a result not to be expected of a beta-hydroxy acid, it is concluded that the methylol group entered alpha to the keto group. The isolation of the keto acid XXVIII from the saponification of the keto lactone LXVIIIa provided confirmation that alkali caused reversal of the original condensation. The possibility that

the rings underwent substitution is remote since there are no reported examples of aromatic ethers reacting with formaldehyde under alkaline conditions. The activation of the methylene group adjacent to the trimethoxyphenyl group is believed to be too feeble to permit condensation under the conditions employed in view of the electron releasing properties of the methoxyl groups.

The hydrogenation of the keto lactone using palladium-charcoal in cyclohexane proceeded slowly and incompletely unless large quantities of catalyst were employed. The hydrogenation proceeded fairly rapidly in ethanol using palladium-charcoal or platinum. Ethyl acetate was an unsatisfactory solvent for the hydrogenation. Attempted hydrogenolysis of the keto lactone to the methylene compound LXXI using palladium-charcoal in acetic acid failed to afford the desired product.

Initial attempts to isolate a crystalline product from the hydrogenations were unsuccessful. No separation could be achieved through chromatography on silicic acid or alumina, and direct crystallization was fruitless.

Despite the possibility of translactonization, a reduction was tried using aluminum isopropoxide in isopropyl alcohol in the hope that a different ratio of isomers would be formed that would permit isolation of a crystalline product. Although reduction took place as evidenced by the formation of acetone, no crystalline product was isolated.

Ultimately, a sample of the product II from the palladium catalyzed hydrogenation deposited crystals after standing in the cold. The crude solid was obtained in approximately seventy percent yield. Recrystallization was difficult, and a sharp melting point could not be obtained. However,

the analytical data were in agreement with theory for the hydroxy lactone.

The infrared spectrum (Chart 14), determined on a five percent solution of II in chloroform, exhibits a weak absorption at 2.80 microns, attributed to OH stretching. The stronger absorption at 3.31 microns occurs in the region of CH stretching. The pronounced peak at 5.67 microns is close to the value of 5.65 microns attributed by Rasmussen and Brattain (37) to the carbonyl stretching vibration in gamma lactones. The significance of the other bands is not known. The spectrum shown appears to be in agreement with the structure II.

The noncrystalline fraction from the formaldehyde condensation with the keto acid XXVIII was insoluble in sodium bicarbonate solution and was thought to be primarily the isomeric keto lactone LXVIIIb. When the material was subjected to hydrogenation using platinum as a catalyst, a very rapid absorption of hydrogen occurred until forty-five percent of the expected absorption had taken place. The absorption of hydrogen then slowed markedly and stopped when eighty-five percent of the expected absorption had taken place. This behavior indicated that the original material was a mixture. A thirteen percent yield of an acidic, crystalline solid was isolated from the reduction mixture by direct crystallization from benzene. Extraction of the benzene mother liquor with sodium bicarbonate afforded an additional quantity of acidic material, but this was not obtained in a pure condition.

The initial rapid absorption of hydrogen suggested the possibility that the noncrystalline fraction contained some of the methylene derivative

LXXII. The primary reduction product of the methylene derivative would be the keto acid LXXIII. It might be expected that the carbonyl group would be further reduced to the corresponding hydroxy acid LXXIV, but this is not supported by the hydrogen consumption observed. Furthermore, the acidic substance melted at 167° with no evidence of decomposition. It seems very unlikely that the hydroxy acid LXXIV would fail to lactonize under these conditions. However, the acidic substance failed to give any evidence of reaction with 2,4-dinitrophenylhydrazine.

The analytical data and neutralization equivalent were in reasonably good agreement with the empirical formula $C_{22}H_{24}O_8$ for LXXIII.

The infrared spectrum of the acidic material (Chart 14) exhibited a very weak absorption at 2.85 microns and a broad intense band at 3.20 microns. This latter band is in the CH stretching region and also in the region of bonded OH stretching. A sharp, intense peak at 5.86 microns is attributed to the carbonyl stretching of the carboxyl group. The band close by at 5.99 microns is in the region of the conjugated carbonyl group.

Since the infrared spectrum of the acidic product could be interpreted in terms of the keto acid LXXIII, the infrared spectrum of the similar keto acid XXVIII was examined (Chart 14). The striking resemblance between the two spectra, particularly in the 5–8 micron region, makes it seem likely that the acidic substance is LXXIII. The more intense OH stretching band exhibited by LXXIII can be satisfactorily accounted for by the presence of an additional methyl group in LXXIII.

Although the chemical evidence is not entirely in support of this structure, it is possible that the factors which inhibited the reduction of the carbonyl group might also inhibit the formation of a 2,4-dinitrophenylhydrazone.

EXPERIMENTAL

All melting points were determined in a Hershberg precision melting point apparatus using total-immersion, Anschutz thermometers, and are corrected. Pressures below 2.5 mm. were determined using a McLeod gauge. The term "petroleum ether" refers to the fraction b.p. 60 - 80°. With the exception of percent composition, all calculations reported were performed with a slide-rule.

The author wishes to express his gratitude to Mrs. Mary H. Aldridge, Miss Kathryn Gerdeman, and Mr. Byron Baer for performing the microanalyses reported herein. The author would also like to thank Mr. Carl Brainard for determining the infrared spectra, and Dr. Robert Spurr for assistance in interpreting the infrared spectra.

Ethyl 3,4,5-Trimethoxybenzoate (IV). In a 3-l. two-necked flask were placed 635 ml. of absolute ethanol, 310 ml. of benzene, 188 g. (0.887 mole) of 3,4,5-trimethoxybenzoic acid (m.p. 170 - 171.4°) (58), and 6 g. of p-toluenesulfonic acid monohydrate. The mixture was heated under an efficient fractionating column, and the benzene-alcohol-water azeotrope was distilled out intermittently. The process required four days, and several portions of benzene were added during this time to maintain the volume. When no more water was formed, as evidenced by a rise in the vapor temperature to 75°, the mixture was cooled, and 500 ml. of benzene was added. The mixture was washed with water and then with five percent sodium bicarbonate solution. The aqueous extracts were washed twice with benzene, and the combined benzene solutions were dried

briefly over magnesium sulfate. The benzene solution was concentrated under diminished pressure. Distillation of the pale yellow residue afforded 202 g. (95%) of ethyl 3,4,5-trimethoxybenzoate, b.p. 117°/1 mm., m.p. 52.5-54.5° (lit. m.p. 53-55°) (59). Although the ester could be recrystallized from petroleum ether by cooling in an ice-salt mixture, no improvement in the melting point resulted. The material from the distillation was used directly in the next step.

3,4,5-Trimethoxybenzyl Alcohol (V). Method A. A 250-ml. three-necked flask fitted with a mercury-sealed Hershberg stirrer, a dropping funnel, and a reflux condenser protected by a drying tube, was thoroughly flamed and flushed with dry nitrogen. Fifty milliliters (0.105 mole) of 2.1 M lithium aluminum hydride in tetrahydrofuran was placed in the flask, and to this was added a solution of 24.0 g. (0.100 mole) of ethyl 3,4,5-trimethoxybenzoate in 50 ml. of tetrahydrofuran over a period of twenty minutes. The tetrahydrofuran refluxed gently during the addition, and after the addition was complete, refluxing was continued for two hours. No precipitate formed during this time. After cooling the mixture in ice, the excess lithium aluminum hydride was decomposed by the cautious addition of water, and the resulting sludge was treated with 100 ml. of cold, ten percent sulfuric acid. The pale yellow, organic solution was separated from the aqueous phase, and the latter was washed five times with ether. Addition of the ethereal extracts to the original organic solution caused the separation of another aqueous phase which was removed. The organic solution was washed successively with water, saturated salt solution, and five percent sodium bicarbonate. The bicarbonate wash discharged the yellow color and became

deep red. The solution was dried over magnesium sulfate and concentrated. Distillation of the residue in a Hickman distillation apparatus afforded 15.6 g. (79%) of a clear, viscous oil, which distilled at a bath temperature of 115-120° and a pressure of 0.03-0.04 mm.

The use of a Hickman apparatus was believed necessary to prevent decomposition during distillation, but later work showed that the alcohol could be distilled in a conventional apparatus.

Method B. In a 300-ml. three-necked flask equipped with a magnetic stirrer, a dropping funnel, and a reflux condenser protected by a drying tube, were placed 5.0 g. (0.12 mole) of lithium aluminum hydride and 100 ml. of tetrahydrofuran. When the hydride had dissolved, a warm solution of 25.2 g. (0.119 mole) of 3,4,5-trimethoxybenzoic acid (m.p. 168-6-171.6°) in 85 ml. of tetrahydrofuran was added over a period of forty-five minutes. The resulting solution was heated under reflux for twenty-one hours. Most of the solvent was removed by distillation at atmospheric pressure. The cooled, semi-solid residue was cautiously treated with 100 ml. of moist ether, then with water, and finally with sufficient cold, ten percent sulfuric acid to dissolve the aluminum salts. After working up the reaction mixture as described above, there was obtained 13.7 g. (58%) of colorless oil, b.p. 115-120° /0.02 mm., $n_D^{25°}$ 1.5431.

3,4,5-Trimethoxybenzyl Chloride (VI). In a 300-ml. three-necked flask fitted with a mechanical stirrer, a dropping funnel, and a reflux condenser protected by a drying tube and connected to a gas trap, were placed 15.6 g. (0.0785 mole) of 3,4,5-trimethoxybenzyl alcohol, 9.7 g. (0.080 mole) of purified dimethylaniline, and 100 ml. of anhydrous,

thiophene-free benzene. The mixture was chilled in ice, and a solution of 9.4 g. (0.079 mole) of purified thionyl chloride (60) in 25 ml. of benzene was added over a period of eighty minutes. Vigorous stirring was employed during the addition. The mixture initially was orange-yellow in color, but as the addition progressed it became a pale yellow-green. When the addition was complete, the mixture was allowed to warm to room temperature and was then heated under reflux for one hour. The mixture was cooled in ice, and 30 ml. of 1:5 hydrochloric acid was added. The aqueous phase was separated from the yellow benzene solution and extracted with benzene. The combined benzene solutions were washed with five percent sodium bicarbonate solution, shaken briefly with magnesium sulfate, and concentrated under diminished pressure. Distillation of the pale yellow residue afforded 15.0 g. (88.5%) of 3,4,5-trimethoxybenzyl chloride, b.p. 110°/0.1 mm., m.p. 58-61°. Recrystallization of the distillate from 250 ml. of petroleum ether afforded 12.9 g. (75%) of product, m.p. 60-62° (lit. m.p. 60-61°) (5).

Direct Conversion of Ethyl 3,4,5-Trimethoxybenzoate (IV) to 3,4,5-Trimethoxybenzyl Chloride (VI). A solution of 56.9 g. (0.237 mole) of ethyl 3,4,5-trimethoxybenzoate in 125 ml. of tetrahydrofuran was added to 119 ml. (0.250 mole) of 2.1 M lithium aluminum hydride in tetrahydrofuran. After heating under reflux for three hours, the cooled mixture was cautiously treated with ice-water and then with 300 ml. of ten percent sulfuric acid. The aqueous phase was saturated with salt, separated from the organic phase, and extracted three times with ether. The combined organic solutions were then washed with five percent sodium bicarbonate until the bicarbonate washings had no red color. The organic

solution was dried over magnesium sulfate and concentrated under diminished pressure. When most of the solvent had been removed, 400 ml. of anhydrous, thiophene-free benzene was added, and approximately 100 ml. more of solvent was removed. The residual benzene solution was thoroughly dried over magnesium sulfate. After filtration, the chilled benzene solution was treated with 29.1 g. (0.240 mole) of dimethylaniline, whereupon a solution of 28.2 g. (0.239 mole) of thionyl chloride in 75 ml. of benzene was added over a period of seventy minutes. The mixture was warmed to room temperature and then heated under reflux for one hour. The cooled mixture was treated with 60 ml. of 1:5 hydrochloric acid. The aqueous phase was separated and washed with benzene. The combined benzene solutions were then washed with five percent sodium bicarbonate. The yellow benzene solution was dried briefly over magnesium sulfate and concentrated under diminished pressure. Distillation of the residue afforded 44.3 g. (87% overall) of 3,4,5-trimethoxybenzyl chloride, b.p. 110-112°/0.1 mm., m.p. 55-60°. Recrystallization of the distillate from 750 ml. of petroleum ether afforded 38.8 g. (76% overall) of product, m.p. 59.5-61.0°.

Diethyl 3,4,5-Trimethoxybenzylmalonate (VII). Method A. In a 2-l. three-necked flask fitted with a mercury-sealed Hershberg stirrer, a dropping funnel, and a drying tube, was placed 550 ml. of freshly distilled diethyl malonate. To this was added 15.4 g. (0.609 mole, on the basis of ninety-five percent purity) of sodium hydride in small portions. The solution reached a temperature of approximately 75° at the end of the addition. Cooling below 60° caused the sodium salt to precipitate. The solution was warmed in an oil bath while a solution of 131 g. (0.605 mole) of 3,4,5-trimethoxybenzyl chloride (m.p. 60-62°) in 350 ml. of diethyl

malonate was added over a period of one hour. The resulting mixture was heated at 105-110° for twenty hours. The mixture was cooled, a few drops of acetic acid were added, and then 50 ml. of water was added to coagulate the finely divided precipitate of sodium chloride. The pale amber solution was decanted off through a filter, and the coagulated precipitate was washed several times with diethyl malonate. The excess diethyl malonate was removed by distillation (b.p. 40°/0.1 mm.), and the residue was dissolved in 2.5 l. of boiling petroleum ether. The resulting solution was boiled with decolorizing carbon, filtered, and cooled. There was obtained 172.5 g. (84%) of diethyl 3,4,5-trimethoxybenzylmalonate, m.p. 77.0-79.0°. This material could be recrystallized almost quantitatively from petroleum ether. A sample purified for analysis melted at 78.0-79.0° (lit m.p. 67-71°)(5). Anal. Calcd. for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 59.75, 59.84; H, 7.15, 7.10.

Diethyl 3,4,5-Trimethoxybenzalmalonate (XI). A solution of 0.75 g. (0.0038 mole) of 3,4,5-trimethoxybenzaldehyde (m.p. 73.8-75.0°), 0.63 g. (0.0039 mole) of diethyl malonate, 0.45 g. (0.0039 mole) of caproic acid, and 0.15 g. (0.0018 mole) of piperidine in 35 ml. of anhydrous, thiophene-free benzene, was heated under reflux for twenty-seven hours in a 50-ml. flask equipped with a water trap and a reflux condenser. No further evolution of water could be detected at the end of this time. The cooled, yellow solution was washed with water and then with five percent sodium bicarbonate solution, and dried over magnesium sulfate. Evaporation in an air stream afforded an oily residue which crystallized readily. The solution of the residue in 25 ml. of petroleum ether was

boiled with decolorizing carbon, filtered, and cooled. There was obtained 0.95 g. (74%) of pale yellow solid, m.p. 68-70°.

The same product, m.p. 69-70°, was obtained in thirty-eight percent yield from the reaction conducted in ethanol using piperidine benzoate as the catalyst. Although the material was completely soluble in boiling petroleum ether at the time of its formation, after twenty months it was no longer completely soluble in this solvent. The insoluble material was collected and recrystallized from a mixture of benzene and petroleum ether. It melted at 212-213°. The soluble fraction crystallized in large prisms, m.p. 69.2-70.4°. Anal. Calcd. for $C_{17}H_{22}O_7$: C, 60.34; H, 6.56. Found: C, 60.45; H, 6.67. The insoluble product, m.p. 212-213°, gave the following analysis: C, 60.49; H, 6.70. The essential identity of this analysis with that obtained for diethyl 3,4,5-trimethoxybenzalmalonate, m.p. 69.2-70.4°, as well as the mode of formation, makes it seem likely that the product, m.p. 212-213°, is 1,1,3,3-tetracarbethoxy-2,4-di-(3,4,5-trimethoxyphenyl)-cyclobutane (XIV).

Diethyl 3,4,5-Trimethoxybenzylmalonate (VII). Method B. A mixture of 0.75 g. (0.0022 mole) of diethyl 3,4,5-trimethoxybenzalmalonate, 25 ml. of ethanol, and 0.05 g. of Adam's catalyst, was shaken with hydrogen at room temperature and atmospheric pressure. The absorption of one mole of hydrogen was complete in fifteen minutes. After removal of the catalyst, the colorless solution was concentrated in an air stream. The solid residue was recrystallized from petroleum ether to afford 0.64 g. (85%) of fluffy needles, m.p. 77.5-78.5°. A mixed melting point with a sample of material prepared by Method A was undepressed.

Diethyl 3,4,5-Trimethoxybenzoylmalonate (IX). In a 3-l. three-necked flask fitted with a mercury-sealed Hershberg stirrer, a dropping funnel, and a reflux condenser protected by a drying tube, were placed 18.1 g. (0.745 atom) of magnesium turnings, 15 ml. of absolute ethanol, 1.7 ml. of carbon tetrachloride, and 250 ml. of anhydrous ether. The mixture was warmed gently to initiate the reaction, and after a few minutes, a mixture of 119 g. (0.745 mole) of diethyl malonate, 68 ml. of absolute ethanol, and 85 ml. of anhydrous ether was added dropwise with stirring. Upon heating the mixture under gentle reflux for three hours, all the magnesium dissolved to afford a gray solution of diethyl ethoxymagnesiummalonate. To this solution was added dropwise a solution of 155 g. (0.674 mole) of 3,4,5-trimethoxybenzoyl chloride (m.p. 77.0-79.5°) (7) in 1.3 l. of warm, anhydrous ether. Vigorous stirring was essential because of the formation of a heavy precipitate as the addition progressed. When the addition was complete, the mixture was heated at 50° in a water bath for one-half hour. The cooled mixture was acidified with 1:5 sulfuric acid, and benzene was added to dissolve some precipitated material. The aqueous phase was separated and extracted with benzene. The combined benzene solutions were washed with five percent sodium bicarbonate solution and then with water, and were dried over magnesium sulfate. The solvent was removed under diminished pressure, and the residue obtained was dissolved in 600 ml. of ethanol at 50-60°. The solution was filtered, and an equal volume of warm water was added slowly. Upon cooling, there was obtained 217 g. (91%) of diethyl 3,4,5-trimethoxybenzoylmalonate, m.p. 90.5-91.5° (lit. m.p. 89-90°) (8). It was important to conduct the recrystallization as quickly and at as low a temperature as possible to obtain good recovery.

Hydrogenation of Diethyl 3,4,5-Trimethoxybenzoylmalonate (IX) Using Palladium-charcoal. A mixture of 4.5 g. (0.013 mole) of diethyl 3,4,5-trimethoxybenzoylmalonate, 100 ml. of absolute ethanol, and 2.0 g. of ten percent palladium-charcoal was shaken at room temperature with hydrogen under an initial pressure of forty-two pounds per square inch. After the rapid absorption of one mole of hydrogen, shaking was continued for an additional 1.5 hour but no further absorption of hydrogen was observed. Removal of the ethanol under diminished pressure afforded an oily residue which rapidly crystallized. The residue was dissolved in 50 ml. of petroleum ether, and the solution was filtered and chilled. There was obtained 2.4 g. (94%) of crude 3,4,5-trimethoxybenzaldehyde, m.p. 60-67°. A sample of this, purified for analysis, melted at 73.4-74.0° (lit. m.p. 74-75°) (8). Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.42, 61.36; H, 6.40, 6.20.

Hydrogenation of Diethyl 3,4,5-Trimethoxybenzoylmalonate (IX) Using Platinum. A mixture of 20 g. (0.0565 mole) of diethyl 3,4,5-trimethoxybenzoylmalonate, 150 ml. of ethanol and 1.0 g. of Adam's catalyst was shaken at room temperature with hydrogen under an initial pressure of forty-three pounds per square inch. After the absorption of two moles of hydrogen, the rate of absorption became very slow and shaking was discontinued. The solvent was removed under diminished pressure, and the residual oil was distilled in a Hickman distillation apparatus. There was obtained 5.3 g. (59%) of diethyl malonate and 7.6 g. (68%) of 3,4,5-trimethoxybenzyl alcohol. The alcohol was identified by conversion to 3,4,5-trimethoxybenzyl chloride in good yield.

1,2,3,5,6,7-Hexamethoxy-9,10-dihydroanthracene (XIII). A solution of 1.0 g. of 3,4,5-trimethoxybenzyl alcohol in 20 ml. of ten percent

sulfuric acid was boiled for three hours. An oil separated which, upon cooling, solidified to a light brown solid. This was dissolved in ether, and the solution was filtered to remove some carbonaceous material. Upon slow evaporation, the amber ethereal solution deposited a small quantity of a white, crystalline solid. The solution was decanted off, and the solid was washed twice with anhydrous ether. After two recrystallizations from ethanol, there was obtained approximately 20 mg. of product, m.p. 201.5-203° (lit. m.p. 201-202°) (5). Anal. Calcd. for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71; OCH_3, 51.67. Found: C, 66.57, 66.82; H, 6.58, 6.75; OCH_3, 51.66.

Piperonoyl Chloride (XVI). A magnetically stirred mixture of 113.5 g. (0.684 mole) of piperonylic acid (m.p. 230-232°) and 123 ml. (1.71 mole) of purified thionyl chloride was heated under reflux for five hours. Most of the excess thionyl chloride was removed by distillation at atmospheric pressure. The nearly black residue was further concentrated under diminished pressure until it solidified. The residue was treated with 100 ml. of anhydrous, thiophene-free benzene, and the resulting solution was concentrated again. Distillation of the residue through a short Vigreaux column afforded 124 g. (98.5%) of colorless piperonoyl chloride, b.p. 92°/0.025 mm., m.p. 78-83°, which was pure enough to use directly.

When piperonoyl chloride was prepared according to published directions calling for the use of benzene as a diluent, there was obtained an ether-insoluble by-product which was insoluble in cold, dilute alkali and contained no halogen or sulfur. Recrystallization was accomplished from ethanol to afford a product, m.p. 152.6-154.2°. Analysis indicated that

the material was piperonylic anhydride. Anal. Calcd. for $C_{16}H_{10}O_7$: C, 61.15; H, 3.21. Found: C, 61.43; H, 3.43. This was verified by hydrolysis to piperonylic acid, m.p. 231-233°, using boiling, ten percent sodium hydroxide.

Diethyl Piperonoylmalonate (XVII). In a 3-l. three-necked flask fitted with a powerful Hershberg stirrer, a dropping funnel, and an efficient reflux condenser protected by a drying tube, were placed 20.65 g. (0.850 atom) of magnesium turnings, 17.4 ml. of absolute ethanol, and 1.9 ml. of carbon tetrachloride. After heating to initiate the reaction, 300 ml. of anhydrous ether was added. To the stirred mixture a solution of 136 g. (0.850 mole) of diethyl malonate, 77.5 ml. of absolute ethanol and 100 ml. of anhydrous ether was added dropwise. After four hours, the resulting gray solution was treated with a solution of 139 g. (0.755 mole) of piperonoyl chloride, m.p. 78-83°, in 1 l. of anhydrous ether. Stirring was rendered very difficult by the separation of a heavy, yellow-green precipitate. When the addition was complete, refluxing was continued for one-half hour. The cooled mixture was then acidified with ten percent sulfuric acid, and the aqueous layer was separated and washed with ether.

Upon standing overnight, the ethereal solution deposited some large, white crystals of diethyl piperonoylmalonate. A few of these were withdrawn and recrystallized from a mixture of ethyl acetate and petroleum ether, to afford a product, m.p. 69.5-71.0°. Anal. Calcd. for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.47, 58.45; H, 5.39, 5.28.

The remainder of the crude residue obtained by evaporation of the ether was not purified, but was used directly in the next step.

3,4-Methylenedioxyacetophenone (XVIII). Method A. The crude residue from the above experiment was treated with 210 ml. of glacial

acetic acid, 140 ml. of water, and 27 ml. of concentrated sulfuric acid. Upon vigorous boiling, the mixture became homogeneous after two hours, but carbon dioxide evolution continued for an additional three hours. The orange-red solution was cooled and made alkaline with forty percent sodium hydroxide solution. The red, alkaline mixture was extracted four times with a total of 2 l. of ether. The ethereal solution was washed with water and dried over magnesium sulfate. The residue obtained upon removal of the ether was dissolved in 3 l. of petroleum ether, and the resulting solution was boiled with decolorizing carbon, filtered and cooled. There was obtained 97 g. (70%) of pale yellow 3,4-methylenedioxyacetophenone, m.p. 84-87° (lit. m.p. 81° and 87-88°) (20)(22). Acidification of the aqueous solution afforded 6.4 g. of piperonylic acid, m.p. 230°. Corrected for recovered piperonylic acid, the overall yield based on piperonylic acid was 81.5%.

3,4-Methylenedioxyacetophenone (XVIII). Method B. To a solution of methylmagnesium bromide prepared from 9.7 g. (0.40 atom) of magnesium, 45 g. (0.475 mole) of methyl bromide, and 150 ml. of anhydrous ether, was added 36.7 g. (0.20 mole) of anhydrous cadmium chloride over a period of five minutes. No test for methylmagnesium bromide was obtained after the mixture had been stirred and heated under reflux for forty-five minutes. The ether was displaced with 100 ml. of benzene, and the cooled solution was treated with a solution of 16.4 g. (0.089 mole) of piperonoyl chloride in 50 ml. of anhydrous benzene. The mixture was heated under reflux for thirty minutes, cooled, and acidified with 6 N sulfuric acid. The aqueous phase was separated and washed three times with benzene. The combined benzene solutions were washed with five percent sodium bicarbonate

then with water, and were dried over magnesium sulfate. The residue obtained upon removal of the benzene was recrystallized from petroleum ether to afford 10 g. (68%) of 3,4-methylenedioxyacetophenone, m.p. 84-87°. This product was contaminated with a yellow impurity which was only removed by chromatography on alumina.

3,4-Methylenedioxyphenacyl Bromide (XIX). In a 3-l. three-necked flask fitted with a mechanical stirrer, a dropping funnel, and a reflux condenser protected by a drying tube and connected to a gas trap, were placed 49.2 g. (0.300 mole) of 3,4-methylenedioxyacetophenone and 1.5 l. of anhydrous ether. The stirred mixture was chilled in ice. In some experiments, 3,4-methylenedioxyacetophenone separated from solution, but this made no difference. The cold mixture was treated with 48 g. (0.30 mole) of bromine over a period of forty minutes, and the resulting yellow-brown solution was transferred to a 2-l. flask and concentrated under diminished pressure. The use of a magnetic stirrer during the concentration prevented the otherwise troublesome bumping of the suspension which formed. The brick-red, solid residue was treated with 500 ml. of water which discharged most of the color. The solid was collected, washed with a total of 1 l. of water, and dissolved in 4 l. of petroleum ether. The solution was decanted from a small amount of water, boiled with 2 g. of decolorizing carbon for twenty minutes, filtered, and cooled. There was obtained 56 g. (77%) of 3,4-methylenedioxyphenacyl bromide, m.p. 90-92.5° (lit. m.p. 86-87°) (20), which crystallized in white plates. Omission of the carbon treatment afforded a product which quickly assumed a pink color.

Phenacylation of Diethyl Malonate. In a 500-ml. three-necked flask fitted with a mercury-sealed Hershberg stirrer, a dropping funnel, and a reflux condenser protected by a drying tube, were placed 2.67 g. (0.110 mole) of magnesium turnings, 2.5 ml. of absolute ethanol, and 0.25 ml. of carbon tetrachloride. The mixture was heated locally to initiate the reaction, and 40 ml. of absolute ether was added. A mixture of 17.6 g. (0.110 mole) of diethyl malonate, 10 ml. of absolute ethanol, and 15 ml. of anhydrous ether was then added dropwise. The resulting gray solution of diethyl ethoxymagnesiummalonate was treated with a solution of 19.9 g. (0.100 mole) of phenacyl bromide (m.p. 49-51°) in 100 ml. of anhydrous ether. No precipitate formed. The mixture was heated under reflux for 1.5 hours, cooled, and treated with 75 ml. of ten percent sulfuric acid. The aqueous phase which separated was extracted with ether, and the combined ethereal solutions were dried over magnesium sulfate and concentrated under diminished pressure. The residual oil deposited 3 g. of solid, m.p. 117-120°, upon standing in the cold. A sample purified for analysis, m.p. 120.0-121.2°, gave analytical data in agreement with that for diethyl diphenacylmalonate. Anal. Calcd. for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.82; H, 6.04 (lit.m.p. 118-119°) (61).

Distillation of the remaining oil afforded 8.2 g. of diethyl malonate, 3.1 g. of phenacyl bromide and 9.1 g. of diethyl phenacylmalonate.

Diethyl Benzylphenacylmalonate (XXII). In a 500-ml. single-necked flask fitted with a magnetic stirrer, were placed 2.43 g. (0.100 mole) of magnesium turnings, 2.5 ml. of ethanol, and 0.25 ml. of carbon

tetrachloride. To this was added a mixture of 25.0 g. (0.100 mole) of diethyl benzylmalonate (b.p. 100°/0.03 mm., $N_D^{22°}$ 1.4862) and 10 ml. of absolute ethanol. After the mixture was heated under reflux for 1.5 hours, the evolution of hydrogen ceased. The mixture was treated with 150 ml. of anhydrous, thiophene-free benzene, and the excess ethanol was removed by distillation as the benzene-alcohol azeotrope. A solution of 19.9 g. (0.100 mole) of phenacyl bromide in 125 ml. of benzene was added rapidly to the solution of diethyl ethoxymagnesiumbenzylmalonate. The amber mixture was allowed to stand at room temperature for seven days. It was then acidified with 75 ml. of ten percent sulfuric acid, and the aqueous solution was extracted with benzene. The combined benzene solutions were washed with water then with five percent sodium bicarbonate, and were dried over magnesium sulfate. The residue obtained upon concentration of the benzene solution was recrystallized from 400 ml. of petroleum ether to afford 29.8 g. (81%) of diethyl benzylphenacylmalonate, m.p. 75-77° (lit. m.p. 74.5-76.4°) (16).

Benzylphenacylmalonic Acid. To a solution of approximately 200 g. of potassium hydroxide in 600 ml. of absolute ethanol was added a warm solution of 58 g. (0.158 mole) of diethyl benzylphenacylmalonate in 150 ml. of absolute ethanol. The mixture became warm, developed a deep red color, and after a few minutes, a precipitate formed. The mixture was allowed to cool to room temperature and was then chilled in ice. The precipitate was collected in a coarse, sintered glass funnel, washed three times with small portions of cold, absolute ethanol, and finally with anhydrous ether. The white salt was then dissolved in 400 ml. of water, and the chilled solution was acidified

with hydrochloric acid. Benzylphenacylmalonic acid separated as an oil which quickly crystallized. The mixture was thoroughly chilled, and the acid was collected and washed several times with a total of 500 ml. of ice water. The filter cake was sucked as dry as possible. A sample of material prepared in this way melted at 168-170°d. (lit. m.p. 161°(16).

The crude, still moist acid was subjected to thermal decarboxylation according to the procedure of Brown (16). Recrystallization of the crude product from a mixture of 400 ml. of acetic acid and 250 ml. of water yielded 35 g. (82.5% overall) of benzylphenacylacetic acid, m.p. 173-174.5° (lit. m.p. (173) 174.0-174.7°).

Methyl Benzylphenacylacetate. A solution of 4.20 g. (0.015 mole) of benzylphenacylacetic acid, 250 ml. of methanol, and 3 g. of hydrogen chloride was allowed to stand at room temperature for eighteen hours. The methanol was evaporated under reduced prassure,and the residue was dissolved in ether. The ethereal solution was washed with water and then with five percent sodium bicarbonate solution, and was dried over magnesium sulfate. The residue obtained upon evaporation of the ether was recrystallized twice from petroleum ether to afford 3.62 g. (82%) of methyl benzylphenacylacetate, m.p. 68.2-69.0°. Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.59, 76.72; H, 6.52, 6.52.

Diethyl 3,4,5-Trimethoxybenzyl-3',4'-methylenedioxyphenacylmalonate (XX). In a 2-l. single-necked flask containing a magnetic stirrer bar, were placed 5.6 g. (0.230 mole) of magnesium turnings, 0.5 ml. of carbon tetrachloride, and 5.6 ml. of absolute ethanol. After the reaction was initiated by local heating, a mixture of 78.5 g. (0.230 mole) of diethyl 3,4,5-trimethoxybenzylmalonate, 23 ml. of absolute ethanol and 170 ml. of benzene was added. The magnesium dissolved in 2.5 hours, and the

excess ethanol was then removed by distillation as the benzene-alcohol azeotrope. The clear benzene solution was chilled in ice, and a solution of 56 g. (0.230 mole) of 3,4-methylenedioxyphenacyl bromide in 1 l. of benzene was added all at once. After standing at room temperature for seven days, the yellow-green solution, which had deposited a white precipitate, was acidified at room temperature with 100 ml. of five percent sulfuric acid. The aqueous phase was separated and washed twice with benzene. The combined benzene solutions were washed with saturated salt solution then with five percent sodium bicarbonate, and were dried over magnesium sulfate. The benzene solution was concentrated, and the residue was recrystallized from 2 l. of fifty percent aqueous alcohol. There was obtained 95 g. (82%) of the keto diester, m.p. 101-104°; a further recrystallization yielded 88 g. (76%) of product, m.p. 104-105°. Anal. Calcd. for $C_{26}H_{30}O_{10}$: C, 62.14; H, 6.02. Found: C, 62.32, 62.33; H, 6.17, 6.07.

The 2,4-dinitrophenylhydrazone was prepared by treating a solution of 0.10 g. of the keto diester in 10 ml. of warm ethanol with a mixture of 0.10 g. of 2,4-dinitrophenylhydrazine, 0.5 ml. of concentrated sulfuric acid, 1 ml. of water, and 2.5 ml. of ethanol. After the resulting mixture stood for several months in the refrigerator, a precipitate formed. The orange solid was recrystallized from ethanol; its melting point was 172.5-174.0°. Anal. Calcd. for $C_{32}H_{34}O_{13}N_4$: C, 56.30; H, 5.02; N, 8.21. Found: C, 56.39, 56.21; H, 5.04, 5.14; N, 8.49, 8.37.

2-(3,4,5-Trimethoxybenzyl)-2-carbethoxy-4-(3,4-methylenedioxyphenyl)-butyrolactone (XXI). A mixture of 1.0 g. (0.0020 mole) of the keto diester

XX, 1.0 g. of ten percent palladium-charcoal, and 50 ml. of ethanol was shaken with hydrogen at room temperature. The absorption of one mole of hydrogen required eighteen hours. The catalyst was removed, and the ethanolic solution was concentrated under diminished pressure. The residue was recrystallized twice from aqueous ethanol to afford 0.3 g. of white, crystalline product, m.p. 146-147.5°. An analytical sample was prepared, m.p. 149.5-151.0°, whose analysis was in reasonable agreement with theory for the lactone ester XXI. Anal. Calcd. for $C_{24}H_{26}O_9$: C, 62.87; H, 5.72. Found: C, 63.07, 63.29; H, 5.78, 5.82.

3,4,5-Trimethoxybenzyl-3',4'-methylenedioxyphenacylmalonic Acid (XXVII). A solution of 175 g. of potassium hydroxide in 600 ml. of absolute ethanol was mixed with a solution of 33.8 g. (0.0673 mole) of the keto diester XX in 200 ml. of warm absolute ethanol. A precipitate formed within a few minutes. After standing thirty minutes at room temperature, the mixture was cooled to 10°, and the precipitate was collected in a course, sintered glass funnel. The salt was washed three times with 25 ml. portions of cold, absolute ethanol, and then with two portions of anhydrous ether. A solution of the salt in 250 ml. of water was acidified with hydrochloric acid. The acid, which precipitated as an oil, quickly crystallized upon stirring. After chilling the mixture, the white solid was collected, washed several times with cold water, and sucked as dry as possible. Material prepared in this way melted at 130-133°d. after drying. Recrystallization could be accomplished according to the following procedure.

A boiling solution prepared by dissolving 3.4 g. of the crude malonic acid in 50 ml. of ethyl acetate was slowly treated with 50 ml. of petro-

leum ether. Upon cooling the solution, the acid crystallized rapidly. The precipitate was collected and washed several times with petroleum ether. There was obtained 3.3 g. of malonic acid, m.p. 132-133°d. Anal. Calcd. for $C_{22}H_{22}O_{10} \cdot 2H_2O$: C, 54.8; H, 5.4; N.E., 241.2. Found: C, 56.11, 56.28; H, 5.70, 5.71; N.E., 240.6, 240.4.

The poor agreement with theory obtained in the analyses is not understood. The same behavior was observed by Brown (16) with the unsubstituted ketomalonic acid.

3,4,5-Trimethoxybenzyl-3',4'-methylenedioxyphenacylacetic Acid (XXVIII). The moist, crude malonic acid obtained from the above procedure was transferred to a 500-ml. single-necked flask and heated in an oil bath at 150° until it was completely melted. After cooling, the yellow glass was dissolved in 250 ml. of ethyl acetate, and the solution was boiled with decolorizing carbon. The solution was filtered and treated with 350 ml. of petroleum ether. The precipitate obtained on cooling was washed several times by decantation with a mixture of ethyl acetate and petroleum ether. There was obtained 22.8 g. (84.5% overall) of keto acid, m.p. 133.8-135.4°. Anal. Calcd. for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51; OCH_3, 23.14; N.E., 402.4. Found: C, 62.71, 62.91; H, 5.77, 5.81; OCH_3, 23.05, 23.12; N.E., 402.1, 403.9, 404.6.

Methyl 3,4,5-Trimethoxybenzyl-3',4'-methylenedioxyphenacylacetate (XXXII). A mixture of 1.0 g. (0.0025 mole) of XXVIII, 100 ml. of anhydrous methanol, and 3 g. of anhydrous hydrogen chloride was allowed to stand at room temperature for eighteen hours. After removal of the methanol under diminished pressure, the residue was dissolved in ether.

The ethereal solution was washed with water, then with sodium bicarbonate solution, and was dried over magnesium sulfate. The pale yellow oil remaining after concentration of the ethereal solution was recrystallized with some difficulty from a mixture of ethyl acetate and petroleum ether. There was obtained 0.70 g. (68%) of the methyl ester XXXII, m.p. 91.0-92.5°. Anal. Calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81; OCH_3, 29.81. Found: C, 63.43, 63.55; H, 5.97, 5.79. Reproducible results could not be obtained on the methoxyl determination. The average of eight determinations was 29.61; individual determinations varied from 27.71 to 31.28.

Ethyl 3,4,5-Trimethoxybenzyl-3',4'-methylenedioxyphenacylacetate (XXIX). A mixture of 4.69 g. (0.0117 mole) of XXVIII, 500 ml. of absolute ethanol, and 8 g. of anhydrous hydrogen chloride was allowed to stand at room temperature for eighteen hours. After removal of the ethanol under diminished pressure, the residual solid was washed with water, then with sodium bicarbonate solution, and finally with water. The solid was recrystallized from 50 ml. of ethanol to afford 4.70 g. (94%) of the ethyl ester XXIX, m.p. 117-118°. Anal. Calcd. for $C_{23}H_{26}O_8$: C, 64.17; H, 6.09. Found: C, 64.04, 64.26; H, 6.14, 5.94.

The 2,4-dinitrophenylhydrazone was prepared in the usual way. Recrystallization from ethanol afforded a product, m.p. 144-145°. Anal. Calcd. for $C_{29}H_{30}O_{11}N_4$: C, 57.04; H, 4.95; N, 9.18. Found: C, 57.19, 57.00; H, 4.92, 4.92; N, 9.39, 9.26.

2-(3,4,5-Trimethoxybenzyl)-4-(3',4'-methylenedioxyphenyl)-butyrolactone (XXXI). A solution, prepared by titrating 3.1 g. (0.0077 mole) of the keto acid XXVIII with 0.1 N sodium hydroxide solution, was treated

with 1.0 g. of sodium borohydride dissolved in 15 ml. of water. After standing twenty-four hours, the mixture was acidified with 1:1 hydrochloric acid and extracted several times with ether. The ethereal solution was washed with sodium bicarbonate and dried. Evaporation of the ether afforded an oil which could not be induced to crystallize. Acidification of the bicarbonate extract precipitated an oil which was dissolved in ethanol. After standing nearly a year, the oil crystallized. The solid obtained was recrystallized twice from aqueous ethanol to afford 0.9 g. (30%) of bicarbonate-insoluble material, m.p. 95.5-97.5°. Anal. Calcd. for $C_{21}H_{22}O_7$: C, 65.27; H, 5.74. Found: C, 65.04, 64.93; H, 6.03, 5.92.

Benzhydrylsuccinic Acid (XXXVIII). In a 5-l. Erlenmeyer flask equipped with a mechanical stirrer and a thermometer, and mounted on a steam bath, were placed 50 g. (0.161 mole) of benzhydrylidenesuccinic acid ester XXXVI (m.p. 124-126°)(41) and 1.5 l. of ten percent sodium hydroxide solution. The resulting solution was heated to 90°, and 150 g. of Raney nickel alloy was added in portions with stirring over a period of forty-five minutes. The temperature was maintained at 90-95°. When the addition of the Raney nickel alloy was complete, 500 ml. of ten percent sodium hydroxide was added, and the mixture was reheated to 90°. An additional 50 g. of Raney nickel alloy was added in portions, and the mixture was then stirred at 90° for one hour. The hot solution was filtered through #50 paper and the residual nickel was thoroughly washed with two 500-ml. portions of boiling water. After cooling, the pale amber solution was poured into a mixture of 2 kg. of crushed ice and 2 l. of concentrated hydrochloric acid. The heavy, white precipitate which

formed was collected, and most of the hydrochloric acid was removed by washing with water. The filtration and washing were very tedious because of the tenacity with which the precipitate retained water. The wet filter cake was transferred to a 3-l. flask fitted with a water trap and a reflux condenser. Two liters of benzene was added, and the resulting gel-like mixture was heated under reflux. As the water was removed, the suspended solid became more granular, and when all the water had been removed, the addition of 500 ml. of ethyl acetate dissolved the suspended solid. The resulting solution was boiled with 2 g. of decolorizing carbon, filtered, and cooled. The mixture was chilled, and the finely divided precipitate was collected and washed with benzene. There was obtained 38.5 g. (74%) of benzhydrylsuccinic acid hemibenzeneate, m.p. 185-187°. Concentration of the mother liquor to one-third volume afforded a second crop of 6.3 g., m.p. 184-187°. The total yield was eighty-six percent. Anal. Calcd. for $C_{17}H_{16}O_4 \cdot \frac{1}{2}C_6H_6$: C, 74.28; H, 5.92; N.E., 161. Found: C, 73.96, 74.03; H, 5.85, 5.82; N.E., 159, 159, 161.

4-Phenyl-3-carboxytetralone-1 (XL). A solution of 49 g. (0.152 mole) of benzhydrylsuccinic acid hemibenzeneate in 60 ml. of acetyl chloride was heated under reflux for two hours. The acetyl chloride and acetic acid were removed, and the residual benzhydrylsuccinic anhydride was dissolved in 50 ml. of freshly distilled nitrobenzene. This solution was added with stirring to an ice-cold solution of 43 g. (0.32 mole) of aluminum chloride in 250 ml. of nitrobenzene. After stirring in an ice-bath for thirty minutes, the solution was allowed to stand at 0° for fifty-seven hours. The dark red solution was then poured into a

mixture of 400 ml. of hydrochloric acid and 1 kg. of crushed ice. Steam distillation removed the nitrobenzene, and after cooling, the solid was collected. The dark solid was triturated with ether, and the insoluble material was recrystallized from 150 ml. of acetic acid. The yield of 4-phenyl-3-carboxytetralone-1, m.p. 207-210°, was 17.3 g. (43%). Another recrystallization from acetic acid afforded 15 g. of product, m.p. 211-213° (37%). Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.60, 76.67; H, 5.42, 5.42.

4-Phenyl-3-carbethoxytetralone-1 (XLI). A solution of 16.0 g. (0.0677 mole) of the keto acid XL in 1 l. of absolute ethanol was treated with 10 g. of anhydrous hydrogen chloride and allowed to stand for eleven hours. The clear solution was then heated to 60°, and the ethanol was removed under diminished pressure; by keeping the mixture warm, precipitation of the ester was avoided. When nearly all the ethanol had been removed, the residue was cooled and treated with five percent sodium bicarbonate solution. The solid was collected, washed with water and treated with more sodium bicarbonate. After a final water washing, the ester was recrystallized from ethanol to afford 18.7 g. (94.5%) of 4-phenyl-3-carbethoxytetralone-1, m.p. 121.8-123.2°. Another recrystallization afforded a product whose melting point was 122.3-124.2°. Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.45, 77.25; H, 6.14, 5.98.

The 2,4-dinitrophenylhydrazone was prepared in the usual manner. Recrystallization from ethyl acetate afforded an orange solid which melted at 267-268°d. Anal. Calcd. for $C_{25}H_{22}O_5N_4$: C, 63.28; H, 4.67; N, 11.81. Found: C, 63.33, 63.35; H, 4.68, 4.50; N, 11.85, 11.99.

4-Phenyl-3-carboxy-2-hydroxymethylenetetralone-1 (XLIII). To a chilled, stirred mixture of 1.08 g. (0.020 mole) of alcohol-free sodium methoxide, 1.48 g. (0.020 mole) of ethyl formate, and 15 ml. of anhydrous, thiophene-free benzene, under nitrogen, was added a solution of 2.94 g. (0.010 mole) of 4-phenyl-3-carbethoxytetralone-1 in 50 ml. of benzene. The addition required fifteen minutes. As the addition progressed, the mixture assumed a deep red color, and all the suspended sodium methoxide dissolved. After standing overnight at 5°, the mixture was chocolate-brown, and a precipitate was present. Fifty milliliters of water was added, and the deep red aqueous phase was separated. The aqueous solution was washed once with ether to remove turbidity and then acidified under ether. The yellow ether solution which resulted was washed with sodium bicarbonate solution and dried over magnesium sulfate. Removal of the ether afforded 0.4 g. of an oily residue which gave an immediate, deep red color with ferric chloride. This material was presumed to be the hydroxymethylene carboxylic ester XLII.

Upon acidification of the bicarbonate extract, a yellow solid was obtained which sintered at 175° and melted at 184-188°, and which gave an intense red color with alcoholic ferric chloride. Recrystallization from 30 ml. of 1:1 benzene-petroleum ether afforded 1.8 g. of material, m.p. 189-191°. A sample prepared for analysis melted at 190-191°. The analytical data were in agreement with theory for the hydroxymethylene carboxylic acid structure XLIII. Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.46; H, 4.79; N.E., 147. Found: C, 73.09, 73.08; H, 4.83, 4.71; N.E., 150.5, 150.

4-Phenyl-3-carboxy-2-hydroxymethyl-1-hydroxytetralin (XLVIII). Method A. A solution prepared by dissolving 0.40 g. of the hydroxymethylene carboxylic acid in sodium hydroxide solution was treated with 0.3 g. of sodium borohydride. After standing overnight at room temperature, the mixture was acidified with 1:1 hydrochloric acid. A white, granular precipitate separated which gave no color with alcoholic ferric chloride. Recrystallization from a mixture of ethyl acetate and petroleum ether afforded 0.18 g. (45%) of solid, m.p. 187-188°d. The melting point depended on the rate of heating. Values of 188-189.5°d. and 187.5-188°d. were obtained on purified samples which were heated rapidly and slowly respectively. Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.47, 72.61; H, 6.38, 6.38.

Lactone of 4-Phenyl-3-carboxy-2-hydroxymethyl-1-hydroxytetralin (XLIX). Upon melting, the dihydroxy acid evolved a gas and rapidly resolidified to the lactone, m.p. 229-233°. A sample of 0.3555 g. of the acid was heated to 195° until no further gas evolution was observed (5-10 minutes). Upon cooling, the pale yellow solid weighed 0.3315 g. For the loss of one molecule of water, the residual solid should have weighed 0.3341 g. The experimental data are regarded as satisfactory confirmation of the loss of a molecule of water. Since the product was neutral, lactonization must have occurred.

The lactone proved to be difficult to recrystallize. Sublimation at one micron failed to afford a pure product. Recrystallization from fifty percent aqueous acetic acid afforded material which sintered at 235° and melted at 240-243°. However, an analytical sample was prepared by carefully purifying a sample of the dihydroxy acid and then heating

the acid under nitrogen to afford the lactone. Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75; S.E., 280. Found: C, 77.37, 77.20; H, 5.53, 5.75; S.E., 272.

4-Phenyl-3-carbethoxy-2-hydroxymethylenetetralone-1 (XLII). To a chilled suspension of 2.34 g. (0.0434 mole) of alcohol-free sodium methoxide in 25 ml. of anhydrous, thiophene-free benzene containing 3.21 g. (0.0434 mole) of anhydrous ethyl formate, was added all at once a solution of 6.38 g. (0.0217 mole) of 4-phenyl-3-carbethoxytetralone-1 in 100 ml. of benzene. The resulting mixture quickly assumed a deep red color. It was stirred in an ice-bath and occasionally shaken vigorously to break up the lumps of sodium methoxide. After one-half hour, the sodium methoxide had completely dissolved. After standing an additional ten minutes, the clear, red solution was treated with 100 ml. of cold water. The light red aqueous solution was separated, and the yellow benzene solution was washed with water. The combined aqueous solutions were washed with ether to remove turbidity and acidified under ether. The pale yellow, ethereal solution was washed with five percent sodium bicarbonate and dried over magnesium sulfate. The nearly colorless, ethereal solution was concentrated to afford 6.0 g. (86%) of amber oil which gave an immediate, deep red color with alcoholic ferric chloride. Although this material was not extracted by sodium bicarbonate, it was possible to titrate it directly with aqueous sodium hydroxide to the phenolphthalein end-point. Titration of the crude hydroxymethylene carboxylic ester indicated a purity of eighty-seven percent. On this basis, the yield of pure material was seventy-five percent.

Purification of the hydroxymethylene carboxylic ester was accomplished in the following manner. An ethereal solution of 3.8 g. of the

crude enol was shaken with 100 ml. of saturated cupric acetate solution. The light green precipitate which formed was collected, and washed successively with water, two 5 ml. portions of ethanol, and anhydrous ether. The dry copper derivative weighed 3.2 g. A suspension of the copper derivative in ether was shaken vigorously with cold, ten percent sulfuric acid. The resulting pale yellow, ether solution of the hydroxymethylene carboxylic ester was washed with five percent sodium bicarbonate and dried over magnesium sulfate. Removal of the ether afforded 2.2 g. (58% recovery) of amber oil. Material purified in this way had a neutralization equivalent of 324 (theory 322). Although a small amount of solid, m.p. 65-75°, could be obtained upon recrystallization from petroleum ether, attempts to obtain material suitable for analysis were unsuccessful. Treatment of an alcoholic solution of the enol with 2,4-dinitrophenylhydrazine afforded an immediate, blood-red precipitate, m.p. 150-160°d. Attempts to purify this product were also unsuccessful.

Evaporation of the original benzene solution from the reaction afforded a small residue. A small amount of white solid, m.p. 229-232°, was obtained after several recrystallizations from benzene. Anal. C, 78.03, 78.20; H, 5.52, 5.60. The identity of this neutral substance was not established.

4-Phenyl-3-carboxy-2-hydroxymethyl-1-hydroxytetralin (XLVIII). Method B. A solution prepared by treating 5.5 g. of the crude hydroxymethylene carboxylic ester XLII with dilute sodium hydroxide was allowed to stand with 3.3 g. of sodium borohydride at room temperature for six hours. The pale yellow solution was chilled and acidified with hydrochloric acid. The precipitate was dissolved in ether, and the ethereal

solution was washed several times with sodium bicarbonate solution. Acidification of the combined bicarbonate extracts afforded 1.9 g. of white solid, m.p. 165-175°d. This material gave no color with alcoholic ferric chloride. An additional 0.3 g. of solid, m.p. 150-165°, was deposited by the solution upon standing. The combined material upon recrystallization from a mixture of 200 ml. of ethyl acetate and 250 ml. of petroleum ether afforded 1.44 g. (25%) of dihydroxy acid, m.p. 188.5-189.0°d.

4-Phenyl-3-carbethoxy-2-hydroxymethyl-1-hydroxytetralin (XLVII). A solution of 1.0 g. of the crude hydroxymethylene carboxylic ester in 10 ml. of absolute ethanol was treated with a solution of 0.3 g. of sodium borohydride in 10 ml. of absolute ethanol. A vigorous reaction ensued. Another 0.2 g. of sodium borohydride was added, and the mixture was allowed to stand five days. After removal of most of the ethanol under diminished pressure, the residue was dissolved in water. Acidification of the yellow solution afforded a gummy precipitate which was dissolved in ether. After washing with sodium bicarbonate and then sodium hydroxide, the ethereal solution was dried and concentrated. The residue obtained solidified. A small amount of solid, m.p. 128-131.5° was obtained after several recrystallizations from a mixture of benzene and petroleum ether. Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.59; H, 6.80. Found: C, 73.37, 73.39; H, 6.89, 6.92.

4-Phenyl-3-carbethoxy-1-hydroxytetralin (LI). A mixture of 2.94 g. (0.010 mole) of 4-phenyl-3-carbethoxytetralone-1 and 30 ml. (0.030 mole) of 1 M aluminum isopropoxide in isopropyl alcohol was heated under a short

Vigreaux column fitted with a distilling head. The distillate was removed intermittently, until no test for acetone was obtained with 2,4-dinitrophenylhydrazine (4 hours). The isopropyl alcohol was removed under reduced pressure, and the residue was treated with cold, dilute (1:4) hydrochloric acid. The aqueous mixture was extracted with ether. The ethereal solution was washed with water and then with sodium bicarbonate solution, dried over magnesium sulfate, and concentrated. The residual oil was subjected to direct saponification. However, a small amount of material was isolated in a crystalline condition, m.p. 116-117°. Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.03, 77.20; H, 7.13, 7.07.

Lactone of cis-1-Hydroxy-3-carboxy-4-phenyltetralin (LII).

Saponification of the above crude hydroxy ester mixture afforded 1.9 g. (70%) of hydroxy acids, m.p. 150-158°d. Upon recrystallization from a mixture of 40 ml. of ethyl acetate and 150 ml. of petroleum ether, there was obtained 1.5 g., m.p. 163-165°d.

A sample of 0.716 g. of the product, m.p. 163-165°d., was heated for several minutes at 180°. The cooled, glassy residue weighed 0.675 g. The loss in weight corresponded to eighty-six percent of the maximum possible, and, on this basis, it is assumed that the original mixture contained approximately eighty-six percent of the cis isomer. The colorless glass was dissolved in ether. The ethereal solution was washed with cold sodium bicarbonate, then with water, and dried over magnesium sulfate. Evaporation of the ether afforded 0.53 g. of crystalline solid, m.p. 100-125°. Recrystallization of this material proved difficult. The use of fifty percent aqueous acetic acid afforded the lactone LII

which sintered at 120° and melted at 125-127°. Sublimation of a sample of this at 110°/0.01 mm., afforded material, m.p. 126-128°. Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.93, 81.86; H, 5.93, 5.83.

trans-1-Hydroxy-3-carboxy-4-phenyltetralin (LIV). Acidification of the sodium bicarbonate extract obtained above afforded 0.09 g. of trans-1-hydroxy-3-carboxy-4-phenyltetralin. The product melted at 191-193° after two recrystallizations from a mixture of ethyl acetate and petroleum ether. Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.12, 75.92; H, 6.02, 6.13.

cis-1-Hydroxy-3-carboxy-4-phenyltetralin (LIII). A mixture of 0.1 g. of the lactone and 2 ml. of ten percent sodium hydroxide solution was warmed gently on the steam bath. A small amount of solid which failed to dissolve was removed by filtration. Acidification of the filtrate afforded a white solid which was recrystallized from a mixture of ethyl acetate and petroleum ether to afford the cis hydroxy acid, m.p. 169-170°d. Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.02, 76.04; H, 6.25, 6.23.

Ethyl α-methyl-β-benzoylpropionate (XLV). A mixture of 21.1 g. (0.11 mole) of α-methyl-β-benzoylpropionic acid, m.p. 138-142 (62), 500 ml. of absolute ethanol, and 5 g. of anhydrous hydrogen chloride was allowed to stand at room temperature for twenty-two hours. The ethanol was removed under diminished pressure, and the pale yellow, residual oil dissolved in ether. The ethereal solution was washed with water and then with sodium bicarbonate solution, and dried over magnesium sulfate. The yellow oil obtained upon removal of the ether was distilled. There was obtained 20.6 g. (85%) of ethyl α-methyl-β-benzoylpropionate, b.p.

93°/0.1 mm., $n_D^{25.4^\circ}$ 1.5060, sp.gr. $\frac{25}{25}$ 1.0733. Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H. 7.32; S.E., 220. Found: C, 71.19, 70.94; H, 7.36, 7.34; S.E., 219.

Reaction of Formaldehyde with Benzylphenacylacetic Acid. 2-Benzyl-3-benzoylbutyrolactone (LXIV) and 2-Benzyl-3-hydroxymethyl-3-benzoylbutyrolactone (LXV). A suspension of 2.68 g. (0.010 mole) of benzylphenacylacetic acid in 6 ml. of distilled water was treated with 3.2 ml. (0.011 mole) of 3.45 N sodium hydroxide solution. The resulting yellow solution was then treated with 8.7 ml. (0.12 mole) of formalin and allowed to stand at room temperature for eighteen hours. The yellow color was discharged at the end of this time. Acidification of the chilled solution afforded an oil which was taken up in ether. The ethereal solution was washed thoroughly with water, dried over magnesium sulfate, and evaporated. The residual oil had a saponification equivalent of 291. A solution of 1.75 g. of the oil in 15 ml. of benzene was passed through silicic acid contained in a 2x20 cm. chromatograph tube. Elution with benzene afforded 0.55 g. of noncrystalline keto lactone LXIV. Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75; S.E., 280. Found: C, 77.16, 77.13; H, 5.94, 5.81; S.E., 279. This material afforded a yellow 2,4-dinitrophenylhydrazone, m.p. 197-199°. Anal. Calcd. for $C_{24}H_{20}O_6N_4$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.75; H, 4.39; N, 11.90, 12.11.

Elution with five percent ethanol in benzene afforded 0.70 g. of the noncrystalline keto methylol lactone LXV. Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85; S.E., 310. Found: C, 73.97; H, 6.03; S.E., 293. This material failed to give a precipitate with 2,4-dinitrophenylhydrazine.

2-Benzyl-3-benzylbutyrolactone (LXIV). A solution prepared by dissolving 7.12 g. (0.0265 mole) of benzylphenacylacetic acid in 31.7 ml. (0.0294 mole) of 0.926 N sodium hydroxide was treated with 2.40 ml. (0.032 mole) of 37% formalin. The mixture stood in a stoppered flask at room temperature for forty-eight hours. The mixture was then chilled and acidified with 10 ml. of 1:1 hydrochloric acid. The gummy precipitate was taken up in thiophene-free benzene, and the benzene solution was washed twice with water. The solution was dried briefly over magnesium sulfate, filtered, and concentrated to 150 ml. on the steam bath. The colorless benzene solution was passed through silicic acid contained in a 2x20 cm. chromatograph tube. Elution with 500 ml. of anhydrous, thiophene-free benzene afforded 6.4 g. (86.5%) of the noncrystalline keto lactone (LXIV) after removal of the benzene. Seeding the oil with some previously obtained crystalline keto lactone caused the mixture to become semisolid. The mass was triturated with 50 ml. of petroleum ether to which 35 ml. of thiophene-free benzene was added in portions with continuous stirring. The insoluble, white solid was rendered quite granular by this treatment. After standing overnight in the refrigerator, there was obtained 2.54 g. of crude keto lactone which sintered at 97° and melted from 107-109°. Recrystallization from a mixture of 20 ml. of thiophene-free benzene and 80 ml. of petroleum ether afforded 2.40 g. (32.5%) of white solid, m.p. 108.0-110.0° (LXIVa). Anal. Calcd. for $C_{18}H_{18}O_3$: C, 77.12; H, 5.75. Found: C, 77.40; H, 5.85.

No crystalline material was isolated from the soluble fraction removed by the trituration.

2-Benzyl-3-(α-hydroxybenzyl)-butyrolactone (LXVIa). A mixture of 2.38 g. (0.0085 mole) of the crystalline keto lactone (LXIVa), m.p. 108.0-110.0°, 50 ml. of ethanol, and 0.5 g. of ten percent palladium-charcoal was shaken with hydrogen at room temperature and atmospheric pressure. The absorption of one mole of hydrogen was complete within twenty minutes. After removal of the catalyst, the colorless alcoholic solution was evaporated in a stream of air. When two-thirds of the solvent had been removed, a precipitate formed. After chilling the mixture, the precipitate was collected. There was obtained 0.98 g., m.p. 150-156°. Further concentration of the filtrate to a volume of 10 ml. and chilling to -20° afforded a second crop of solid, making the total yield 1.10 g. (49%). Recrystallization of this from 5 ml. of ethanol afforded 1.01 g. (42%), m.p. 149-160°. A sample recrystallized from a mixture of benzene and petroleum ether melted at 149-160°. Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 77.4, 77.41; H, 6.50, 6.48.

The failure of the recrystallizations to alter the melting point is not understood.

This material was also prepared by the palladium catalyzed hydrogenation of the keto lactone in cyclohexane. The same wide melting range was observed.

2-Benzyl-3-(α-hydroxybenzyl)-butyrolactone (LXVIb). A mixture of 3.9 g. (0.014 mole) of the noncrystalline keto lactone, 50 ml. of ethanol, and 0.5 g. of ten percent palladium-charcoal was shaken with hydrogen at room temperature and atmospheric pressure. The absorption of ninety-two percent of the theoretical amount of hydrogen was complete in six hours. After removal of the catalyst, the alcoholic solution was evaporated in

an air stream. A precipitate formed as the solution became more concentrated. There was obtained 1.2 g. (31%) of crude hydroxy lactone LXVIb. Recrystallization from a mixture of 10 ml. of benzene and 15 ml. of petroleum ether afforded 1.11 g. (28%) of product, m.p. 102-104°. A sample prepared for analysis melted at 103.0-103.5°. Anal. Calcd. for $C_{18}H_{18}O_5$: C, 76.57; H, 6.43. Found: C, 76.61, 76.77; H, 6.62, 6.49.

2-(3,4,5-Trimethoxybenzyl)-3-(3',4'-methylenedioxybenzoyl)-4-hydroxybutyric Acid (LXVII). A solution prepared by dissolving 16.1 g. (0.040 mole) of the keto acid XXVIII in 48 ml. of 0.926 N sodium hydroxide solution was treated with 4.5 ml. (0.060 mole) of 37% formalin. Upon standing at room temperature for forty-four hours, the originally yellow solution was nearly colorless. The mixture was chilled in ice and made strongly acid with hydrochloric acid. The gummy precipitate which formed was collected and washed several times with water. After several triturations with ether, 10.9 g. (63%) of the methylol acid, m.p. 131-134° d. was obtained. When the melting point was taken slowly, the material melted from 131-140°. This was apparently due to gradual conversion to the corresponding lactone.

A sample purified for analysis by recrystallization from a mixture of ethyl acetate and petroleum ether melted at 135-137° d. Anal. Calcd. for $C_{22}H_{24}O_9$: C, 61.10; H, 5.59; OCH_3, 21.53; N.E., 432. Found: C, 61.10, 61.27; H, 5.73, 5.76; OCH_3, 21.53, 21.33; N.E., 435, 442.

2-(3,4,5-Trimethoxybenzyl)-3-(3',4'-methylenedioxybenzoyl)-butyrolactone (LXVIIIa). Two grams (0.0046 mole) of the methylol acid (LXVII) was heated at 150° until the sample was completely melted (2-3 minutes). The glassy material obtained upon cooling was recrystallized

from 50 ml. of ethanol to afford 1.73 g. (90%) of keto lactone, m.p. 140.4-143.0°. A sample purified for analysis melted at 141.0-143.0°.

Anal. Calcd. for $C_{22}H_{22}O_6$: C, 63.76; H, 5.35; OCH_3, 22.47; S.E., 414. Found: C, 63.72, 63.75; H, 5.44, 5.43; OCH_3, 22.54, 22.45; S.E., 416.

The saponification equivalent was determined by dissolving 0.4070 g. of the keto lactone in 25 ml. of warm ethanol and adding 20.00 ml. of 0.1225 N sodium hydroxide to the solution. The clear solution stood at room temperature for one-half hour. Distilled water was added, and the solution was titrated to the disappearance of the color of phenolphthalein with 14.53 ml. of 0.1005 N hydrochloric acid. The ethanol blank was 0.10 ml. of the sodium hydroxide solution.

When the saponification equivalent was determined by boiling the keto lactone with excess sodium hydroxide, a value of 372 was obtained. Continued boiling of the same sample with sodium hydroxide lowered the value to 330. From this treatment there was isolated approximately twenty-five percent of the keto acid XXVIII, m.p. 133-134°. A mixed melting point with an authentic sample of the keto acid (m.p. 134.5-135.5°) was 133.5-136°. A mixed melting point with the keto lactone (m.p. 141-143°) was 119-134°.

The keto lactone formed a yellow precipitate with 2,4-dinitrophenylhydrazine, but the product did not exhibit a sharp melting point despite repeated recrystallizations (m.p. 145-160°). No analyses were obtained on this material.

2-(3,4,5-Trimethoxybenzyl)-3-(α-hydroxy-3',4'-methylenedioxybenzyl)-butyrolactone (II). A mixture of 4.14 g. (0.010 mole) of the keto lactone, 50 ml. of ethanol, and 1.3 g. of ten percent palladium-charcoal was shaken

with hydrogen at room temperature and atmospheric pressure. The absorption of one mole of hydrogen took place in 3.5 hours. The rate slowed markedly at this point. After removal of the catalyst, the ethanol was evaporated to afford a colorless glass. Anal. Calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81; S.E., 416. Found: C, 63.35, 63.16; H, 5.96, 6.11; S.E., 421.

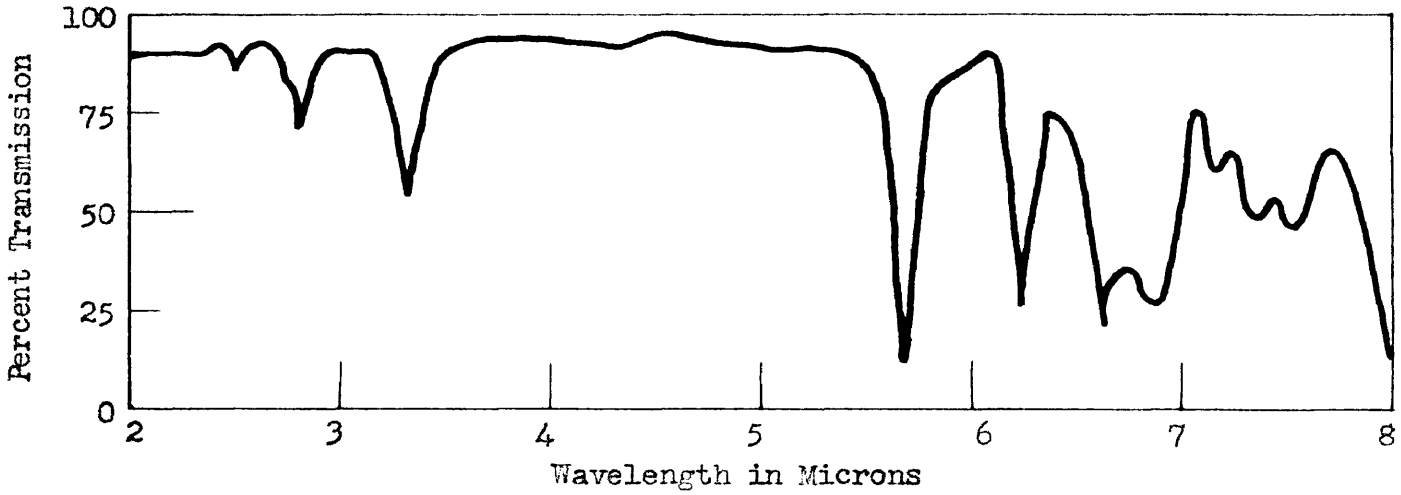
The glass was very resistant to crystallization. Ultimately, a sample crystallized from a mixture of ethyl acetate and petroleum ether to afford a product, m.p. 100-105°. A solution of 3.5 g. of the crude hydrogenation product in 45 ml. of ethyl acetate at room temperature was treated with 60 ml. of petroleum ether. The resulting solution was seeded and allowed to stand at -20°. After several days, the precipitate was collected and washed with a cold mixture of ethyl acetate and petroleum ether (2:3). There was obtained 2.53 g. (72%) of white powder, m.p. 102-108°. After another recrystallization, the yield was 1.87 g. (53%) of product, m.p. 104-108°. Further recrystallization afforded material, m.p. 105-109°. Anal. Calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81; OCH_3, 22.36. Found: C, 63.61, 63.35; H, 6.13, 5.81; OCH_3, 22.36, 22.42.

2-(3,4,5-Trimethoxybenzyl)-3-(3',4'-methylenedioxybenzoyl)-butyric Acid (LXXIII). A mixture of 10 g. of the yellow glass, 50 ml. of ethanol and 0.5 g. of Adam's catalyst was shaken with hydrogen at room temperature and atmospheric pressure. A very rapid absorption of hydrogen took place, corresponding to forty-five percent of the expected absorption assuming the material to be the keto lactone LXVIIIb. Continued shaking resulted in the slow absorption of hydrogen until eighty-five percent of the expected absorption took place. After removal of

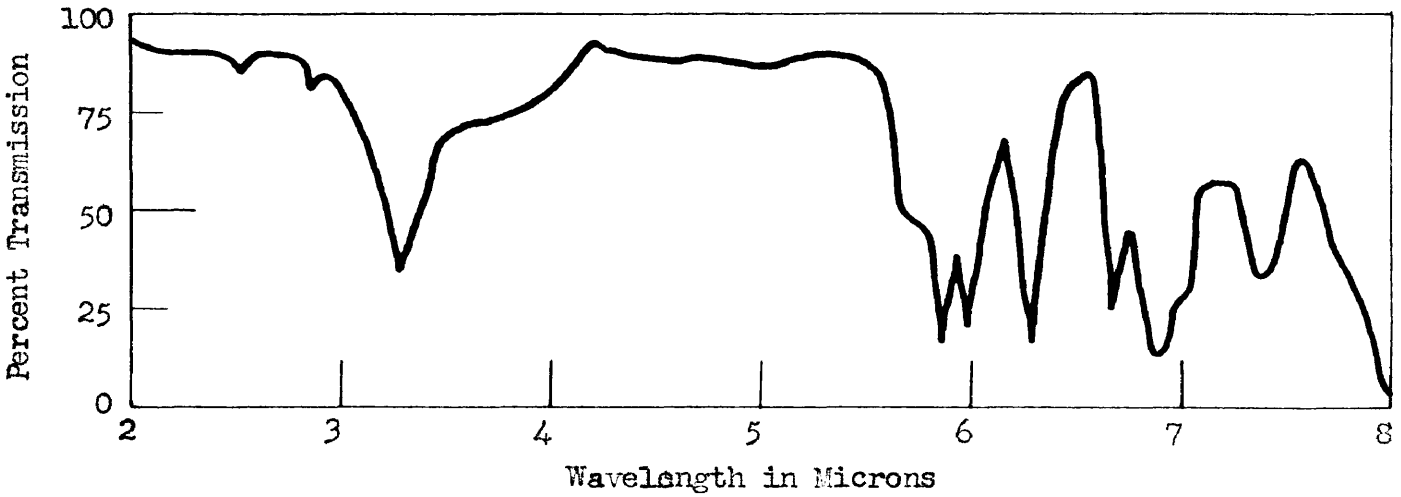
the catalyst, the solution was concentrated in an air stream. The semi-solid residue was triturated with benzene containing a little petroleum ether. The gummy, insoluble solid was recrystallized twice from 75 ml. of benzene to afford 1.3 g. of material, m.p. 166-167°. This material was soluble in five percent sodium bicarbonate. Anal. Calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81; OCH_3 22.36; N.E., 414. Found: C, 63.84. 63.90, 63.85, ave. 63.86; H, 5.99, 5.85, 5.89, ave. 5.91; OCH_3, 22.53, 22.65, ave. 22.59. N.E., 415.

Infrared Spectra. The infrared spectra were determined by using a Perkin-Elmer Infrared Spectrometer Model 12 C containing a rock-salt prism. Five percent solutions of the compounds in chloroform were employed. The cell thickness was 0.1 mm.

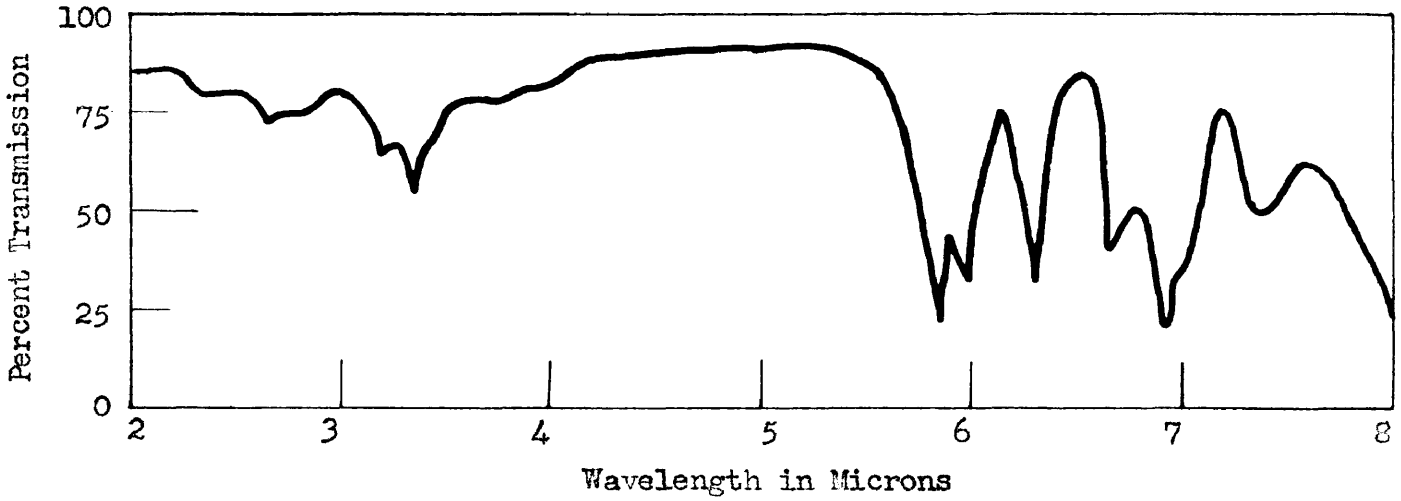
Chart 14



II



LXXIII



XXVIII

LITERATURE CITED

1. Hartwell, J. L., and M. J. Shear, Cancer Research 7, 716 (1947)

2. Hartwell, J. L., and A. W. Schrecker, J. Am. Chem. Soc. 72, 3320 (1950)

3. Borsche, W., and J. Niemann, Ann. 492, 59 (1932)

4. Späth, E., F. Kessely, and E. Nadler, Ber. 65B, 1773 (1932)

5. Cook, J. W., W. Graham, A. Cohen, R. W. Lapsley, and C. A. Lawrence, J. Chem. Soc. 1944, 322

6. Adams, R., M. Harfenist, and S. Loewe, J. Am. Chem. Soc. 71, 1624 (1949)

7. Reeve, W., and J. D. Sterling, Jr., J. Am. Chem. Soc. 71, 3657 (1949)

8. Huang, H. T., D. S. Tarbell, and H.R.V. Arnstein, J. Am. Chem. Soc. 70, 4101 (1948)

9. Lund, H., Ber. 67B, 935 (1934)

10. Martin, E. L., "The Clemmensen Reduction", Organic Reactions, I, 155 (1942)

11. Todd, D., "The Wolff-Kishner Reduction", Organic Reactions, IV, 378 (1948)

12. Mindler, K., and L. Blaas, Ber. 76B, 1211 (1943)

13. Horning, E. C., and D. B. Reisner, J. Am. Chem. Soc. 71, 1036 (1949)

14. Mosettig, E., and R. Mozingo, "The Rosenmund Reduction of Acid Chlorides to Aldehydes", Organic Reactions, IV, 373 (1948)

15. Weiss, G., "The Acid Catalyzed Aldol Condensations of Acetophenones." Thesis, University of Maryland, College Park, Maryland (1951), p. 47

16. Brown, A. E., "The Synthesis of Some Lactones Related to Podophyllotoxin." Thesis, University of Maryland, College Park, Maryland (1950)

17. Tsao, M. U., J. Am. Chem. Soc. 73, 5495 (1951)

18. Pratt, E. F., and E. Werble, J. Am. Chem. Soc. 72, 4638 (1950)

19. Karrer, P., Organic Chemistry. 3rd. edition; New York; Elsevier Publishing Company, 1947, p. 636

20. Späth, E., and E. Lederer, Ber. 63B, 743 (1930)

21. Klages, A., Ber. 36, 3595 (1903)

22. Gaunther, F., J. prakt. Chem. 115, 321 (1927)

23. Rosetti, E., and L. Jovanovic, Monatsh. 53-54, 427 (1929)

24. Bottcher, K., Ber. 42, 256 (1909)

25. Walker, H. G., Jr., and C. R. Hauser, J. Am. Chem. Soc. 68, 1386 (1946)

26. Bowman, R. E., J. Chem. Soc. 1950, 322

27. Ponken, G. S., and W. S. Johnson, J. Am. Chem. Soc. 74, 831 (1952)

28. Bruchhausen, F. v., and H. Gerhard, Ber. 72B, 830 (1939)

29. Cason, J., and H. Rapoport Laboratory Text in Organic Chemistry. New York: Prentice-Hall, Inc., 1950, p. 73.

30. Girard, A. and G. Sandulesco, Helv. Chim. Acta 19, 1095 (1936)

31. Ray, P. K., and J. N. Ray, J. Chem. Soc. 127, 2721

32. Johnson, W. S., J. K. Anderson, and V. E. Shelberg, J. Am. Chem. Soc. 66, 218 (1944)

33. Johnson, W. S., and V. E. Shelberg, J. Am. Chem. Soc. 67, 1745 (1945)

34. Johnson, W. S., and M. Posvic, J. Am. Chem. Soc. 69, 1361 (1947)

35. Johnson, W. S., J. H. Peterson, and C. D. Gutsche, J. Am. Chem. Soc. 69, 2942 (1947)

36. Moffatt, J. S., G. Newbery, and W. Webster, J. Chem. Soc. 1946, 451.

37. Anwers, K. v., Ber. 71B, 2082 (1938)

38. Hauser, C. R., and B. E. Hudson, Jr., "The Acetoacetic Ester Condensation and Certain Related Reactions", Organic Reactions, I, 266 (1942)

39. Hudson, B. E., and C. R. Hauser, J. Am. Chem. Soc. 63, 3156 (1941)

40. Haworth, R. D., and G. Sheldrick, J. Chem. Soc. 147, 636

41. Daub, G. H., and W. S. Johnson, J. Am. Chem. Soc. 72, 501 (1950)

42. Stobbe, H., Ann. 308, 100 (1899)

43. Johnson, W. S., A. R. Jones, and W. P. Schneider, J. Am. Chem. Soc. 72, 2395 (1950)

44. Schwenk, E., D. Papa, B. Whitman, and H. W. Ginsberg, J. Org. Chem. 9, 175 (1944)

45. Newett, C. L., J. Chem. Soc. 1936, 595

46. Snyder, H. R., and F. Werber, J. Am. Chem. Soc. 72, 2965 (1950)

47. Campbell, K. N., A. Schrage, and B. K. Campbell, J. Org. Chem. 15, 1135 (1950)

48. Borsche, W., Ber. 47, 1108 (1914)

49. Swamer, F. W., and C. R. Hauser, J. Am. Chem. Soc. 68, 2647 (1946)

50. Borsche, W., Ann. 526, 1 (1936)

51. Dreiding, A. S., and J. A. Hartman, J. Am. Chem. Soc. 75, 939 (1953)

52. Wilds, A. L., "Reductions with Aluminum Alkoxides", Organic Reactions, II, 192 (1944)

53. Hednick, E., "The Infrared Spectra of Model Compounds Related to Podophyllotoxin." Thesis, University of Maryland, College Park, Maryland (1953)

54. Fuson, R. C., W. E. Ross, and C. H. McKeever, J. Am. Chem. Soc. 60, 2935 (1938)

55. Fuson, R. C., W. E. Ross, and C. H. McKeever, J. Am. Chem. Soc. 61, 414 (1939)

56. Haworth, R. D., and G. Sheldrick, J. Chem. Soc. 1941, 289

57. Rasmussen, R. S., and R. R. Brattain, J. Am. Chem. Soc. 71, 1073 (1949)

58. Bogert, M. T., and D. B. Coyne, J. Am. Chem. Soc. 51, 571 (1929)

59. Herzig, J., Monatsch. 33, 845

60. Cottle, D. L., J. Am. Chem. Soc. 68, 1380 (1946)

61. Kues, W., and C. Paal, Ber. 19, 3144 (1886)

62. Dixon, C., H. Gregory, and L. F. Wiggins, J. Chem. Soc. 1949, 2139

ABSTRACT

William Bruce Tuemmler, Ph. D., 1953 (B.S. University of Maryland, 1950)

Title of Thesis: The Synthesis of an Open-chain Analogue of Podophyllotoxin.

Thesis directed by Professor Nathan L. Drake.

Major: Organic Chemistry, Department of Chemistry.

Minors: Physical Chemistry, Inorganic Chemistry.

Pages in thesis, 90. Words in abstract, 350.

The discovery that podophyllotoxin (I) damages malignant tumors in experimental animals has excited interest in this compound and in compounds related to it as possible chemotherapeutic agents for cancer. The high toxicity of podophyllotoxin has prevented its use in cancer therapy, and this has prompted a search for analogous compounds having lower toxicities but still retaining the desirable property of attacking tumors.

This thesis describes the synthesis of the open-chain analogue of podophyllotoxin, 2-(3,4,5-trimethoxybenzyl)-3-(α-hydroxy-3',4'-methylenedioxybenzyl)-butyrolactone (II). This substance was prepared from 3,4,5-trimethoxybenzoic acid (III) on one hand, and piperonylic acid (XV) on the other.

Esterification of III, followed by reduction of the ethyl ester using lithium aluminum hydride in tetrahydrofuran afforded 3,4,5-trimethoxybenzyl alcohol (V). Conversion of V to the corresponding chloride, and reaction of the chloride with diethyl sodiomalonate, afforded diethyl 3,4,5-trimethoxybenzylmalonate (VII) in an overall yield of sixty-one percent, based on III.

Piperonylic acid was converted to the acid chloride, and the latter was reacted with diethyl ethoxymagnesiummalonate to afford diethyl piperonoylmalonate (XVII). Acid hydrolysis and decarboxylation of XVII afforded 3,4-methylenedioxyacetophenone (XVIII), which was brominated to afford 3,4-methylenedioxyphenacyl bromide (XIX). The overall yield of XIX based on XV was sixty-three percent.

The ethoxymagnesium salt of VII reacted with XIX in benzene at room temperature to afford diethyl 3,4,5-trimethoxybenzyl-3',4'-methylenedioxyphenacylmalonate (XX) in yields of seventy-six to eighty-one percent. This appears to be a satisfactory general method for conducting the phenacylation of monosubstituted malonic esters.

Saponification of XX and decarboxylation of the resulting malonic acid afforded 3,4,5-trimethoxybenzyl-3',4'-methylenedioxyphenacylacetic acid XXVIII in eighty-five percent yield.

The sodium salt of XXVIII reacted with formaldehyde to afford 2-(3,4,5-trimethoxybenzyl-3-(3',4'-methylenedioxybenzoyl)-4-hydroxybutyric acid (LXVII) in sixty-three percent yield.

Lactonization of LXVII followed by hydrogenation of the keto lactone afforded II.

Attempts to condense the ethyl ester of XXVIII with ethyl formate failed. Studies on similar keto esters indicate that a steric factor prevented the condensation. While ethyl benzylphenacylacetate failed to condense with ethyl formate, the cyclic analogue, 4-phenyl-3-carbethoxy-tetralone-1, condensed readily to afford the hydroxymethylene keto ester XLII. Reduction of this by sodium borohydride afforded the dihydroxy acid XLVIII which lactonized to form a stripped analogue of podophyllotoxin.

VITA

Name: William Bruce Tuemmler

Permanent Address: 4509 Beechwood Road, College Park, Maryland

Degree to be conferred; date: Doctor of Philosophy, 1953

Date of birth: December 27, 1927

Place of birth: Flushing, New York

Secondary Education: Montgomery Blair High School, Silver Spring, Maryland

Collegiate Institutions attended	Dates	Degree	Date of Degree
Georgetown University	1945		
University of Maryland	1946-1950	B.S.	1950
University of Maryland	1950-1953	Ph.D	1953

Positions held:

Graduate Assistant, Research Assistant, Research Fellow: University of Maryland. 1947-1953.

Prospective Position: Research Chemist, Central Research Department, Monsanto Chemical Company, Dayton 7, Ohio. 1953