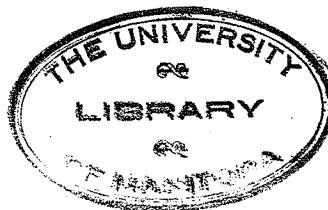The Action of Formaldehyde and Concentrated

Hydrochloric Acid on Some Substituted

o-Toluic Acids

By

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A Thesis presented to the Faculty of Graduate
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Manitoba in Partial Fulfillment of the Require-
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1951

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THE ACTION OF FORMALDEHYDE AND CONCENTRATED HYDROCHLORIC ACID ON SOME SUBSTITUTED p-TOLUIC ACIDS

Introduction

This investigation was undertaken with the object of determining the products formed by the action of a mixture of 40% formaldehyde solution and concentrated hydrochloric acid on 5-hydroxy-o-toluic acid, 5-bromo-o-toluic acid, and some other aromatic acids.

A survey of the literature showed the existence of six possible types of reaction when aromatic acids are treated with a mixture of 40% formaldehyde solution and concentrated hydrochloric acid: they are (1) no reaction; (2) simple phthalide formation; (3) chloromethylphthalide compound; (4) dioxanylphthalide structure; (5) dimer or resin; and (6) a combination of types. In addition, aromatic compounds, excluding acids, have been found to yield chloromethyl derivatives, benzylalcohol substances, and diphenylmethane structures under similar conditions.

Only phenolic acids gave dioxanylphthalide structures. Anderson (1), by refluxing 3-hydroxy-p-toluic acid with 40% formaldehyde solution in the presence of concentrated hydrochloric acid, obtained the lactone of 6-hydroxymethyl-1, 3-benzodioxan-8-methyl-5-carboxylic acid.
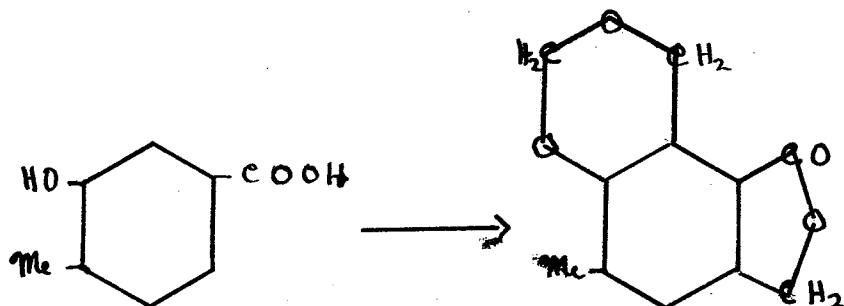
Buehler, Harris, Schaklett, and Block (8) obtained a
similar ring structure by the condensation of m-hydroxy-
benzoic acid under somewhat similar conditions. Their
product was the lactone of 6-hydroxymethyl-1,3-benzodioxan-
5-carboxylic acid.
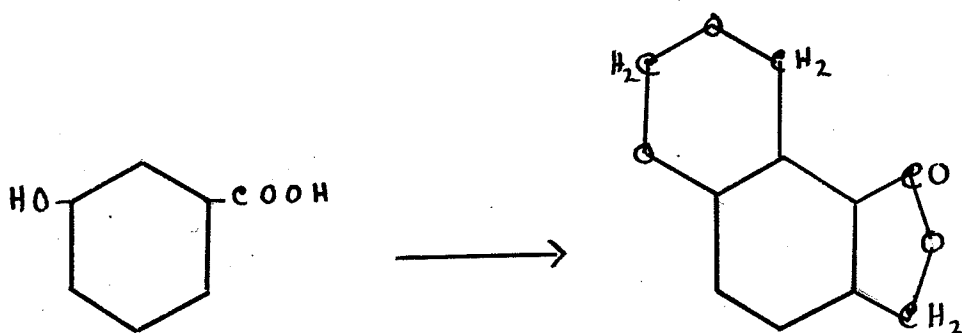
In 1944, Buehler, Powers, and Michels (7) isolated under
different conditions another condensation product of m-hydr-
oxybenzoic acid which they identified as 3-hydroxyphthalide.
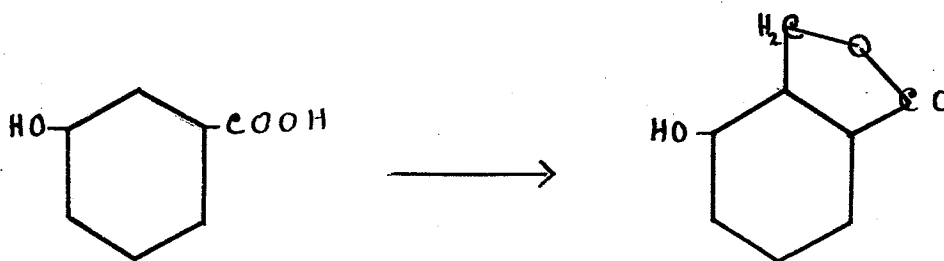
The condensation of 5-hydroxy-o-toluic acid, another
phenolic acid, might lead to two diverse products as in
Buehler's case or to one product as in Anderson's reaction.
The predominance of either reaction seems to be dependent

on the conditions employed. In order to identify the nature
of the condensation product from 5-hydroxy-o-toluic acid,
the following series of reactions, similar to the set
suggested for 3-hydroxy-p-toluic acid by Winestock (48)
and completed by Anderson, were proposed.
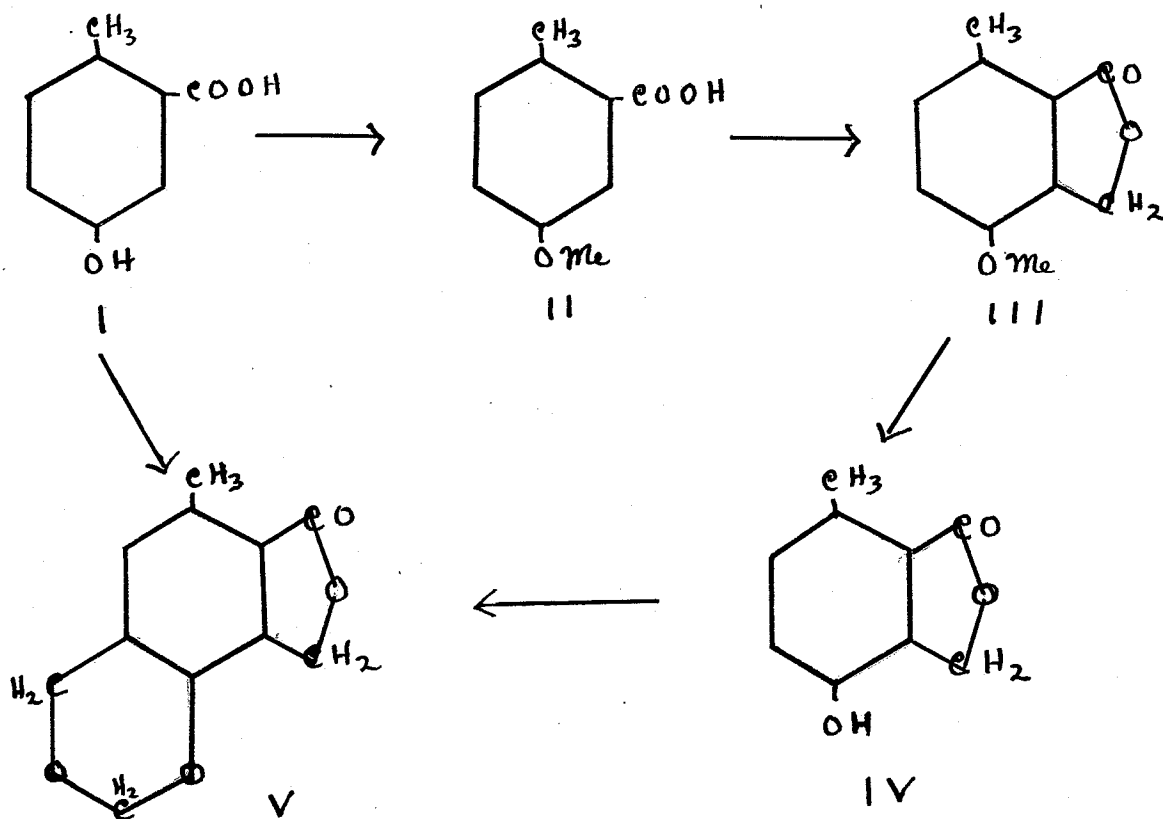
The condensation of (I) would give either the normal phthalide
(IV) or the dioxanylphthalide (V). Compounds (IV) and (V)
can be prepared by indirect means as illustrated by the
preceding series from known compounds (I), (II), and (III).
Separate mixed melting point determinations between known
compounds (IV) and (V) with the condensation product of
5-hydroxy-o-toluic acid would confirm the ring structure

of the latter substance. This structure would be substantiated by means of combustion analysis and molecular weight determination. Buehler was the only person to do any oxidative work on dioxanylphthalide structure. His scheme of oxidation seemed satisfactory but he, himself, had doubts as to the configuration of the rings. Buehler, Harris, Schaklett, and Block's (8) synthetic and oxidative work indicated that one of the condensation products of m-hydroxybenzoic acid was the lactone of 6-hydroxymethyl-1,3-benzodioxan-5-carboxylic acid. He also mentioned that there was some evidence favoring the second possible structure, the lactone of 6-hydroxymethyl-1,3-benzodioxan-7-carboxylic acid.
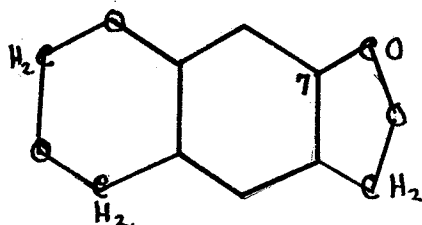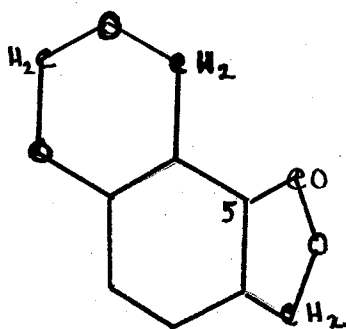
In 1950, Buehler and Block (9) presented a paper on the degradative products of this latter lactone. Recently in 1951, Buehler, Slack, Shirley, Sanguinetti, and Frey (10) were able to substantiate the earlier oxidative work which stated that one of the lactones formed in the condensation of m-hydroxybenzoic acid was the lactone of 6-hydroxymethyl-1,3-benzodioxan-5-carboxylic acid. The other lactone was also obtained by careful recrystallization of the 5-carboxylic

acid lactone. Winestock (48) stated that 3-hydroxyphthalide
could be procured by a slightly different method to that
of Buehler, Powers, and Michels (7). In addition, by
further treatment of 3-hydroxyphthalide with formaldehyde
and hydrochloric acid, Winestock claimed the preparation
of Buehler's dioxanylphthalide having the third possible
formula, the lactone of 8-hydroxymethyl-1,3-benzodioxan-
7-carboxylic acid. It was decided that Winestock's work
should be repeated.
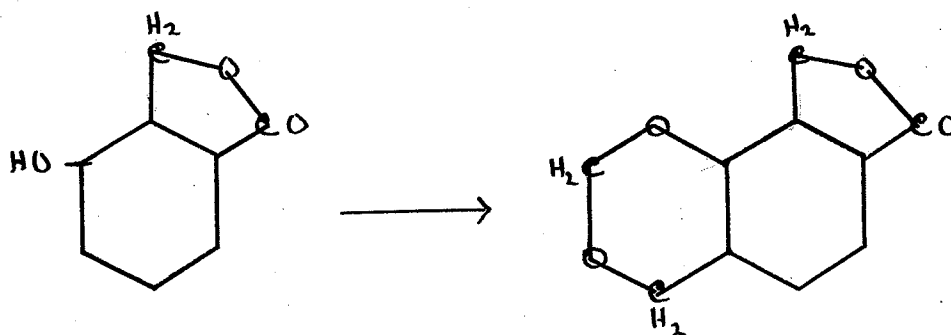
The effect of the substituted bromine group in aromatic
acids on chloromethylation and subsequent phthalide formation
has not been studied. Condensations with 5-bromo-o-toluic
acid and m-bromobenzoic acid were planned. The action of
formaldehyde and hydrochloric acid on m-aminobenzoic acid
might also lead to phthalide formation.
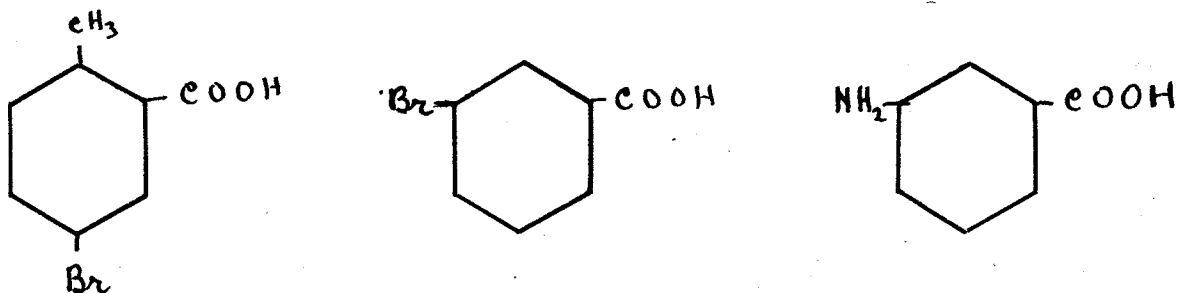
Literature Survey

In order to present a clear picture of the action of
formaldehyde in the presence of concentrated hydrochloric
acid on aromatic acids, it is necessary to designate the
system of numbering that is used in this report. The carbon
atoms of the benzene nucleus of substituted aromatic acids
are numbered counter-clockwise starting with the carbon to
which the carboxyl group is attached; for example, (a)
shows 5-hydroxy-o-toluic acid. The simple phthalides are
numbered clockwise; for example, (b) represents 3-hydroxy-
6-methyl phthalide. The dioxane ring structures have two
rings numbered; for example, (c) is the lactone of 8-hydroxy-
methyl-1,3-benzodioxan-6-methyl-7-carboxylic acid.
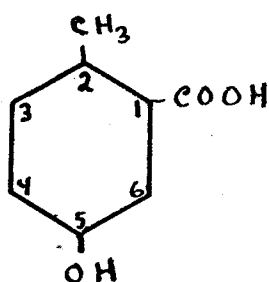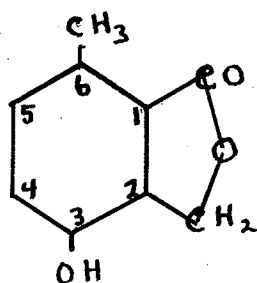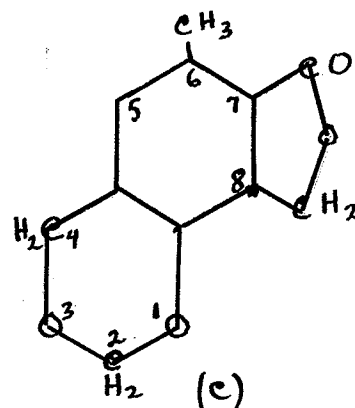
(a)   (b)   (c)

In cases where the methyl group is present in the compound,
the symbol "Me" is used for convenience instead of "CH_3"
and "OMe" in place of "OCH_3."

Stephen, Short, and Gladding (40) were the first to
systematically study the preparation of chloromethyl deriv-
atives of mono-substituted benzenoid compounds. The chloro-
methyl derivatives were prepared by the condensation of

s-dichloromethyl ether, which was obtained from the action

of hydrochloric gas on 40% formaldehyde solution, with the

aromatic compound in the presence of a dehydrating agent

such as anhydrous zinc chloride. Chlorobenzene produced

p-chloromethyl-chlorobenzene.
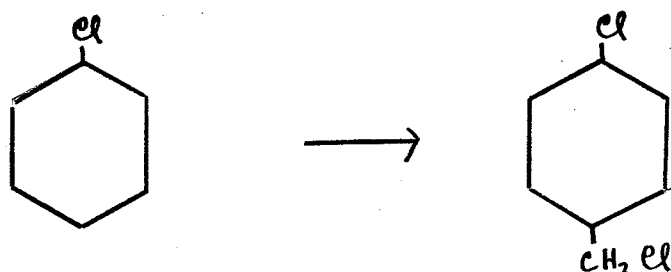
They found that the formation of the chloromethyl aromatic

compound was usually accompanied by the production of a

diphenylmethane derivative, which was formed by the conden-

sation of the chloromethyl compound and the original aromatic

substance. The presence of this diphenylmethane derivative

depended chiefly on the temperature of the reaction being

over 35°C. and to a lesser extent on the type of dehydrating

agent used. In the case of benzene, the benzyl chloride

and diphenylmethane were formed.
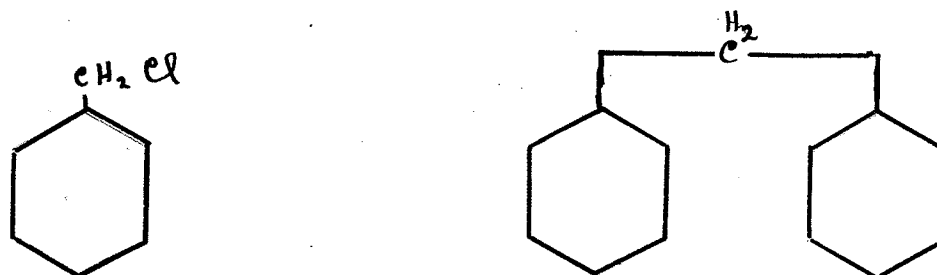
Condensations were repeated using a mixture of 40%formalde-
hyde solution and concentrated hydrochloric acid instead of
s-dichloromethyl ether in the presence of a dehydrating
agent. The yield of chloromethyl compound was poor in
comparison to the previous method. The above authors found
that chloromethylation appeared exclusively in the para-
position with reference to the original substituted ortho-
para orientating group. The presence of a nitro group
resulted in chloromethylation of the meta position.

Stoermer and Behn (41) found that the action of formalde-
hyde solution in the presence of concentrated hydrochloric
acid on certain aromatic compounds led to the synthesis of
aromatic alcohols. These authors deduced from their experi-
mental results that the presence of a negative group such
as -CHO, $-NO_2$ and -Cl, in the ortho position relative to
the hydroxyl group of phenols, caused the latter to condense
with formaldehyde in the presence of hydrochloric acid to
form hydroxy-benzylalcohols containing the methylol group
in the para position with respect to the hydroxyl group.
o-Nitrophenol gave 4-hydroxy-3-nitrobenzylalcohol.
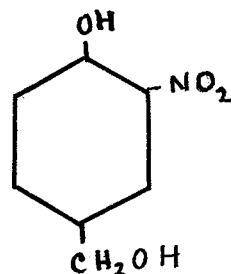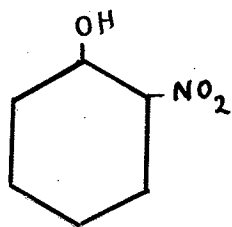
This rule incorporated the carboxyl group in their paper, on the basis that the carboxyl group was meta-directing similar to the nitro and aldehyde groups. It was also stated that the introduction of the chloromethyl group was probably the first stage in the reaction, with the subsequent formation of the alcohol.

R. Quelet(31) and his co-workers produced many chloromethyl compounds by the action of formaldehyde and concentrated hydrochloric acid in the presence of a dehydrating agent on di-substituted aromatic compounds.

Blanc (4) employed Quelet's method to repeat the preparation of some of the chloromethyl compounds formed by Stephen, Short, and Gladding. In addition to mono-chloromethyl compounds, he obtained bis-chloromethyl substances; for example, benzene produced benzyl chloride and p-xylene dichloride.

$$CH_2Cl \quad \text{(benzene ring)} \qquad CH_2Cl \quad \text{(benzene ring)} \quad CH_2Cl$$

In 1925, Edwards, Perkin, and Stoyle (13) used the mixture of formaldehyde and hydrochloric acid to prepare meconine from o-veratric acid.
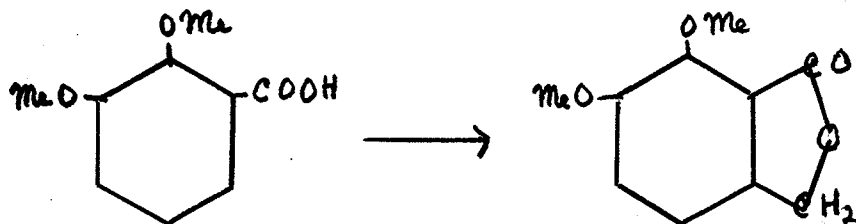
This lactone ring formation of o-veratric acid was a great
improvement over the older Fritsch (17) method which required
several steps before the same phthalide was obtained. The
above Edwards, Perkin, and Stoyle reaction will be referred
to simply as the condensation. It was extended by the same
authors to 3,4-dimethoxybenzoic acid and to 2,3-methylene-
dioxybenzoic acid but not to 3,4-methylenedioxybenzoic acid.
The latter compound showed no signs of reaction.
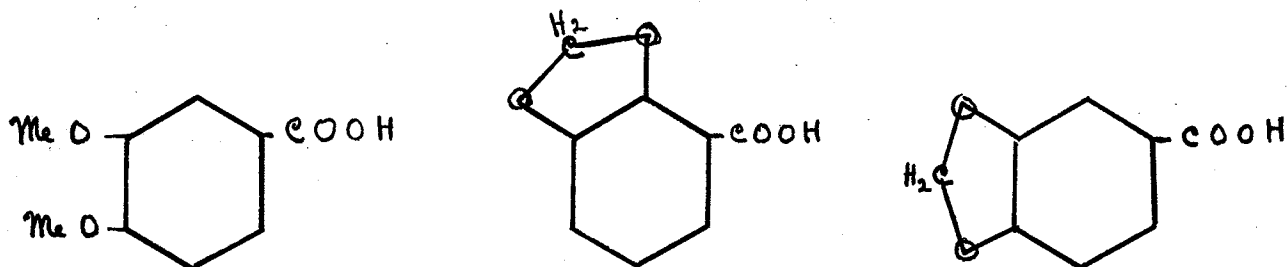
Ray and Robinson (33) improved the yield of meconine
from o-veratric acid by adding glacial acetic acid to the
reacting mixture. They were able to condense 2-bromo-3,4-
dimethoxybenzoic acid using this modification.

Paul's (28) condensation of 3,4,5-trimethoxybenzoic acid
with acetic acid resulted in 3,4,5-trimethoxy-6-chloro-
methylphthalide.
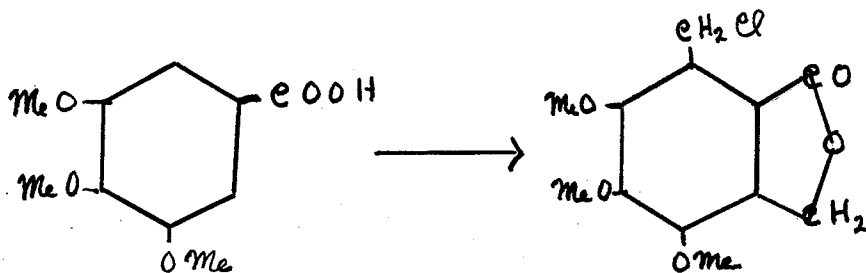
King and King (22) applied Edwards, Perkin, and Stoyle
published conditions of reaction to 3,4,5-trimethoxybenzoic
acid and obtained the same chloromethyl phthalide. In
addition, by using considerably less hydrochloric acid,
they isolated the normal 3,4,5-trimethoxyphthalide.
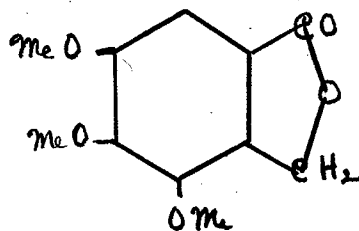
King and King found that the treatment of the once-recrystal-
lized specimens of the 3,4,5-trimethoxyphthalide or of its
chloromethyl derivative with boiling alcohol gave a sparingly
soluble residue which they identified as the dimer, the
methylenebis-phthalide.
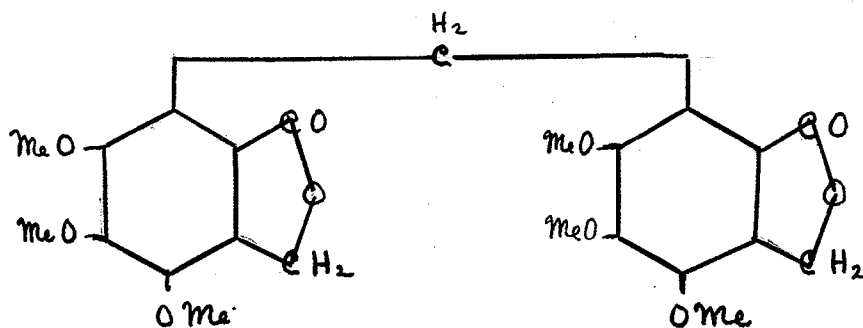
Syringic acid was reported by King and King to give the
6-chloromethyl-4-hydroxy-3,5-dimethoxyphthalide together
with 6,6[1]-methylenebis-4-hydroxy-3,5-dimethoxyphthalide.
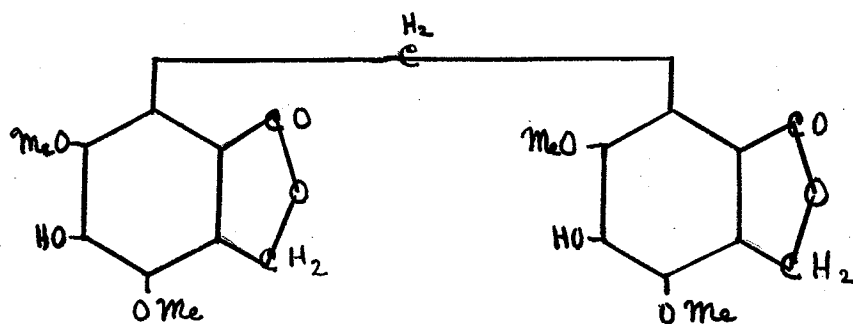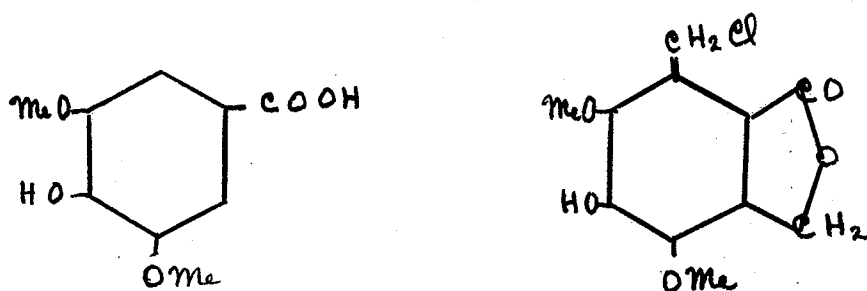
This latter compound was methylated to give the same dimer
as obtained previously from trimethylgallic acid. However,
pyrogallolcarboxylic acid-3,4-dimethyl ether did not condense
normally but gave according to King and King the 5,5[1]-methylene-

bis-2-hydroxy-3,4-dimethoxybenzoic acid. This is an illustration of a new case of dimerization without phthalide formation.
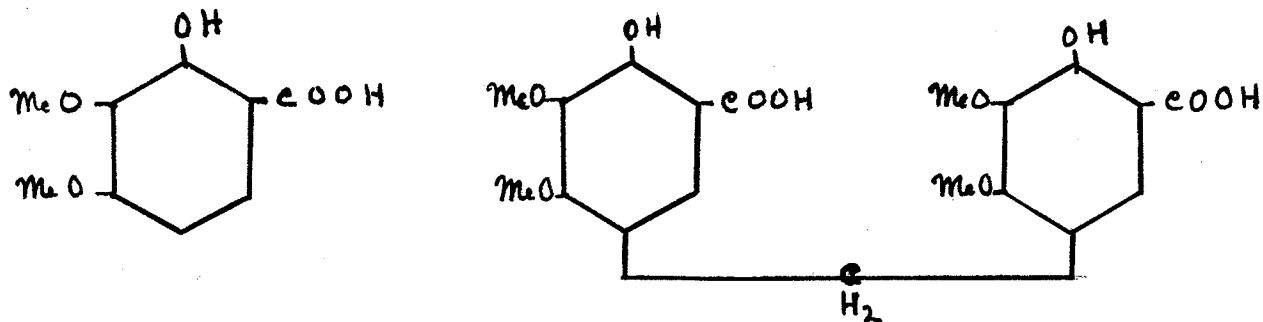
Robinson and Charlesworth (36) isolated a chlorocompound in their treatment of 3,5-dimethoxy-p-toluic acid following the condensation conditions outlined by Edwards, Perkin, and Stoyle. It was later reported by Charlesworth, Rennie, Sinder, and Yan (12) as 3,5-dimethoxy-6-chloromethyl-4-methylphthalide. The latter authors obtained also a chloromethyl derivative from 5-methoxy-m-toluic acid.
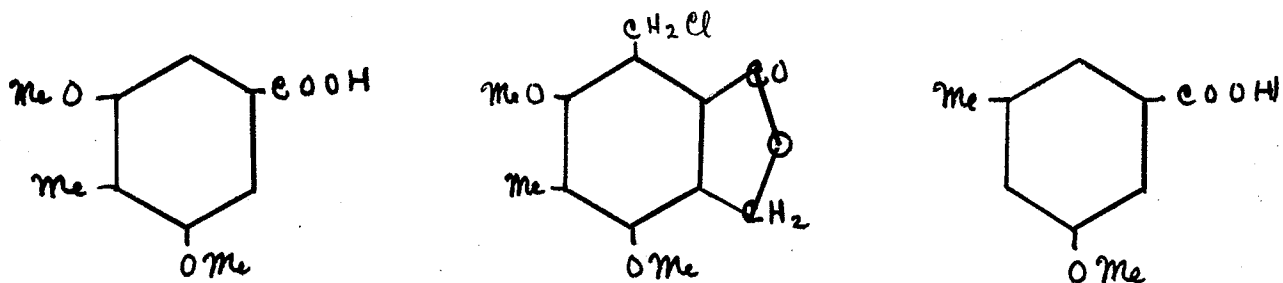
Buehler, Powers, and Michels (7) found in 1944, that the condensation of m-hydroxybenzoic acid with formaldehyde and hydrochloric acid in the presence of sulphuric acid gave two products; one of which, melting at 254°C., was isolated

and identified as the simple 3-hydroxyphthalide.
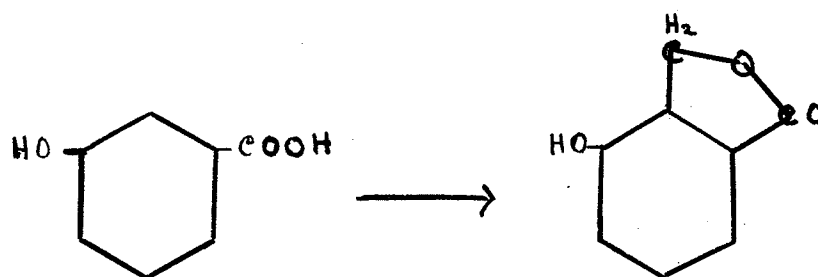
The oxidation product of the 3-methoxyphthalide and other
derivatives were not identical to those of 5-methoxyphthalide
and its derivatives reported by Chakravarti and Perkin (11)
and others.
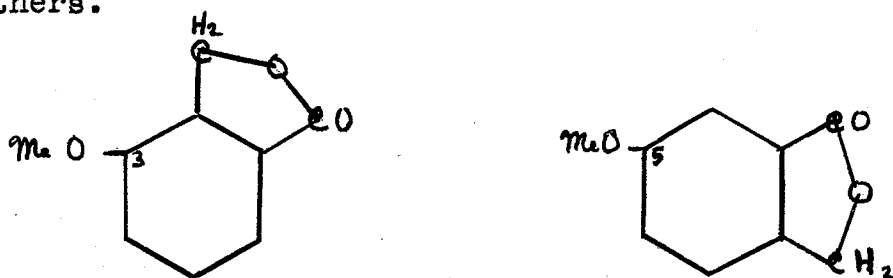
In 1946, Buehler, Harris, Schaklett, and Block (8) dis-
covered the nature of the second condensation product as
being the lactone of 6-hydroxymethyl-1,3-benzodioxan-5-
carboxylic acid. This substance reacted favorably to the
basic indication tests of dioxane and phthalide rings.
The structure of the benzodioxan compound made through the
action of formaldehyde on o-nitrophenol, has been proven
by Borsche and Berkhout (6).
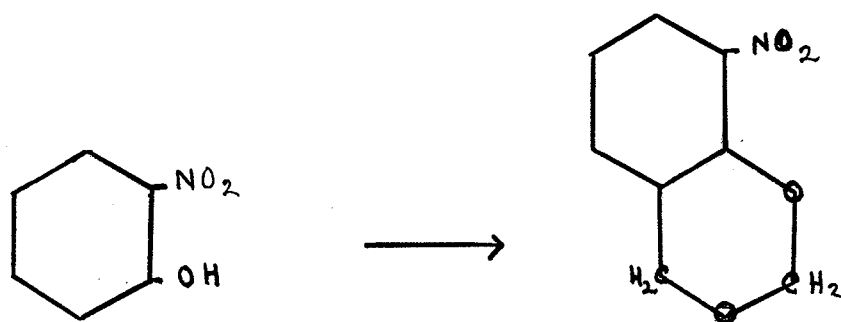
In Buehler's case, there were three possible formulae for the dioxanylphthalide compound. They were (VI), (VII), and (VIII).
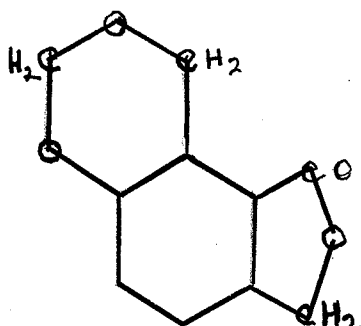
VI
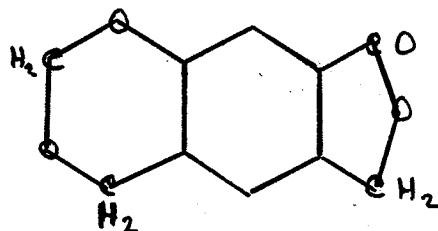
VII
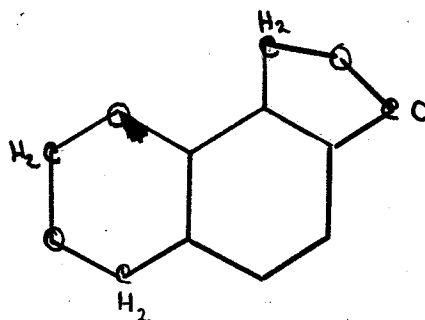
VIII

However, structures (VII) and (VIII) were ruled out on the basis of oxidative and synthetic work. Alkaline permanganate oxidation of the benzodioxan lactone (VI) produced a di-

carboxylic acid (IX) which on heating with hydrochloric
acid rearranged to form a hydroxy-carboxyphthalide (X)
which, in turn, on decarboxylation in quinloine gave a
hydroxyphthalide (XI) identical to the simple phthalide
obtained in the original condensation of m-hydroxybenzoic
acid.
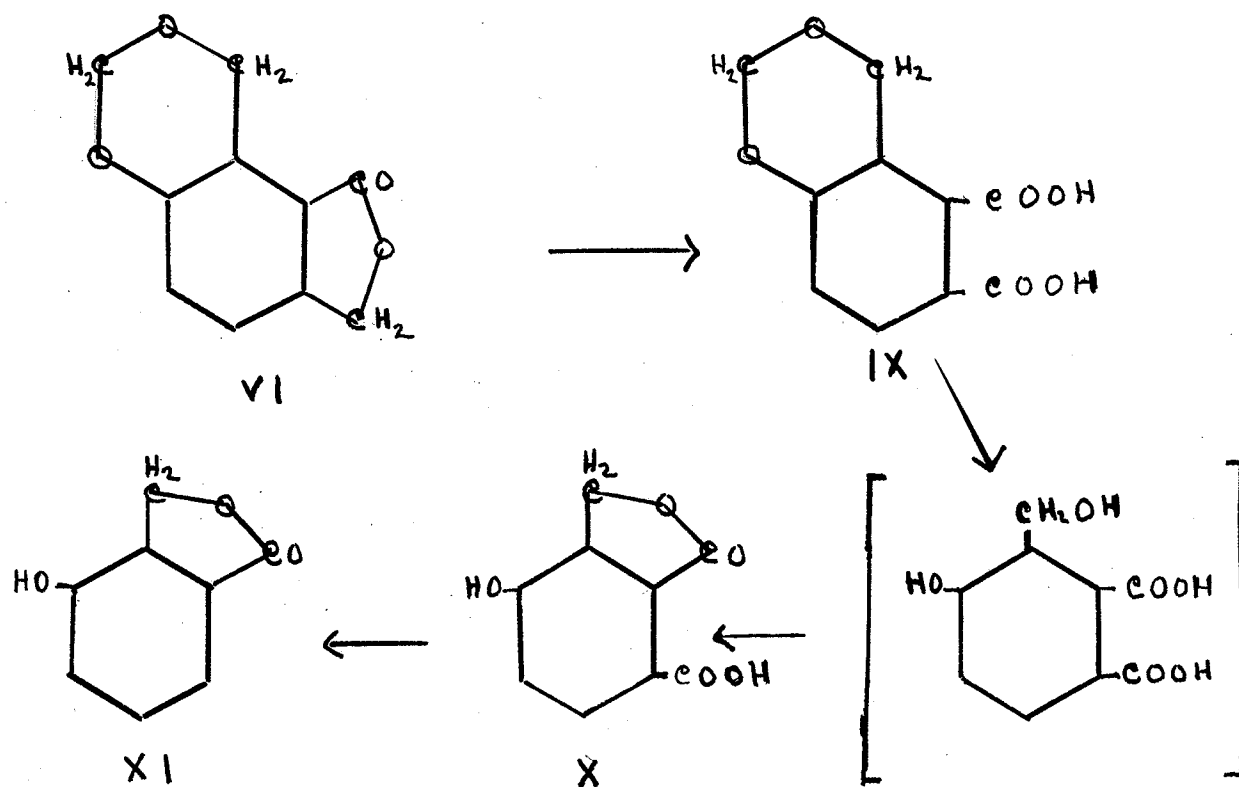
Comparative work, by synthesis of structures (VI)
and (VII) but not (VIII) favored the formula (VI). The
direct bromination of m-hydroxybenzoic acid gave the 4-bromo-
3-hydroxybenzoic acid which condensed with formaldehyde and
hydrochloric acid into the bromo-dioxanylphthalide.
Debromination of this lactone produced the compound of
structure (VI).

VI
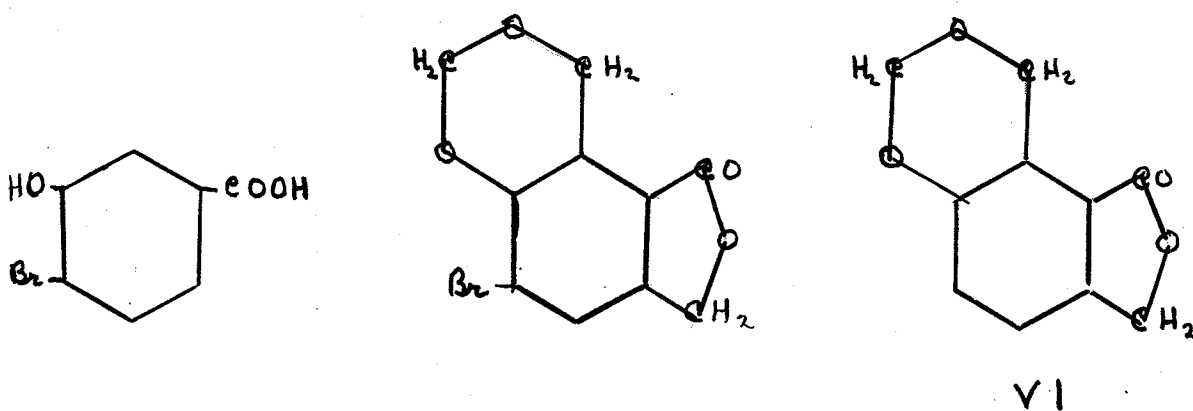
Similarly, the chlorination of m-hydroxybenzoic acid resulted in the formation of the 2-chloro-3-hydroxybenzoic acid which condensed to give the chlorodioxanylphthalide. Structure VII was obtained on dechlorination.

VII
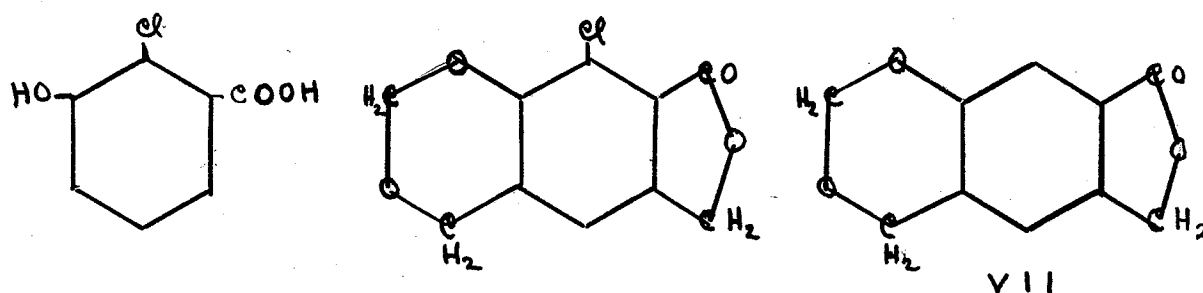
In 1950, Buehler and Block (9) reported the degradation products of the lactone of 6-hydroxymethyl-1,3-benzodioxan-7-carboxylic acid (VII) which had been previously prepared as directed by Buehler, Harris, Schaklett, and Block (8) in 1946. However, no mention was made with regard to whether the lactone was the direct condensation product of m-hydroxybenzoic acid or the synthetic compound obtained from the dechlorination of the chlorodioxanylphthalide (XII).

In 1951, Buehler, Slack, Shirley, Sanguinetti, and Frey (10)
confirmed the structure of the 5-carboxylic acid lactone
(VI) by oxidative work to the known trimethyl-4-methoxy-
benzene-1,2,3-tricarboxylate (XVII). Two different oxida-
tive steps were performed in which each attached ring in
turn was opened by two different ways. The first method
was an extension of the 1946 work whereby the dioxanyl-
phthalide compound (VI) was oxidized to the dicarboxylic
acid (IX) with alkaline permanganate. The two ortho carboxyl
groups were stabilized by conversion to the anhydride (XIII)
and then to the imide (XIV). Mild oxidation of the dioxane
ring with chromium trioxide in acetic acid resulted in the
formation of the dioxanone imide (XV) which on alkaline
hydrolysis gave the known 4-hydroxybenzene-1,2,3-tricarboxylic
acid (XVI). Complete methylation produced the known trimethyl-
4-methoxybenzene-1,2,3-tricarboxylate (XVII).

VI   IX

IX

XIII

XV

XIV

XVI

XVII
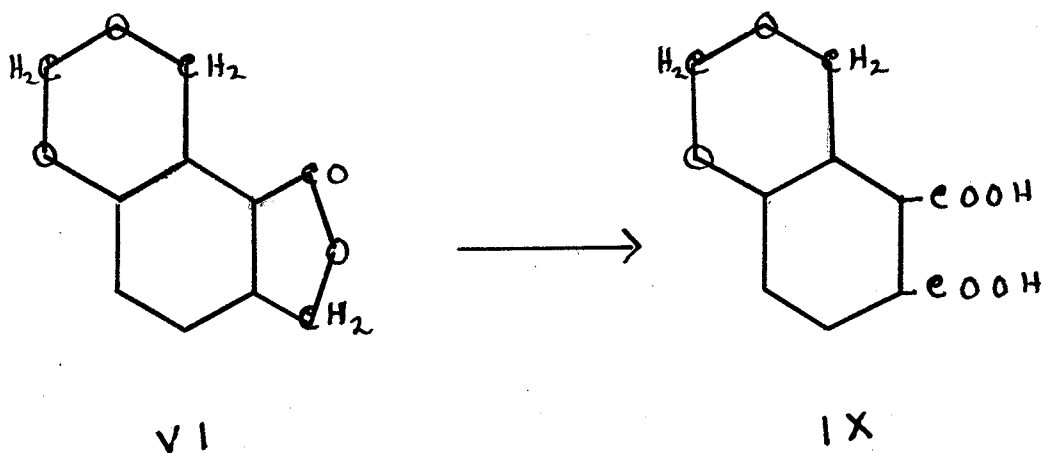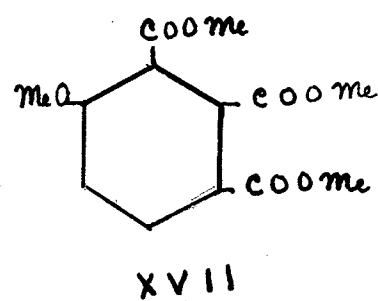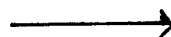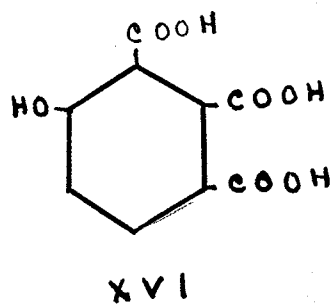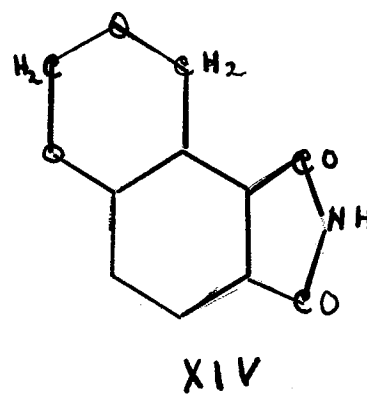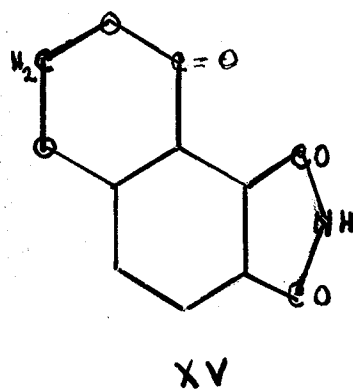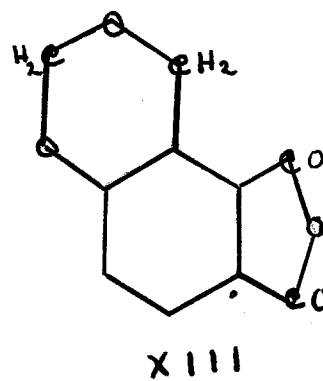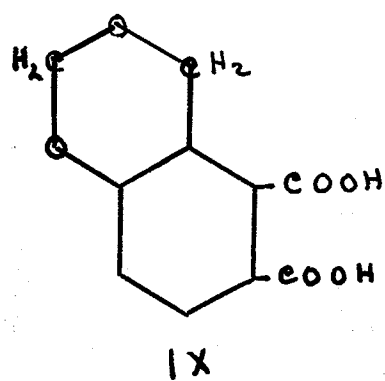
The second method consisted of opening the dioxane ring by
mild oxidation, then the phthalide ring by stronger oxidation.
First step was performed by mild oxidation of the lactone
compound (Vl) with chromium trioxide in acetic acid to give
the dioxanone (XVlll), followed by alkaline hydrolysis
of this ester to the hydroxy-carboxyphthalide (XlX).
Methylation of the latter compound produced the methoxy-
carboxyphthalide (XX) which on oxidation with alkaline
permanganate gave the known 4-methoxybenzene-1,2,3-tricar-
boxylic acid (XXl). Methylation with diazomethane gave
the known trimethyl-4-methoxybenzene-1,2,3-tricarboxylate
(XVll).

V I   XVlll

XX   XIX
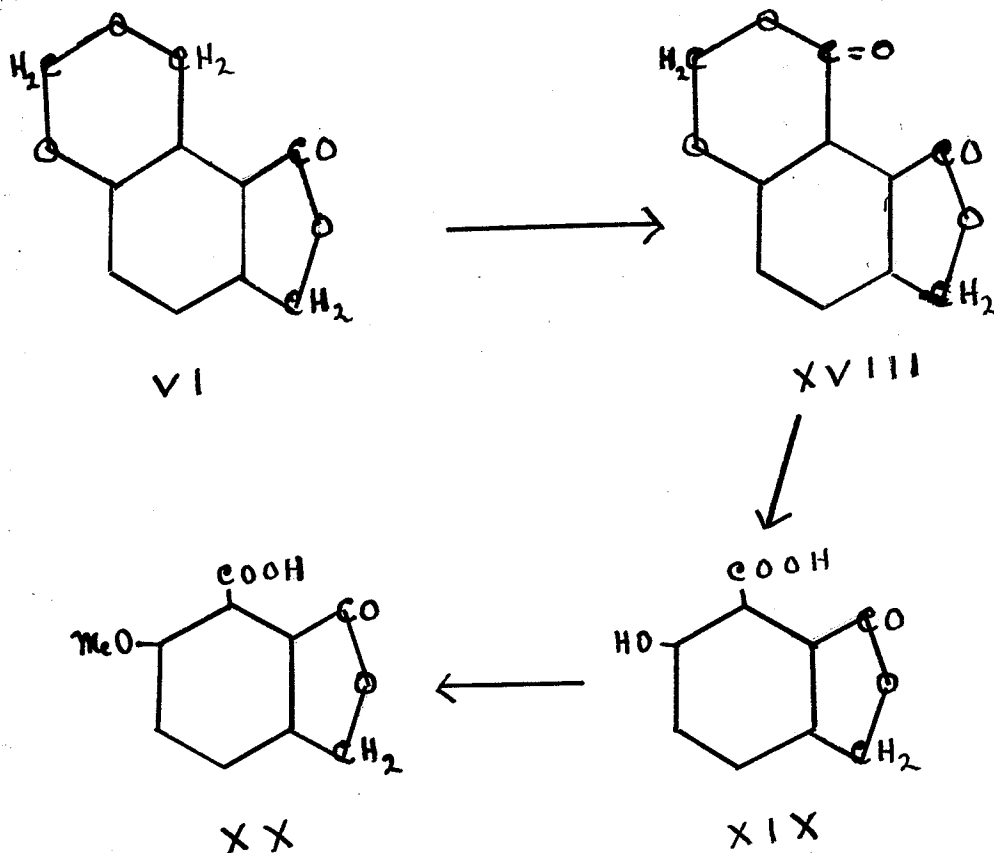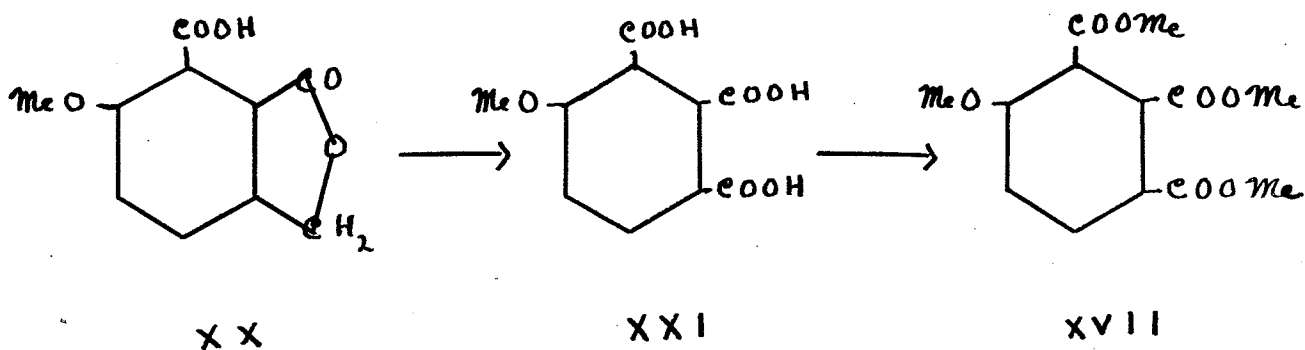
It was also mentioned that there was some evidence that 5- and 7-carboxylic acid lactones were formed together in the condensation reaction of m-hydroxybenzoic acid.

Stephen, Short, and Gladding's idea on chloromethylation were extended by Yan (49) and Sinder (39) to phthalide formation. The former authors showed that the action of formaldehyde on hydrochloric acid led to the formation of s-dichloromethyl ether (XXII). The hydrolysis of this ether in the presence of a dehydrating agent was shown to lead to chloromethyl products. Yan and Sinder proposed a mechanism for phthalide formation based on the introduction of the chloromethyl group ortho to the carboxyl group resulting in an unstable intermediate (XXIII) which underwent an intramolecular reaction to form the desired lactone (XXIV) by two different possible steps outlined in the following diagram. They argued that in chloromethyl compounds where the entering group is not ortho to the carboxyl, hydrolysis occurs only in alkaline solutions. Hence it is not likely that the reaction proceeds along the chloromethylalcohol formation and dehydration stage since the reaction is carried out in acid solution.

XXII

XXIII

HOH

XXIV
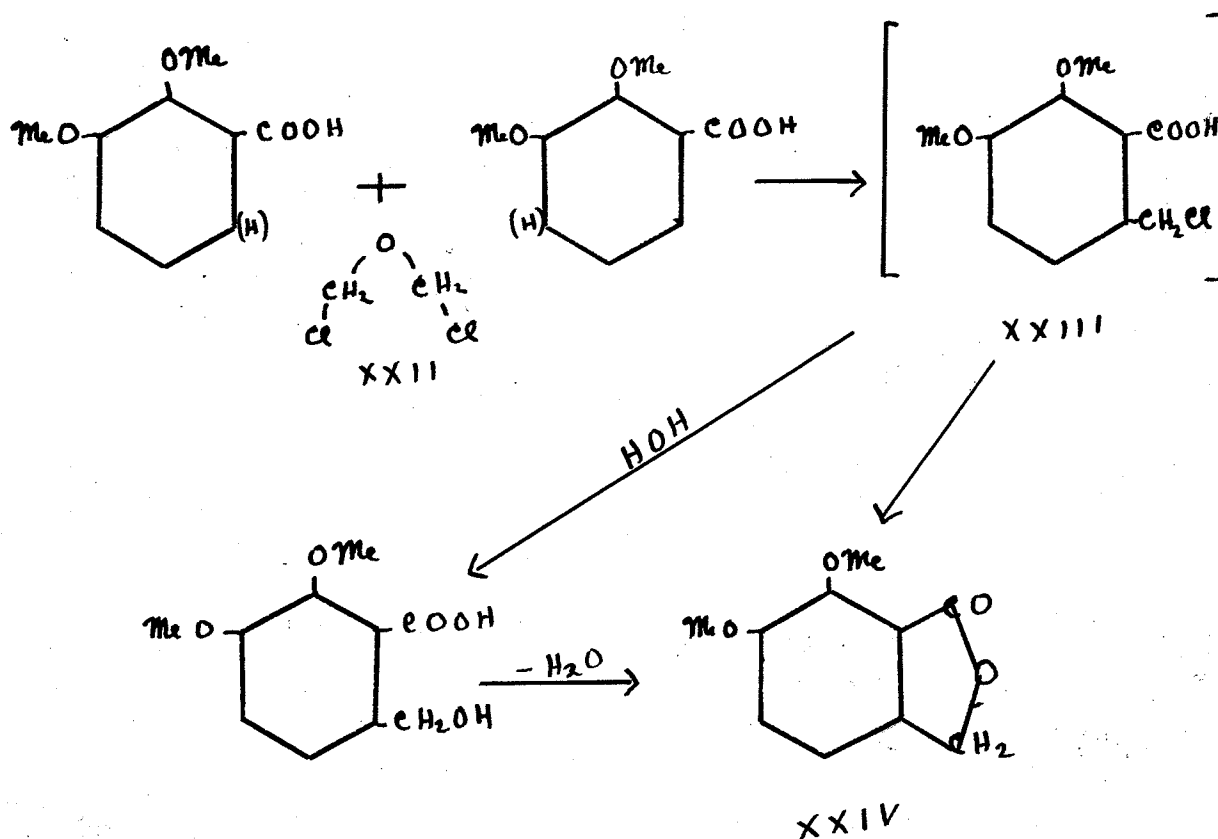
Rennie (34) suggested that the methyl and methoxyl group are an aid to chloromethylation, and hence, subsequent phthalide formation, while the carboxyl group is a hindrance. This has been confirmed by Vavon, Bolle, and Calin (46) who measured the rate of halogen methylation for variously substituted aromatic compounds. They found that the rate is increased by $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-OCH_3$, $-OC_3H_7$; and decreased by $-Cl$, $-Br$, $-I$, $-CH_2Cl$, $-COOH$ and $-NO_2$ when these groups are substituted on the nucleus.

Further, the conditions under which the reaction proceeds have a definite influence on the products produced. In many cases, where a mixture of products is obtained, a variation in the condensation time and reaction temperature will cause one or other of the products to predominate; for example,

there is Buehler's work. More recently Manske and Ledingham
(23) have found that a slight variation in the relative
amounts of reactants in the condensation of o-veratric
acid produces a chlorocompound almost to the exclusion of
meconine.
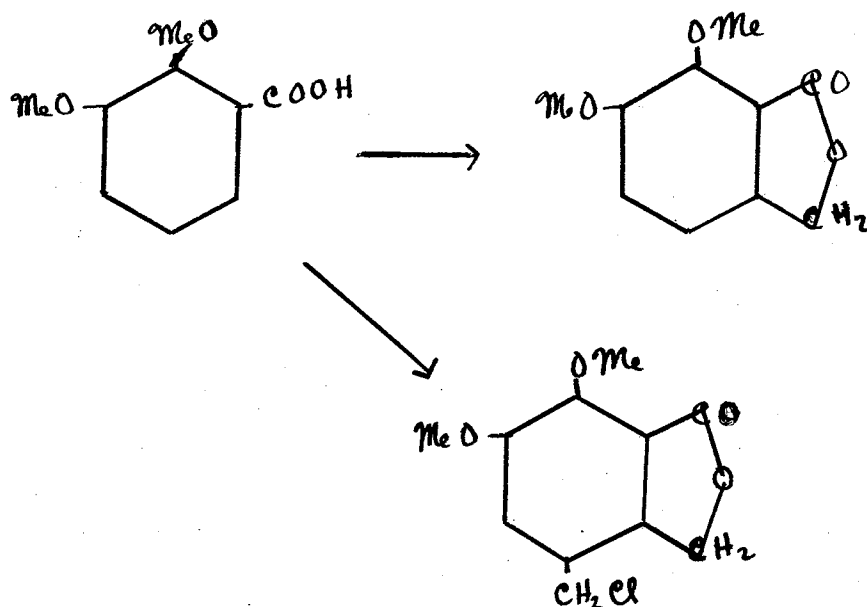
Winestock (48) suggested that the ortho and para
directing groups, in substituted benzoic acid compounds,
which activated the unoccupied 6-position in the nucleus,
would lead to primary chloromethylation and subsequent
phthalide formation. On this basis, for simple lactone
condensation of 5-methoxy-o-toluic acid, the 3-, 4-, and
6-positions are activated but the 6-position is predominately
affected.
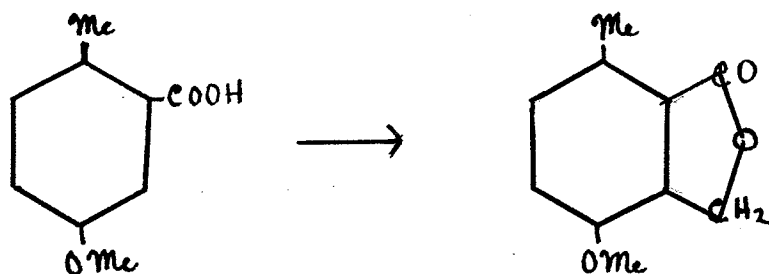
Similarly, when the 2- and 6-positions are unoccupied and
are simultaneously activated as in m-methoxybenzoic acid,
the reaction occurred at the 6-position because Winestock
claimed that the 2-position was sterically blocked by the
methoxyl group.
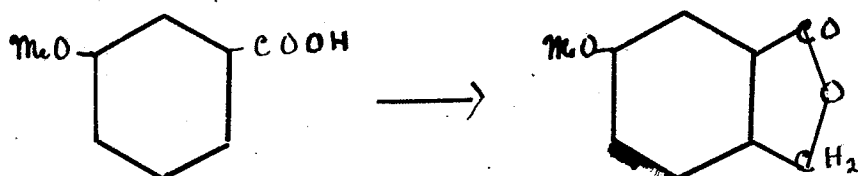
Winestock's ideas on steric hindrance were not tenable,
because Anderson (I) pointed out that chloromethylation
occurred in the 6-position of 5-methoxy-o-toluic acid even
though, in the 5-position, there was a methoxyl group which
should have prevented the displacement.

The condensation product of 2,4-dimethoxybenzoic acid
seemed to be an exception to Winestock's suggestions, if
simple phthalide formation, secondary chloromethylation and

dimerization did take place as he believed since the isolation of a dimer was claimed.
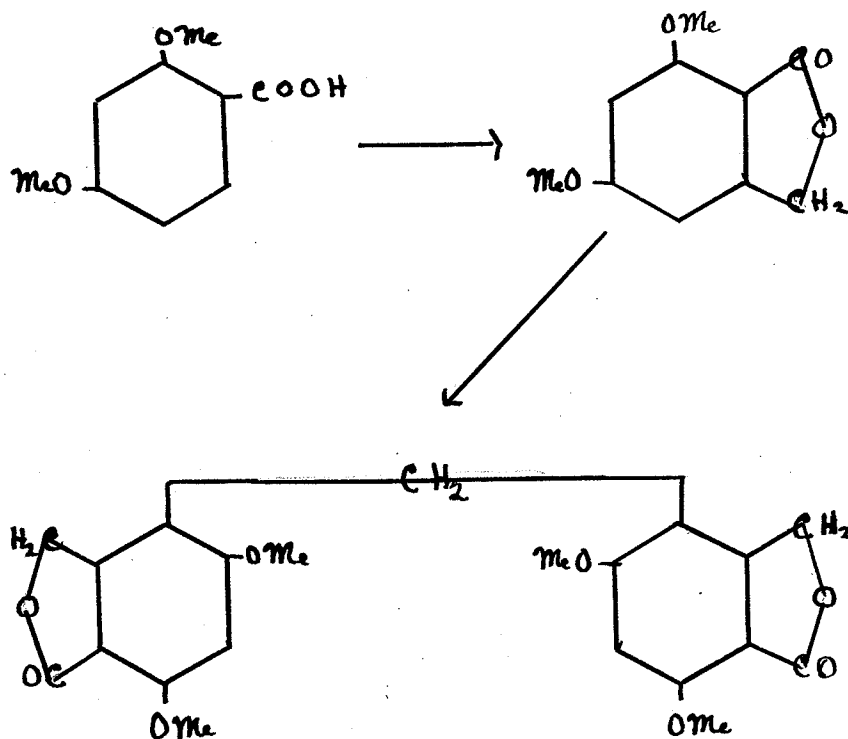
This exception, especially with respect to simple phthalide formation, would be highly improbable since orientation rules would be violated. However, chloromethylation and then dimerization without phthalide formation, could be acceptable if the reaction did occur.

Very little work has been done on chloromethyl phthalide reactions. These compounds seemed to be formed only when methyl or methoxyl groups were in the 3- and 5-position. Paul (28) and King and King (22) worked under these above mentioned conditions in the presence of small amounts of acetic acid. Charlesworth, Rennie, Sinder, and Yan (12)

isolated a chloromethyl compound without the aid of a
catalyst.

Anderson (I) formulated a set of rules for predicting
the products of the Perkin, Edwards, and Stoyle condensation.
These rules were derived by a careful study of all attempted
condensations which are in table I, page 30, which was
extended to include the present research. He noticed, in
the directing powers of the ortho-para substituent groups
in the benzoic acid compounds, that the para orientating
forces were predominant in nearly all cases. Secondly,
whenever simple phthalide formation occurred, there was in
the 3-position, a methoxyl group whose para directing
powers activated the 6-position. There were three exceptions:
(a) 5-methoxy-o-toluic acid; (b) 3,5-dihydroxy-p-toluic
acid; (c) m-hydroxybenzoic acid.
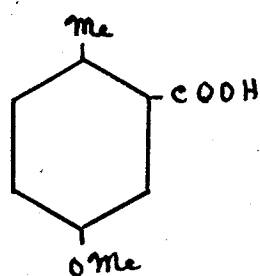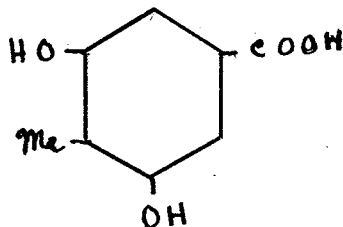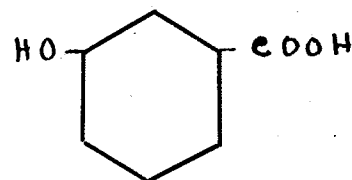
(a)   (b)   (c)

In 5-methoxy-o-toluic acid, lactone formation was due
to ortho directing forces of the methoxy group in the
5-position, since the 3-position was vacant and the para
directing forces could not activate the 6-position. As
for 3,5-dihydroxy-p-toluic acid, there is a hydroxyl group
with ortho and para orientating properties in the 3-position.
Buehler's condensation of m-hydroxybenzoic acid led to the

formation of the lactone in the 2-position. The ortho
orientating forces of the hydroxyl group in the 3-position
seemed to predominate.

Anderson's extension of his theory to other cases
besides the normal phthalide reaction did not conflict
with his two rules which dealt with the latter case.
Chloromethyl phthalide structures were explained on the
basis of a secondary directing methoxyl group in the 2- or
5-position. Simple phthalide reaction, activated as out-
lined, was followed by the introduction of a secondary
chloromethyl group para to this secondary methoxyl group.
5-Methoxy-m-toluic acid complied with his specifications;
with the exception that a methyl group instead of a methoxyl
group was present in the 3-position with para directing
powers.
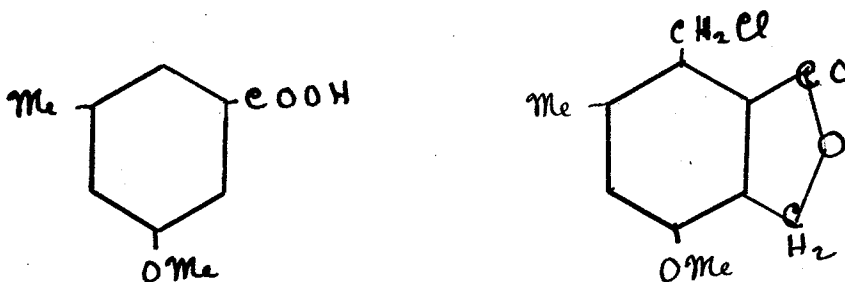
Dimerization or resinification took place whenever
one or more of the following conditions were fulfilled;
(1) a hydroxyl group is in the 5-position of the original
acid; (2) there is no ortho-para directing group in the
3-position of the original acid; and, (3) a chloromethyl
phthalide is formed during the condensation of the original
acid. Very little investigation has been done on dimers

or resins, but it seems likely that in some cases a phthalide
ring may not be formed. Since the 3-position was not occupied,
phthalide formation could not be possible until dimerization
had occurred. Possibly if a diphenylmethane derivative
was formed through the 3-position this group might direct
the second chloromethyl group to the 6-position where
phthalide formation could take place.

Dioxane ring formation like chloromethyl phthalide
formation was secondary to the introduction of the phthalide
ring. Anderson found only two cases. In each case, there
was a hydroxyl group in the 3-position and the 2-position
was open.

According to Anderson, the methylenedioxy-ring has
been assumed to give the positions in the ring to which
it is attached the same properties as a methoxyl group.
This seemed to be the case in the simple lactone condensation
of 2,3-methylenedioxybenzoic acid.
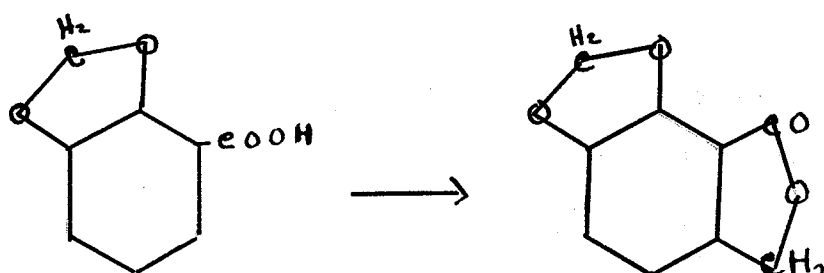
However, 3,4-methylenedioxybenzoic acid, (piperonylic acid),
tried by Perkin, Edwards, and Stoyle (13) and Sinder (39)

showed no reaction. If the above hypothesis is correct, then, 3,4-methylenedioxybenzoic acid is an exception to the rule. Also, 2,3-methylenedioxybenzoic acid satisfies the conditions for chloromethyl phthalide formation but no evidence of this has yet been obtained.

m-Toluic acid did not form a simple phthalide even though there was a para directing methyl group in the 3-position. Possibly the methyl group alone was insufficient to activate the ring.
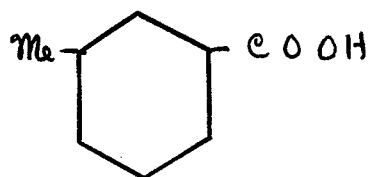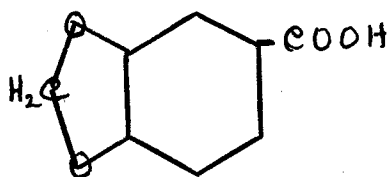
CONDENSATION OF AROMATIC ACIDS WITH FORMALDEHYDE

AND HYDROCHLORIC ACID

Benzoic acid	no reaction (34)
o-Toluic acid	no reaction (49)
m-Toluic acid	no reaction (34)
p-Toluic acid	no reaction (34)
o-Methoxybenzoic acid	no reaction (34)
m-Methoxybenzoic acid	5-methoxy-phthalide (11)
p-Methoxybenzoic acid	no reaction (34) (49)
o-Hydroxybenzoic acid	dimer or resin (48)
m-Hydroxybenzoic acid	3-hydroxy-phthalide and dioxanyl phthalide (7)(8)(48)
p-Hydroxybenzoic acid	diphenylmethane derivative (14)
5-Methoxy-o-toluic acid	3-methoxy-6-methyl phthalide (12)
5-Methoxy-m-toluic acid	3-methoxy-5-methyl-6-chloromethyl phthalide(12)
3-Methoxy-p-toluic acid	5-methoxy-4-methyl phthalide (12)
3,5-Dimethoxy-o-toluic acid	3,5-dimethoxy-6-methyl phthalide (12) (27)
4,5-Dimethoxy-o-toluic acid	no substance isolated (23)
3,5-Dimethoxy-p-toluic acid	3,5-dimethoxy-4-methyl-6-chloromethyl phthalide (12)(34)
2,3-Dimethoxybenzoic acid	5,6-dimethoxy phthalide and 3-chloromethyl phthalide (13)(23)

2,3-Dimethoxy-5-methylbenzoic acid	5,6-dimethoxy-3-methyl phthalide (23)
3,4-Dimethoxybenzoic acid	4,5-dimethoxy phthalide (13) (33)
2,4-Dimethoxybenzoic acid	dimer or resin (39) (48)
2-Bromo-3,4-dimethoxybenzoic acid	6-bromo-4,5-dimethoxy phthalide (33)
3,4,5-Trimethoxybenzoic acid	3,4,5-trimethoxy phthalide, 6-chloromethyl phthalide and dimer or resin (28)(49)(22)
3,4-Methylenedioxybenzoic acid	no reaction (13) (39)
2,3-Methylenedioxybenzoic acid	5,6-methylenedioxy phthalide (29)
3-Methoxy-4,5-methylenedioxy-benzoic acid	5-methoxy-3,4-methylenedioxy phthalide and 6-chloromethyl phthalide (28)
3,5-Dimethoxy-4-hydroxybenzoic acid	3,5-dimethoxy-4-hydroxy phthalide and 6-chloromethyl phthalide (22)
2-Hydroxy-4-methoxybenzoic acid	dimer or resin (48)
5-Hydroxy-o-toluic acid	3-hydroxy-6-methylphthalide and dioxanylphthalide ("p")
5-Hydroxy-m-toluic acid	dimer or resin (49)
3-Hydroxy-p-toluic acid	dioxanylphthalide (49) (1)
3,5-Dihydroxy-p-toluic acid	3,5-dihydroxy-4-methyl phthalide and dimer (1)
3,4,5-Trihydroxybenzoic acid	dimer or resin (48)

m-Bromobenzoic acid   no reaction (p)

5-Bromo-o-toluic acid   no reaction (p)

"p."– present research.

DISCUSSION OF EXPERIMENTAL RESULTS

The Structures of the Condensation Products of 5-Hydroxy-o-Toluic Acid

The condensation of 5-hydroxy-o-toluic acid with formaldehyde and concentrated hydrochloric acid led to the formation of the 3-hydroxy-6-methylphthalide (XXV) and the lactone of 8-hydroxymethyl-1,3-benzodioxan-6-methyl-7-carboxylic acid (XXVI). There was also some evidence that dimerization may have occurred.
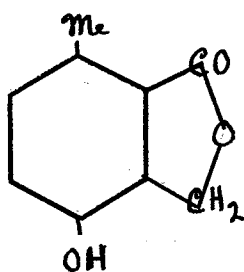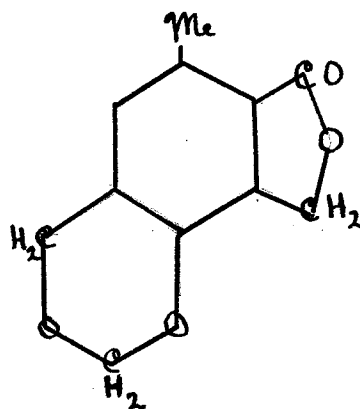
XXV   XXVI

Since 5-hydroxy-o-toluic acid is an isomer of 3-hydroxy-p-toluic acid, an attempt was made to perform the condensation under the same conditions as described by Anderson (I)in order to obtain a similar dioxanylphthalide structure. However, higher yields were obtained by heating the reaction mixture for a longer period of time. The possibility of an intermediate simple phthalide necessitated a longer heating period.

Recrystallization of the condensation product from ethyl
alcohol gave a white needle-like crystalline substance melting
at 171 - 172°C. Combustion analysis, substantiated by a mole-
cular weight determination of 204, indicated a formula of
$C_{11}H_{10}O_4$ for the lactone of 8-hydroxymethyl-1,3-benzodioxan-
6-methyl-7-carboxylic acid (XXVI). This dioxanylphthalide
condensed with phloroglucinol and sulphuric acid, according
to Mehta and Ayyar's (24) directions for a dioxane ring test,
to give the characteristic orange-red precipitate. The blank
run with 5-hydroxy-o-toluic acid resulted in a dark red pre-
cipitate. The dioxanylphthalide reacted favorably to the
phthalide ring test with resorcinol and concentrated sulphuric
acid. Dilution of the red-colored mixture with water produced
an orange-yellow solution which exhibited a green fluorescence.
This fluorescence was greatly intensified by the addition of
excess alkali. No such changes were noticed in the blank run
with 5-hydroxy-o-toluic acid. Thorpe and Whitely (45) produced
the same type of fluorescence with succinic acid. This test
seems to be an indication that a phthalide ring exists.

In order to distinguish the dioxanylphthalide from the
simple phthalide $C_9H_8O_3$ (XXV), 3-hydroxy-6-methylphthalide
(XXV) was prepared in a series of reactions as outlined below:
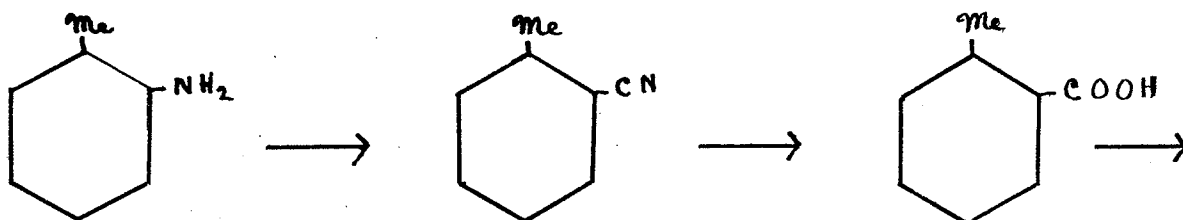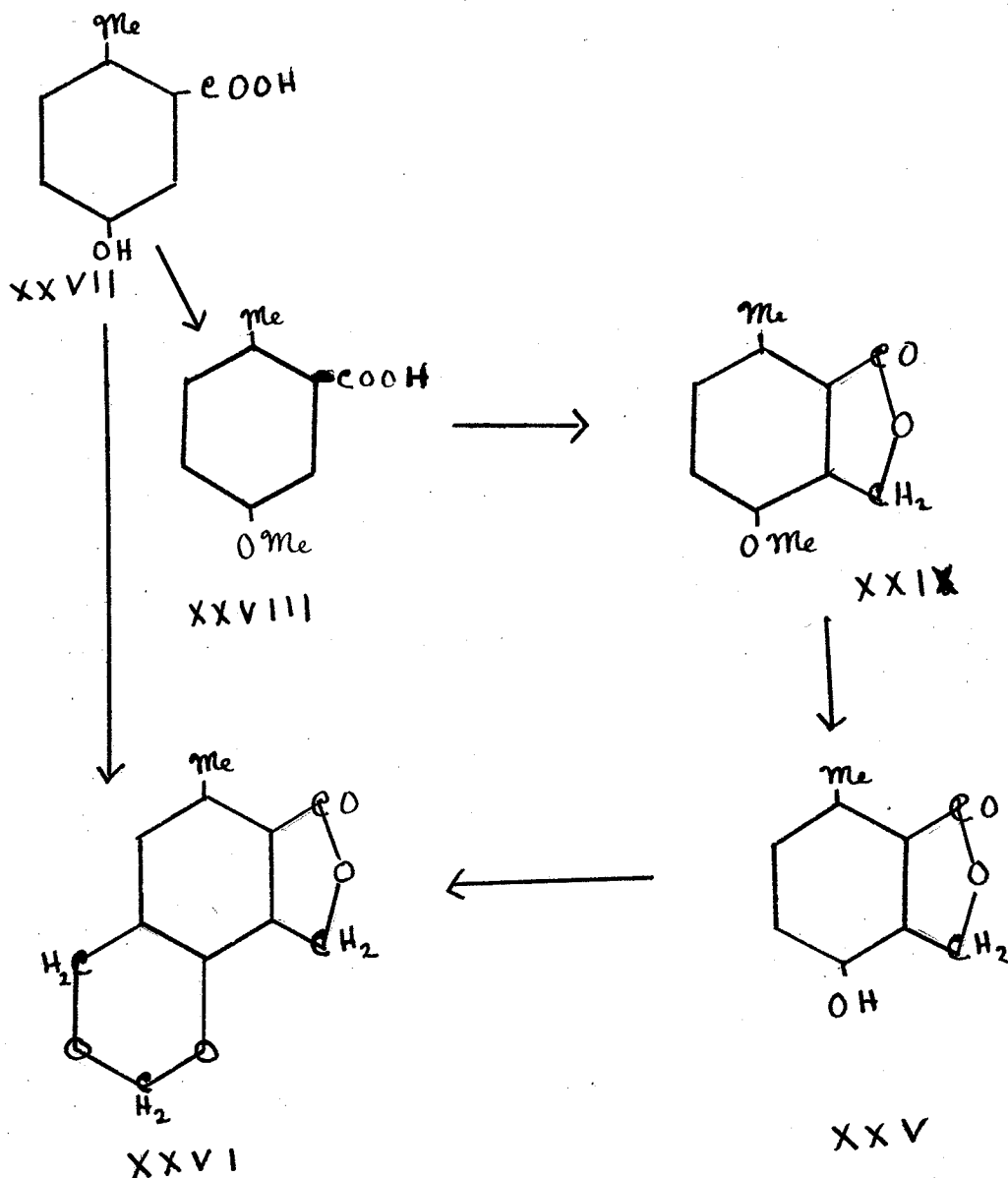
The 5-hydroxy-o-toluic acid (XXVII) was prepared from o-toluidine in a series of preliminary reactions. By means of the Sandmeyer reaction, o-toluidine was converted to o-toluic nitrile which was hydrolyzed to o-toluic acid. Sulphonation of o-toluic acid followed by alkali fusion of the potassium salt of 5-sulpho-o-toluic acid produced the desired 5-hydroxy-o-toluic acid. Tambor's (43) method outlined by Rennie (34), was used in methylating 5-hydroxy-o-toluic acid (XXVII). Rennie was able to condense 5-methoxy-o-toluic acid (XXVIII) to 3-methoxy-6-methylphthalide (XXIX).

A demethylation, with either hydrogen iodide and phosphorus
or aluminum chloride in benzene produced for the first time
3-hydroxy-6-methylphthalide (XXV) melting at 223 - 224°C.
Physical properties, combustion analysis and a molecular
weight determination of 169, confirmed the structure of this
simple phthalide. Condensation of this simple phthalide with
formaldehyde and concentrated hydrochloric acid produced the
lactone of 8-hydroxymethyl-1,3-benzodioxan-6-methyl-7-carboxylic
acid (XXVI). A mixed melting point of this latter substance
with that of the dioxanylphthalide compound obtained through
the condensation of 5-hydroxy-o-toluic acid, showed no depression
in the melting point. Dimerization was ruled out on the basis
of molecular weight determinations which gave 204 for the
dioxanylphthalide structure (XXVI) and 164 for the 3-hydroxy-
6-methylphthalide (XXV), a dimer of the type (XXX) would give
a calculated molecular weight of 340.
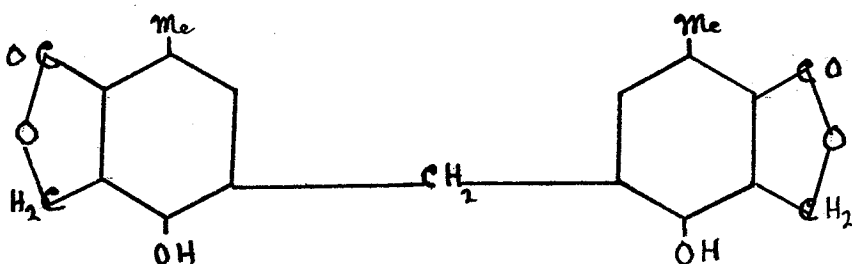
$$X X X$$

A negative test for chlorine by the sodium fusion method
removed any doubt as to the existence of a chloromethyl compound
derivative.

Alkaline permanganate oxidation of the lactone of 8-hydroxy-methyl-1, 3-benzodioxan-6-methyl-7-carboxylic acid gave an acidic substance, probably dibasic, melting at 282°C. with decomposition. Buehler, Harris, Schaklett, and Block (8) carried out the same type of oxidation on the lactone of 6-hydroxymethyl-1, 3-benzo-dioxan-5-carboxylic acid. Their oxidative product was the 1, 3-benzodioxan-5, 6-dicarboxylic acid. In addition, anhydride formation was indicated by the bluish coloration of anhydrous copper sulphate upon heating a sample of the acid at the melting point in a sealed dry melting tube. However, decomposition of the acid by some other means might have caused the liberation of water. Consequently, a possible structure for the oxidative product of the lactone of 8-hydroxymethyl-1, 3-benzodioxan-6-methyl-7-carboxylic acid might be 1, 3-benzodioxan-6-methyl-7, 8-dicarboxylic acid (XXXl).

XXXl
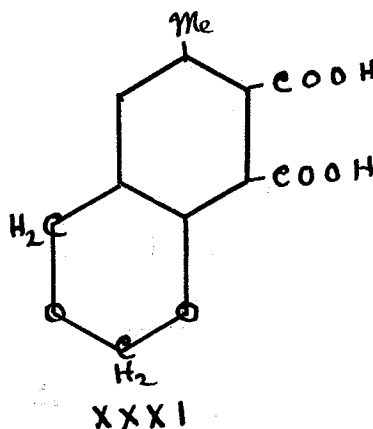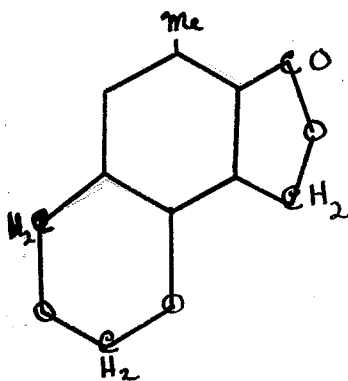
A mixture of 5-hydroxy-o-toluic acid, concentrated hydro-chloric acid, and 40% formaldehyde was allowed to stand at room temperature overnight. The contents of the flask yielded a white crystalline product which on recrystallization from a minute quantity of alcohol melted at 223 - 224°C. A mixed

melting point determination of this sample with 3-hydroxy-6-
methylphthalide showed no depression of the melting point.

A similar trial with the dioxanylphthalide compound obtained
by the first condensation, resulted in a great depression of
the melting point of the mixture in comparison to the melting
point of the simple phthalide; the depression was from 223°
to 175°C. Due to this lowering of the melting point of the
mixture down to the melting point of the dioxanylphthalide
structure, the formation and purification of the latter compound
had to be done with extreme care. If the simple phthalide is
formed as an intermediate at the temperature of the reaction
under reflux, a longer reaction time should have converted it
to the dioxanylphthalide compound. The concentration of the
alcoholic filtrate, from which the dioxanylphthalide had been
recrystallized, revealed the presence of the simple phthalide.

The formation of the simple phthalide from 5-hydroxy-o-
toluic acid was another exception to Anderson's rule, resembling
5-methoxy-o-toluic acid. There is no methoxyl or any other para-
directing group in the 3-position. Here the two groups have
their para-directing powers mutually blocked. The occurrence
of the reaction can only be explained on the basis of the
secondary ortho-directing properties of the hydroxyl group.

The production of the dioxanylphthalide structure did
not seem to conflict with Anderson's ideas on similar compounds.
In the present case, there is a vacant ortho position next to
the hydroxyl group. Dioxane ring formation may be a secondary
reaction since the simple phthalide has been isolated and was

readily converted to the dioxanylphthalide structure.

The possibility of 5-hydroxy-o-toluic acid forming a dimer seems highly probable since it complies with two of the conditions, of which only one is needed, namely:

(1) there is a hydroxyl group in the 5-position of the original acid.

(2) there is no ortho-para directing group in the 3-position. Dimerization might be borne out by a small organic residue of very high indeterminable melting point separated from the hot alcoholic filtrate during the recrystallization of the lactone of 8-hydroxymethyl-1,3-benzodioxan-6-methyl-7-carboxilic acid. King and King (22) reported the isolation of a dimer under the same conditions.

PART II

The Attempted Condensations of 5-Bromo-o-Toluic Acid, m-Bromobenzoic Acid, 3-Hydroxyphthalide, and m-Aminobenzoic Acid

The preparation of 5-bromo-o-toluic acid was necessary before condensation experiments with formaldehyde and concentrated hydrochloric acid could be carried out. It was noticed that Jacobsen and Wierss (20) had claimed that the action of bromine on o-toluic acid gave 6-bromo-2-methylbenzoic acid of melting point 167°C. Beilstein and Heilbron reported the presence of two acids, one melting at 167°C. and the other at 174-6°C., as 5-bromo-2-methylbenzoic acid (XXXII). Meyer (26) synthesized 5-bromo-2methylbenzoic acid melting at 167°C. from p-toluidine.

Keuning and Evenhuis confirmed that Victor Meyer's acid was
identical with Jacobsen and Wierss' product; both melting on
recrystallization from alcohol at 170°C. In addition, they
proved that the acid melting at 174-6°C. was impure 4-bromo-
2-methylbenzoic acid.

The failure of 5-bromo-o-toluic acid (XXXII) to condense
even though 5-methoxy-o-toluic acid and 5-hydroxy-o-toluic were
successful in forming simple phthalides, seemed to substantiate
Vaven, Bolle, and Calin's (46) theory that the bromine group
was not as active as the methoxyl or hydroxyl group.
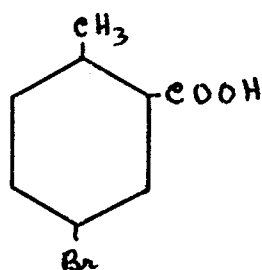
$$\text{X X X I I}$$
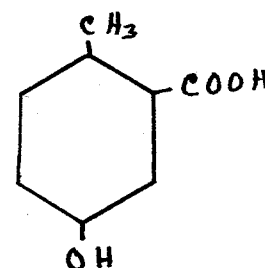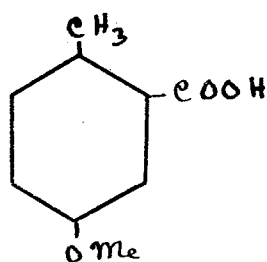
The bromine group may assist the rate of phthalide formation
if other activating groups bearing on the 6-position are present;
for example, 5-bromo-m-toluic acid (XXXIII). If the para-directing
powers of the bromine group are stronger that the ortho oreintating
forces, then 3-bromo-o-toluic acid (XXXIV) could be chloromethyl-
ated to form a lactone under suitable conditions. This seems
highly improbable since m-bromobenzoic acid did not react which
indicated that the bromine group alone is insufficient to
activate the benzene ring.
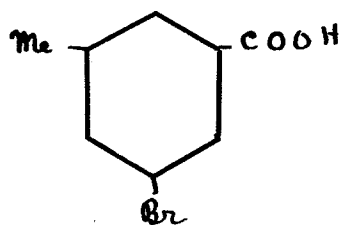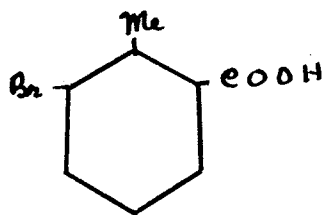
XXXIII   XXXIV
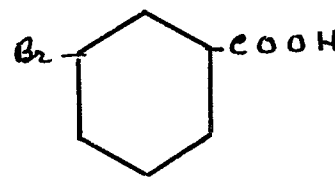
In the process of bromination of o-toluic acid, the
2-bromomethyl benzoic acid (XXXV) was prepared. The stability
of a bromomethyl group ortho to a carboxyl group indicates
the possibility of a bromomethylation; maybe chloromethylation
without lactone formation. The 2-bromomethyl benzoic acid
was quite stable in contact with concentrated hydrochloric
acid but not in the presence of alkali. It was reported in
Beilstein that in the presence of alkali, the phthalide
(XXXVl) is formed.
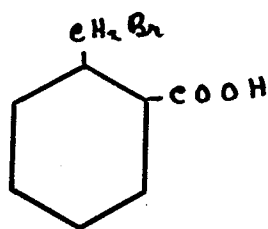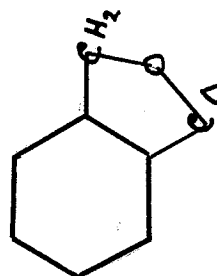
XXXV   XXXVI

The attempt to prepare 3-hydroxyphthalide by the direct
condensation of m-hydroxybenzoic acid with formaldehyde and
hydrochloric acid, as had been reported by Winestock (48),
resulted in the recovery of the original material with no

indication of a positive phthalide test. The 3-hydroxyphthalide
was prepared as directed by Buehler, Powers, and Michels (7).
Next, Winestock claimed that the condensation of 3-hydroxy-
phthalide with formaldehyde and hydrochloric acid formed the
lactone of 8-hydroxymethyl-1,3-benzodioxan-7-carboxylic acid.
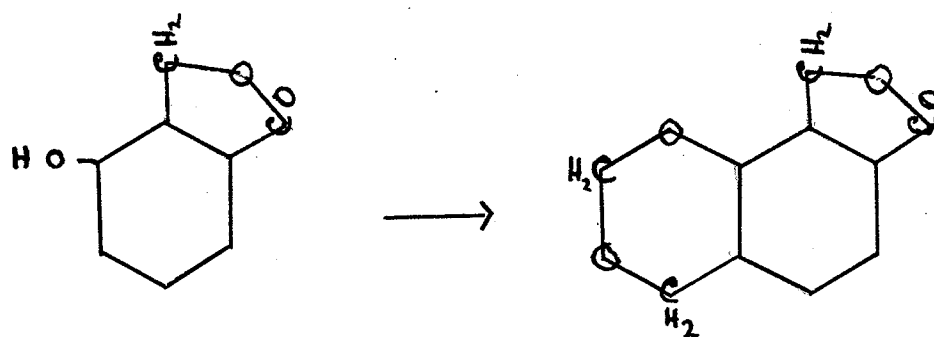
The repetition of this experiment produced only a dimer of
high indeterminable melting point.

The condensation of m-aminobenzoic acid led to the isolation
of a green, nitrogen-containing substance, melting around 220° C.
with decomposition. It was not acidic; might be basic since it
dissolved in hydrochloric and sulphuric acid. It was insoluble
or sparingly soluble in the common organic solvents. If
diazotization did occur, no coupling with β -naphthol was
observed as in the case of m-aminobenzoic acid. The only
indication of a phthalide ring test, according to the directions
of Thorpe and Whiteley (45), was the formation of a green color
on the addition of excess alkali to the light blue solution.

EXPERIMENTAL

Section One

The Action of Concentrated Hydrochloric Acid and Formaldehyde on 5-Hydroxy-o-Toluic Acid

Preparation of 5-Hydroxy-o-Toluic Acid

(a) o-Toluic Nitrile

The preparation of o-toluic nitrile from o-toluidine by the Sandmeyer method, consists of the action of cuprous cyanide on the diazonium salt of o-toluidine, by the method outlined in Organic Syntheses by Gilman and Blatt (18).

$$CH_3C_6H_4NH_2 + HCl + HNO_2 \longrightarrow CH_3C_6H_4N_2Cl + H_2O$$
$$CH_3C_6H_4N_2Cl + CuCN \longrightarrow CH_3C_6H_4CN + N_2 + CuCl$$
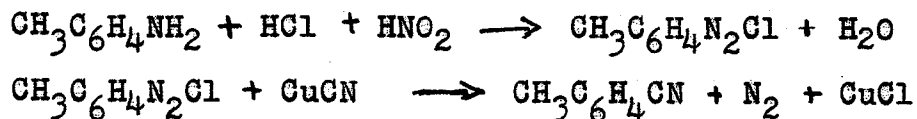
(1) Preparation of Cuprous Cyanide Solution

Cuprous chloride was prepared by adding a solution, consisting of 55 grams (0.5 moles) sodium bisulphite and 35 grams (0.9 moles) sodium hydroxide in 400 cc. of water, to a solution, consisting of 260 grams (1 mole) crystallized copper sulphate and 94 grams (1.6 moles) sodium chloride in 800 cc. water, over a period of fifteen minutes. The cuprous chloride, a white precipitate, was washed with water twice by decantation and suspended in 500 cc. of cold water in a two litre flask fitted with a mechanical stirrer. Solid sodium cyanide, 127 grams, (2.6 moles) was added in small portions

and the mixture was stirred until all the cuprous chloride
had reacted. The solution was cooled.

(ii) Preparation of the diazonium solution

In a large beaker, 86 grams (0.8 mole) of o-toluidine
was mixed with 228 cc. of 37% hydrochloric acid (sp.gr. 1.18)
and about 800 grams of ice to bring the temperature of the
mixture to 0°C. A solution of 56 grams (0.8 mole) of sodium
nitrite in 160 cc. of water was added, with stirring, to the
o-toluidene hydrochloride over a period of fifteen minutes,
the temperature being kept at 0-5°C. by the addition of
cracked ice; the addition was completed when the mixture
showed a distinct test for free nitrous acid on testing with
starch iodide paper. The mixture was carefully neutralized
with approximately 40 grams of anhydrous sodium carbonate as
indicated by the litmus paper.

(iii) Preparation of o-toluic nitrile

The cold cuprous cyanide solution was chilled to 0-5°C.
by the addition of ice, and 500 cc. of toluene was poured on
the surface. To this mixture was added slowly the cold dia-
zonium solution. During the addition, which required sixty
minutes, vigorous stirring was maintained and the temperature
was kept at 0-5°C. by occasionally adding cracked ice. An
orange precipitate was formed, which in turn, decomposed giving
off nitrogen gas; the resulting nitrile was taken up by the
toluene layer as indicated by its reddish color. After the
addition, the reaction mixture was stirred and kept at 0-5°C.
for thirty minutes and then was allowed to rise to that of

room temperature and left standing overnight. After stirring

for two hours longer, the motor was stopped and the reaction

mixture was warmed to 50°C. by means of a large water bath.

The mixture was allowed to stand until cool, then the aque-

ous layer was siphoned off. The residue toluene mixture was

steam distilled until no more oil passed over. The toluene

layer containing the nitrile was separated and the aqueous

portion of the distillate was extracted with small portions

of toluene. The toluene layer was removed by simple distil-

lation and the impure nitrile was purified by the use of

fractional distillation under reduced pressure. The portion

which boiled over at 90-96°C. / 20 mm. pressure was collected.

The yield of 58 grams of slightly yellow-coloured o-tolunitrile

was 62 per cent of the theoretical amount.

(b) o-Toluic acid

Cohen's method for the preparation of o-toluic acid by

the hydrolysis of o-toluic nitrile with 75% sulphuric acid

under reflux gave in our case, 20-30% yields on recrystalliz-

ation from water. When the crude toluic acid was placed in

hot water, the impurities separated in the form of an oily

brown layer. The nature of this layer may be due to either

decomposition or sulphonated products. Senderens and Abou-

lenc (38) reported that the use of concentrated sulphuric

acid at 150°C. in the sulphonation of o-toluic acid did lead

to some decarboxylation. When a higher concentration of sulph-

uric acid was employed the yields were poorer and the impuri-

ties were of a still darker oily nature. The solubilities of the organic acid or acid impurities may have caused the existence of a miscibility gap, but this seemed highly improbable as no such oil phase appeared on acidification of the hot alkaline solution of o-toluic acid with dilute sulphuric acid.

Blatt's (5) method was a decided improvement in the hydrolysis of o-toluic nitrile. The slow addition of the nitrile to the hot sulphuric acid solution with stirring provided better contact between the reacting substances. Secondly, the proportions of nitrile to sulphuric acid were half as great as that employed in sulphonations. Thus, the possibility of decomposition products would be lessened. Thirdly, the purification of the organic acid by conversion to the sodium salt, assisted in the recovery of the possible intermediate by-product toluamide which could be rehydrolyzed to o-toluic acid. Hydrolysis with 90% sulphuric acid instead of approximately 75% sulphuric acid (sp. gr. 1.67) gave poorer yields. Another modification with 43% sulphuric acid resulted in the recovery of over 63% of the o-toluic nitrile. Concentrated hydrochloric acid was useless as a hydrolyzing agent since over 60% of the nitrile was recovered with only a trace of o-toluic acid. The slow addition of nitrile and a longer heating rate at 150-160°C. are recommended for better yields. The crystallization of o-toluic acid from benzene may be improved by the use of a benzene-petroleum ether mixture.

A supply of o-toluic acid may be built up (1) by the

action of solid carbon dioxide on the Grignard of o-bromo-
toluene, (2) by the alkaline hydrolysis of o-toluic nitrile,
and (3) by the preparation of o-toluamide by Vogel (47)
through the action of hydrogen peroxide on o-toluic nitrile
and subsequent hydrolysis.

o-Toluic acid was prepared by hydrolysis of o-toluic
nitrile by method outline in Organic Syntheses by Blatt (5).
In a three necked flask fitted with a mechanical stirrer, re-
flux condenser, and separatory funnel was placed 200 grams of
74% sulphuric acid (sp. gr. 1.67). The solution was heated to
140°C., the stirrer started and o-toluic nitrile, 60 grams
(0.51 mole), was added over a period of four hours. The temp-
erature was raised to 190°C. for one hour. The reaction mixture
was cooled, poured into ice water, and filtered. The crude
precipitate was dissolved in an excess of 10% sodium hydroxide
solution, filtered hot to remove insoluble toluamide, and the
filtrate acidified with dilute sulphuric acid. The crude
precipitate (67 grams) was dried and recrystallized from
benzene. The yield of o-toluic acid, melting at 102-103°C.
was 33 grams or 47% of the theoretical.

(c) The potassium salt of 5-sulpho-o-toluic acid

Direct mono-sulphonation of o-toluic acid by commercial
concentrated sulphuric acid employing the method of Meldrum
and Perkins (25), resulted in a charry mass. Senderens and
Aboulenc (38) suggested the use of fuming sulphuric acid (20%
SO_3 content) below 100°C. instead of concentrated sulphuric
acid at higher temperatures. A sulpho-o-toluic acid was

formed at the lower temperature without any decomposition. However, the precipitate formed seemed quite deliquescent and very difficult to purify by washing with very minute amounts of water. This resulted in poor alkali fusions and consequently poor yields of 5-hydroxy-o-toluic acid. Good yields were obtained by conversion to the potassium salt of 5-sulpho-o-toluic acid by the method of Ashino and Asano (2) after sulphonation with fuming sulphuric acid (20% SO_3 content).

Method of Senderens and Aboulenc (38) combined with Ashino and Asano (2) led to a potassium salt of 5-hydroxy-o-toluic acid in good yield. A mixture of 10 grams toluic acid and 60 grams of fuming sulphuric acid (20% SO_3 content) was heated around 90-100°C. for eight hours. It was then cooled, dissolved in 250 cc. of water, neutralized first with solid barium hydroxide, and then with barium carbonate until it was faintly basic as indicated by litmus paper. The barium sulphate was filtered off from the wash liquid. The combined filtrates were evaporated down to a 100 cc. A slight residue of barium sulphate was filtered off. The filtrate was acidified with concentrated hydrochloric acid to bring down the white precipitate of the barium salt of 5-sulpho-o-toluic acid. The precipitate was filtered and washed with a small amount of water. The filtrate was evaporated down to half its original volume and cooled to give more barium salt of sulpho-o-toluic acid which was filtered off and washed with water. Total yield was 20 grams. Potassium carbonate

solution, 15 grams in 200 cc. of water, was added to the
solution of barium salt in 200 cc. of hot water until the
latter solution was basic (precipitation of barium carbonate
ceased). The barium carbonate was filtered off. Evaporation
of the filtrate to dryness yielded a gummy precipitate of the
potassium salt.

(d) <u>Alkali fusion of the potassium salt of 5-sulpho-o-toluic acid</u>

The later stage of the evaporation of the potassium salt
was done in a nickel crucible. Cautiously, potassium hydroxide
pellets, 83 grams, were added in small portions to the potass-
ium salt in the crucible at 200-210°C. After the addition was
completed, the temperature was raised to 260°C. for 45 minutes.
The sample was cooled and leached with 250 cc. of hot water,
the resulting solution was neutralized with 20% sulphuric acid
and made just basic with a few pellets of potassium hydroxide.
On cooling a large quantity of potassium sulphate settled out
and was filtered off. The filtrate was evaporated to about
150 cc., cooled, and more potassium sulphate removed. On
acidifying the solution with concentrated hydrochloric acid
5-hydroxy-o-toluic acid (4.7 grams) was precipitated. Con-
centration of the filtrate to half its original volume gave
0.6 gram. The yield of the product, melting at 183-184°C.
was about 47% theoretical, based on o-toluic acid.

Preparation of the Lactone of 8-Hydroxymethyl-1,3-Benzodioxan-6-Methyl-7-Carboxylic Acid (XXVI)

(a) Methylation of 5-hydroxy-o-toluic acid

The method of Tambor (43) was used. The 5-hydroxy-o-toluic acid (8.4 gm.) was dissolved in 20% sodium hydroxide solution (42 gm.) in a three neck flask. While the solution was stirred in an inert atmosphere of nitrogen, dimethyl sulphate (12.2 gm.) was added drop by drop over a period of fifteen minutes. The reaction mixture was stirred a half hour longer, then sodium hydroxide (2.1 gm.) was added and the mixture refluxed for 45 minutes to destroy any excess dimethyl sulphate. The solution was cooled and the sodium sulphate which came down was filtered off. The filtrate was acidified with concentrated hydrochloric acid to give a white precipitate which was filtered, washed with water, and dried. The yield of 5-methoxy-o-toluic acid of M.P. 144-145°C. was 65% of the theoretical.

(b) 3-Methoxy-6-methylphthalide

Rennie's (34) method was used. A mixture of 5-methoxy-o-toluic acid (5.9 gm.), concentrated hydrochloric acid (35 cc.), and 40% formaldehyde (35 cc.) was refluxed on a steam bath for four hours and then over a wire gauze for one hour. The crude product was filtered off, washed with water, dried, and then recrystallized from 95% ethyl alcohol to give 3-methoxy-6-methylphthalide (3.6 gm. or 60% of theoretical) of melting

melting point 165-166°C.

(c) 3-Hydroxy-6-methylphthalide (XXV)

A mixture of 3-methoxy-6-methylphthalide (2.0 gm.), 50%
hydrogen iodide (20 cc.), and red phosphorus (5 gm.) was re-
fluxed gently on a steam bath in an inert atmosphere of nitro-
gen for 3 hours. The solid material was filtered off, washed
with water, and treated with hot alcohol. Charcoal was added
to the solution to remove traces of color impurities. The
filtrate was concentrated to a small volume, 20-30 cc., and
cooled in the refrigerator. White precipitate which settled
out was filtered off. The yield was 0.7 gm. of M.P. 223-224°C.
Further concentration of solution gave 0.1 gm. of M.P. 223-
224°C. Total yield of 3-hydroxy-6-methylphthalide was 44%
of theoretical.

Anderson used a modification of the method of Fernholtz
and Finklestein (15) which in his case gave better demethyl-
ation results with no resinous precipitate. A mixture of 3-
methoxy-6-methylphthalide (1.1 gm.) and anhydrous aluminum
chloride (2.7 gm.) in dried benzene (40 cc.) was refluxed for
ten hours on a water bath at 60-70°C. The solid was filtered
off, washed with water, and dried. Crude product was re-
crystallized from 95% ethyl alcohol to give 0.26 gm. of M.P.
223-224°C. This yield was about 26% of theoretical. 3-Hydroxy-
6-methylphthalide gave the phthalide ring test according to
Thorpe and Whitely's (45) directions. This simple phthalide
was soluble in ethyl alcohol, acetone, and ether. It was

soluble in hot sodium hydroxide but insoluble in water and in 5% sodium bicarbonate solution.

Analysis

Combustion of 3-hydroxy-6-methylphthalide was done on a semi-micro scale according to the method devised by Sucharda and Bobranski (42).

Material	Determination	
	Trial 1. Weight in Milligrams	Trial 2. Weight in Milligrams
Sample	36.92	38.23
$CaCl_2$ tube after combustion	122.98	140.56
$CaCl_2$ tube before combustion	106.50	123.53
H_2O absorbed	16.48	17.03
Ascarite tube after combustion	309.10	401.65
Ascarite tube before combustion	220.01	309.48
CO_2 absorbed	89.09	92.17

Percentage Hydrogen $\quad \dfrac{11.19 \times 16.48}{36.92} = 4.99\% \quad \dfrac{11.19 \times 17.03}{38.23} = 4.98\%$

Percentage Carbon $\quad \dfrac{27.273 \times 89.09}{36.92} = 65.81\% \quad \dfrac{27.273 \times 92.17}{38.23} = 65.75\%$

Calculated for $C_9H_8O_3$ $\qquad$ % H = 4.88% $\qquad$ % C = 65.85%

Molecular weight determination of 3-hydroxy-6-methylphthalide

The cryoscopic method as given by Fisher (16) and Belcher and Godbert (3) was used to determine the molecular weight of 3-hydroxy-6-methylphthalide. This phthalide was dissolved in hot camphor to form a solution which on cooling produced a homogeneous solid. By means of the apparatus designed by

Pritchard (30), the melting points of the mixture and pure camphor were obtained. Since the depression of the melting point, the composition of the mixture, and the molal depression constant of camphor were known, it was possible to calculate approximately the molecular wieght of the 3-hydroxy-6-methylphthalide.

Trial No.	Melting point of Camphor	of Mixture	Difference	Calculated Molecular Weight	Deviation
1	174.7	162.0	12.7	175	+ 6
2	173.0	159.6	13.4	166	- 3
3	172.1	159.3	12.8	173	+ 4
4	171.3	157.1	14.2	157	- 12
5	172.3	159.3	13.0	171	+ 2
6	169.7	157.0	12.7	175	+ 6
7	170.7	158.0	12.7	175	+ 6
8	172.3	158.6	13.7	162	- 7
		Average	13.15	169	± 6

Weight of Hydroxyphthalide $=$ 7.57 mg.
Weight of Camphor $=$ 143.70 mg

Rate of heating $=$ 0.5°C. per 30 seconds

$$M = \frac{1000\ K\ W}{w\ d}$$ where
W $=$ weight of solute
w $=$ weight of solvent
K $=$ 40.0
d $=$ difference in melting point between camphor and mixture

$$M = \frac{1000 \times 40 \times 7.57}{143.70 \times 13.15} = 169 \pm 6$$

Calculated value for $C_9H_8O_3$ = 164

(d) <u>Preparation of the lactone of 8-hydroxymethyl-1, 3-</u>
<u>benzodioxan-6-methyl-7-carboxylic acid (XXVI) from the con-</u>
<u>densation of 3-hydroxy-6-methylphthalide</u>

A mixture of 3-hydroxy-6-methylphthalide (0.5 gm.),
concentrated hydrochloric acid (10 cc.), and 40% formal-
dehyde (10 cc.), was heated under reflux on a water bath
for four hours. The solution was cooled, solid was fil-
tered off, washed with water and dried to give a crude product
(0.61 gm.) of M.P. 168-171°C. The crude product was recrys-
tallized from 95% ethyl alcohol to give 0.45 gm. melting at
171-172°C. The yield was 73% of the theoretical. A mixed
melting point with the product below showed no depression
of the melting point. This confirmed the compound as the
lactone of 8-hydroxymethyl-1,3-benzodioxan-6-methyl-7-
carboxylic acid.

(e) <u>Preparation of the lactone of 8-hydroxymethyl-1,3-</u>
<u>benzodioxan-6-methyl-7-carboxylic acid (XXVI) and 3-hydroxy-</u>
<u>6-methylphthalide (XXV) from the condensation of 5-hydroxy-</u>
<u>o-toluic acid</u>

A mixture of 5-hydroxy-o-toluic acid (16.1 gms.), con-
centrated hydrochloric acid (160 cc.), and 40% formaldehyde
(160 cc.) was placed in a flask fitted with a reflux condenser
and was allowed to stand overnight. A reaction was observed
in the flask. Some of the solid on top of the liquid layer
was extracted, washed with water and dried to give 1-2 grams
of white solid melting at 221-223°C., which on recrystalliz-
ation from ethyl alcohol raised it to 223-224°C. A mixed

melting point with 3-hydroxy-6-methylphthalide showed no
depression of the melting point. This showed that the
simple phthalide reaction occurred at room temperature. A
mixed melting point with the 8-hydroxymethyl-1,3-benzodioxan-
6-methyl-7-carboxylic acid showed a depression from 223°C.
down to 175°C. The remainder of the mixture was heated under
reflux on the water bath for nine hours. The crude product
was filtered off, washed with water, dried and weighed to
give a white solid (18.9 gm.) of melting point 169-173°C.
Addition of water to the filtrate to twice its original
volume yielded no further precipitate. The crude precipi-
tate was dissolved in 1000 cc. of hot 95% ethyl alcohol, but
not completely, since a residue was filtered off which showed
no signs of melting. The alcoholic filtrate was treated with
charcoal to remove color impurities, filtered hot, and cooled
to give the lactone of 8-hydroxymethyl-1,3-benzodioxan-6-
methyl-7-carboxylic acid (13.2 gm.) of melting point 171-
172°C. This yield was 60% of theoretical. The dioxanyl-
phthalide crystallized from acetone in the form of character-
istic, long needle-shaped crystals. It was soluble in hot
benzene, carbon tetrachloride, and ether. It was very spar-
ingly soluble in hot 10% sodium hydroxide solution. An orange-
red precipitate was obtained on warming the dioxanylphthalide
(0.23 gm.) with 30cc. of a solution of phloroglucinol (3 gm.)
in 60 cc. concentrated sulphuric acid and 200 cc. of water at
80 - 90°C. for two hours. The blank run with 5-hydroxy-o-toluic

acid gave a dark reddish-orange solution under the same conditions. On standing, the latter solution formed a red precipitate. Evaporation of the alcoholic filtrate to a fairly small volume (30-40 cc.) gave a mixture (1.0 gm.) of melting point 167-215°C. which indicated a mixture of the dioxanylphthalide and the simple phthalide.

Analysis

Calculated value for the lactone of 8-hydroxymethyl-1, 3-benzodioxan-6-methyl-7-carboxylic acid was $C = 64.08\%$ and $H = 4.85\%$. Combustion was done on a semi-micro scale according to the method devised by Sucharda and Bobranski (42).
Experimental values obtained were: 1) $C = 63.85\%$ $H = 4.53\%$

2) $C = 64.07\%$ $H = 4.91\%$

Molecular weight determination was carried out by the cryo-scopic method as outlined for the analysis of 3-hydroxy-6-methylphthalide.

Trial No.	Melting Point of Camphor	of Mixture	Difference	Calculated Molecular Weight	Deviation
1	173.0	165.3	7.7	210	+6
2	173.3	165.7	7.6	213	+ 7
3	173.3	165.2	8.1	200	- 4
4	175.3	167.0	8.3	195	- 9
5	173.5	165.5	8.0	202	- 2
		Average	7.94	204	± 5.6

Weight of lactone = 8.55 mg.
Weight of camphor = 211.09 mg.
Average rate of heating = 0.5°C per 40 seconds

Molecular weight $= \dfrac{1000 \times 40 \times 8.55}{211.09 \times 7.94} = 204 \pm 5.6$

Calculated value for $C_{11}H_{10}O_4 = 206$

The Attempted Oxidation of the Lactone of 8-Hydroxymethyl-1, 3-Benzodioxan-6-Methyl-7-Carboxylic Acid

A mixture of the lactone of 8-hydroxymethyl-1,3-benzodioxan-6-methyl-7-carboxylic acid (2.1 gm.), potassium hydroxide (6.6 gm.), and water (75 cc.) was heated until a yellow solution had occurred. Then a solution of potassium permanganate (6.0 gm.) in water (120 cc.) was added dropwise with stirring to the above solution over a period of 1.5 hours. The reaction mixture was allowed to stand overnight. A slight amount of sodium bisulphite was added to convert the excess permanganate and manganate ions to manganese dioxide. The manganese dioxide was filtered off and treated with water. The filtrates were combined, slightly acidified, and evaporated down to a volume of 100 cc. The precipitated inorganic salts were filtered off from the basic solution. The filtrate (1) was acidified with concentrated hydrochloric acid and refrigerated for one hour. The precipitate (1) was filtered off and dissolved in a minimum amount of 5% sodium bicarbonate solution. The insoluble precipitate was treated with acetone. Evaporation of the acetone to a small volume gave white needle-like crystals which was identified as unreacted dioxanylphthalide. The filtrate (2) was strongly acidified with concentrated hydrochloric acid, refrigerated, and allowed to stand overnight. The precipitate (2) which was separated, contained inorganic and organic matter. In

sodium bicarbonate solution, precipitate (2) caused the solution to exhibit a blue fluorescence. The extraction of precipitate (2) with acetone led to the isolation of a white solid (3) which possessed an indeterminable melting point and which was soluble in ethyl alcohol. The solid (3) was organic in nature. The concentration of the acidified filtrate (1), by the slow evaporation at room temperature, gave about 0.2 gm. of organic material (4) melting at 270-274°C. with decomposition. Solid (4) was treated with boiling acetone. The insoluble portion (5) was filtered off and dried to give an acidic substance (p.1 gm.) of melting point 283°C. (corrected temperature 271°C) with decomposition. The precipitate (5) dissolved in 5% sodium bicarbonate solution with evolution of carbon dioxide and formation of a yellow solution. The soluble acetone portion (7) was found to contain unreacted dioxanylphthalide and some acidic organic material. Since Buehler, Harris, Schaklett, and Block (8) performed the same type of oxidation on a similar structure, both products might be dibasic acids.

Brominations of o-toluic acid

The first bromination was attempted at room temperature instead of in the cold as suggested by Jacobsen and Wierss (20). An excess of bromine (12.0 gm.) was allowed to stand overnight with o-toluic acid (5.0 gm.). The solid was filtered off, washed with water, and digested with sodium carbonate solution. After prolonged digestion, a slight residue was removed by filtration. The addition of concentrated hydrochloric acid to

the filtrate, precipitated a crude white solid of melting point range of 120-135°C. The treatment with water of a solution of the crude precipitate in ethyl alcohol gave a white precipitate (0.1 gm.) melting at 164-167°C. Further minute additions of water to the filtrate gave more precipitate of melting point 120-135°C. The repetition of dissolving this crude precipitate of melting point 120-135°C. in ethyl alcohol, then reprecipitating with minute additions of water gave more of the higher melting product of 164-167°C. but in very small quantity.

Secondly, to a cooled solution of o-toluic acid (5.0 gm.) in excess carbon tetrachloride (50 cc.) was added a solution of bromine (5.9 gm.) in carbon tetrachloride (53.0 gm.) in small portions, with stirring, over a period of three hours. On standing one day, the solution had decolorized and deposited a white solid which was filtered off, washed with carbon tetrachloride, and dried. The crude product (6.0 gm.) of melting point 140-145°C. was washed with benzene to remove any unreacted o-toluic acid and dried to give a melting point of 141-142°C. The recrystallization of this latter solid from ether raised the melting point of the substance to 145-146°C. Beilstein listed 2-bromomethylbenzoic acid as having a melting point of 147°C. on recrystallization from ether. It was also reported by Sampey, Fawcett, and Morehead (37) that bromination of the side chain of toluic acids occurred in solvents such as carbon tetrachloride, carbon disulphide, etc.

The third bromination incorporated some of the features of the methods used by Jacobsen and Wierss (20), Racine (32), and Keuning and Evenhuis (21). o-Toluic acid (4.73 gm.) was added with stirring over a period of two and a half hours.

to bromine (12.0 gm.) in a beaker immersed in an ice salt
bath. Hydrogen bromide fumes were evolved during the reaction
so the process was carried out in the fume chamber. The
mixture was stirred for two more hours before being left to
stand for 24 hours. Next, it was placed over sodium hydroxide
in a vacuum dessicator under suction by a water aspirator for
eight hours. The sample was digested in sodium carbonate
solution for half an hour. A slight residue was filtered
off. The filtrate was cooled, acidified with concentrated
hydrochloric acid, and filtered to give a crude precipitate
(13.0 gm.) of melting point 128-153°C. This precipitate was
dissolved in hot carbon tetrachloride; a slight residue of
indeterminable melting point was filtered off. The solution
on cooling, gave a white solid (2.86 gm.) of melting point
158-164°C. Successive recrystallization from carbon tetra-
chloride raised the melting point to 168-170°C. Keuning and
Evenhuis reported a melting point of 170°C. This yield of
5-bromo-o-toluic acid was 38% of the theoretical. Evaporation
of the filtrate to half its original volume gave on cooling
crude toluic acid (2.0 gm.) of melting point 110-118°C.

Preparation of s-dichloromethyl ether

An attempt was made to produce a stronger chloromethyl-
ating mixture than a mixture of 40% formaldehyde and concen-
trated hydrochloric acid. Stephen, Gladding, and Short (40)
prepared s-dichloromethyl ether from the action of hydrogen
chloride gas on formaldehyde solution. Since the above authors
stated the decomposition of the ether by water, it was decided

to use a dehydrating agent. 40% Formaldehyde solution (184 gm.) was allowed to trickle slowly down through solid anhydrous zinc chloride (410 gm.) into an upright air condenser filled with glass beads. At the same time, a stream of dry hydrogen chloride generated by the action of concentrated sulphuric acid on solid sodium chloride was passed up the column. The column became quite warm due to the occurrence of the reaction. A heavy yellow oily liquid was collected in the receiver attached to the bottom of the column. The yield of crude s-dichloromethyl ether (187 gm.) was 53% of the theoretical.

Attempted condensations of 5-bromo-o-toluic acid with formaldehyde in the presence of concentrated hydrochloric acid

In the flask fitted with a condenser were placed 5-bromo-o-toluic acid (2.2 gm.) of melting point 160-164°C., concentrated hydrochloric acid (20 cc.), and 40% formaldehyde (13 cc.). The mixture was refluxed on a water bath at 90°C. for eight hours. No reaction was observed. The solid was filtered off, washed with water, and dried to give 2.0 gm. of melting point 159-164°C. This product was identical with the starting material. Addition of water to the filtrate did not cause the precipitation of more solid. The filtrate was extracted with ether. The ether layer was separated from the aqueous solution and dried with sodium sulphate. A slight trace of a white solid was obtained on evaporation of the ethereal solution. The residue was soluble in hot carbon tetrachloride. On the basis of solubility, the residue could have been unchanged 5-bromo-o-toluic acid.

Attempted condensation of 5-bromo-o-toluic acid with s-dichloromethyl ether at room temperature

5-Bromo-o-toluic acid (2.0 gm.) of melting point 159-164°C. was dissolved in ethyl alcohol (10-20 cc.). The addition of s-dichloromethyl ether (27 gm.) caused the precipitation of a white solid. This mixture was allowed to stand at room temperature for one day. The presence of the alcohol seemed to cause the formation of two layers. The solids obtained from both layers melted around 162-166°C. The main precipitate (1.8 gm.) on filtration melted at 161-164°C. The addition of water to the filtrate resulting after the separation of 1.8 gm. gave more precipitate (0.2 gm.) of melting point 161-164°C. This precipitate was soluble in ether. The solid (1.8 gm.) was dissolved in hot carbon tetrachloride, cooled, refrigerated overnight, filtered, and dried to give 0.93 gm. melting at 166-169°C. The distillation of the carbon tetrachloride yielded a crude residue of melting point 115-119°C. which was confirmed as o-toluic acid.

Attempted condensation of 5-bromo-o-toluic acid with s-dichloromethyl ether at 70°C.

5-Bromo-o-toluic acid (2.86 gm.) of melting point 160-164°C. and s-dichloromethyl ether (33 gm.) was heated under reflux at 70°C. for four hours. No apparent reaction was observed. After cooling the mixture, the precipitate was filtered off, washed with water, and dried to give a white solid (2.70 gm.) of melting point 156-160°C. The addition of

water to the filtrate gave a negligible precipitate. Recrystallization of 2.70 gm. of white solid from carbon tetrachloride resulted in a yield of 1.74 gm. of melting point 165-167°C. Another recrystallization raised it to 166-168°C. Evaporation of the first carbon tetrachloride filtrate gave a residue of 0.22 gm. Some of the substance must have volatized or had been lost in transfer.

Attempted condensation of 5-bromo-o-toluic acid with s-dichloromethyl ether in the presence of aluminum chloride

A mixture of 5-bromo-o-toluic acid (1.3 gm.) of melting point 154-161°C., s-dichloromethyl ether (28 gm.) and anhydrous aluminum chloride (1.0 gm.) was heated under reflux at 70°C. for three hours. The white solid was filtered and washed with water in order to remove a resinous material. Three solid samples of weights, 0.80, 0.40, and 0.14 gm., and of melting points, 155-162°C., 151-156°C., and 149-158°C. respectively, were isolated. Treatment of the combined samples with ethyl alcohol to remove any residual aluminum chloride gave on distillation a white solid (1.3 gm.) of melting point 154-161°C.

Attempted condensation of 5-bromo-o-toluic acid with s-dichloromethyl ether in the presence of concentrated sulphuric acid

A mixture of 5-bromo-o-toluic acid (4.1 gm.) of melting point 160-166°C., s-dichloromethyl ether (80 gm.), and concentrated sulphuric acid (10 cc.) was heated at 60°C. for two hours and at 90°C. for another hour and on a wire gauze for

half an hour. It was filtered, precipitate washed with
water (over 250 cc.), and dried. The filtrate was evaporated
to dryness. The residue was treated with hot carbon tetra-
chloride. The latter was separated and evaporated to dryness.
However, no precipitate was present in the carbon tetrachloride
solution. Crude white product (10.8 gm.) had a very wide
melting point range from 160-265°C. with some unmelted solid
still present. Some of this substance (2.2 gm.) was dissolved
in hot water. An insoluble residue (0.23 gm.) of melting point
161-164°C. was filtered off while the solution was hot. On
cooling, a yield of white solid (0.06 gm.) of melting point
162-166°C. was isolated. The remainder of the solid (8.6 gm.)
was dissolved in hot carbon tetrachloride (200 cc.). An
insoluble inorganic residue (5.1 gm.) was isolated. The
filtrate was concentrated down to 50 cc., cooled, and filtered
to give a white crystalline solid (2.35 gm.) which was iden-
tified as 5-bromo-o-toluic acid melting at 169-170°C. Con-
centration of the carbon tetrachloride filtrate gave a white
solid (0.25 gm.) of melting point 135-157°C. This solid was
soluble in ethyl alcohol. It dissolved in 5% sodium bicarbonate
solution with evolution of carbon dioxide.

Attempted condensation of m-bromobenzoic acid with formal-
dehyde in the presence of concentrated hydrochloric acid

A mixture of m-bromobenzoic acid (5.0 gm.), concentrated
hydrochloric acid (25 cc.), and 40% formaldehyde (40 cc.) was

refluxed on a steam bath for 105 minutes. No apparent reaction was observed. The solid was filtered off, washed with water, and dissolved in hot water. An insoluble residue was isolated and identified as m-bromobenzoic acid of melting point 154-155°C. The filtrate on cooling gave 1.0 gm. of m-bromobenzoic acid melting at 153-155°C. A mixed melting point determination showed no depression in the melting point.

Preparation of 3-hydroxyphthalide by the condensation of m-hydroxybenzoic acid

Winestock (48) stated that 3-hydroxyphthalide could be prepared by heating under reflux a mixture of m-hydroxybenzoic acid (5.0 gm.), 40% formaldehyde solution (25 cc.), and concentrated hydrochloric acid (30 cc.) for 20 minutes. No apparent reaction could be observed. The recovered material exhibited the same solubilities as the starting substance. A negative phthalide test was obtained with the isolated material.

The method of Buehler, Powers, and Michels (7) was used in the preparation of 3-hydroxyphthalide. m-Hydroxybenzoic acid (5.0 gm) was dissolved in 100 cc. of 40% formaldehyde solution with stirring. Then a mixture of 100 cc. of concentrated hydrochloric acid and 5 cc. of concentrated sulphuric acid was added. The solution was stirred at 30-40°C. while dry hydrogen chloride gas was slowly bubbled through the solution over a period of two hours. The excess hydrogen chloride was removed through

an exhaust tube which was attached to a water aspirator pump.
The white precipitate which came out of solution was filtered
off to give a crude product melting at 245-247°C. with decom-
position. One recrystallization from water gave 0.86 gm. of
3-hydroxyphthalide melting at 254-255°C. The filtrate on
refrigeration gave 1.43 gm. of a white solid melting at 144-
165°C. Dilution of the filtrate with water gave more pre-
cipitate (0.83 gm.) melting at 175°C. This latter substance.
was reported by Buehler, Harris, Schaklett, and Block (8)
to possess a dioxanylphthalide structure. This substance
was found to give an orange precipitate with phloroglucinol
and sulphuric acid.

The attempted condensation of 3-hydroxyphthalide

A mixture of 3-hydroxyphthalide (0.80 gm.), 40% formal-
dehyde (5 cc.), and concentrated hydrochloric acid (10 cc.)
was heated under reflux for one hour at 140°C. The solid
went into solution. On cooling the solution, a resinous
gum was formed. Addition of water to the filtrate caused a
white precipitate to come down. The white precipitate was
combined with the resin, then treated with ethyl alcohol.
However, no solid residue was present in the alcoholic
filtrate. The resin dissolved in acetone leaving behind
a white chalky organic solid (0.1 - 0.2 gm.) of high in-
determinable melting point. This chalky solid did not seem
to possess a dioxane ring according to Mehta and Ayyar's (24)
direction. Evaporation of the acetone filtrate gave back the

brown resinous gum. Ether extraction had no effect on this resin. The resin formed an orange precipitate when treated with phloroglucinol and sulphuric acid. Mehta and Ayyar's (24) instructions were followed.

Attempted Condensation of m-Aminobenzoic Acid

m-Aminobenzoic acid was placed in 40 cc. of concentrated hydrochloric acid. Then 40% formaldehyde (40 cc.) were added. The mixture was heated on an oil bath at 140°C. for two hours. A dark orange solution was formed during the reaction but disappeared after awhile. A creamy solid (1) was filtered off and washed with water. Solid (1) was treated with 5% sodium bicarbonate solution to remove any acidic substances. The residue solid (2) was found to be organic and to have an indeterminable melting point. The filtrate was treated with ether. A yellow-greenish solid (0.1 gm.) was obtained on evaporation of the ether solution. The filtrate was neutralized with sodium bicarbonate solution and concentrated down to a small volume. Acidification of this filtrate gave a darkish-brown solid (4). All the solids were combined, treated with 5% sodium bicarbonate, solution, then water, and ethyl alcohol, and dried. This purification of the condensation product of m-aminobenzoic acid led to the isolation of a green, nitrogen-containing substance, melting around 220°C. with decomposition. It was not acidic; might be basic since it dissolved in hydrochloric and sulphuric acid. It was insoluble or sparingly soluble in the common

solvents. If diazotization did occur, no coupling with
β-napthol was observed as in the case of m-aminobenzoic acid.
The only indication of a phthalide ring test, according to
the directions of Thorpe and Whiteley (45), was the formation
of a green color on the addition of excess alkali to the light
blue solution. The formation of this condensation product
from m-aminobenzoic acid might have been due to a Mannich
reaction in which an active hydrogen atom of the phthalide
ring had condensed with formaldehyde and the amino group.

SUMMARY

1. 3-Hydroxy-6-methylphthalide has been prepared for the first time by the demethylation of the known 3-methoxy-6-methylphthalide which had been identified by Rennie (34). It has been found also to be one of the condensation products of 5-hydroxy-o-toluic acid. Combustion data, molecular weight analyses, and condensation work gave substantial proof of its structure.

2. 3-Hydroxy-6-methylphthalide has been converted to the lactone of 8-hydroxymethyl-1,3-benzodioxan-6-methyl-7-carboxylic acid. This lactone has been obtained also from the condensation of 5-hydroxy-o-toluic acid. Combustion and molecular weight analyses indicated this structure as the other main product formed in the condensation of 5-hydroxy-o-toluic acid.

3. Oxidation of the lactone of 8-hydroxymethyl-1,3-benzodioxan-6-methyl-7-carboxylic acid in alkali solution with potassium permanganate gave an acidic substance melting at $283^{\circ}C$. with decomposition, probably dicarboxylic in behaviour.

4. The attempted condensations of 5-bromo-o-toluic acid and m-bromobenzoic acid, were not successful since the original material was recovered.

5. An attempt was made to convert Buehler's 3-hydroxyphthalide into a dioxanylphthalide structure by treatment with formaldehyde and hydrochloric acid. The isolation of a dimer

or resin was not in agreement with the work of Winestock.

6.   The condensation of m-aminobenzoic acid gave a dimer or resin, melting around 220°C. with decomposition.

RECOMMENDATIONS FOR FUTURE WORK

1)   The oxidative work on the lactone of 8-hydroxymethyl
-1,3-benzodioxan-6-methyl-7-carboxylic acid might be carried
out according to the method of Buehler, Slack, Shirley,
Sanguinetti, and Frey (10).

2)   Chromyl chloride has been reported to specifically
oxidize the alkyl group of substituted benzene compounds to
an aldehyde group.   Further oxidation with hydrogen peroxide
can lead to a carboxyl group which can readily be removed.
If such a scheme was applicable to the lactone of 8-hydroxymethyl
-1,3-benzodioxan-6-methyl-7-carboxylic acid the product would
be the lactone of 8-hydroxymethyl-1,3-benzodioxan-7-carboxylic
acid; this latter dioxanylphthalide is the third possible
structure that may be assigned to Buehler, Harris, Schaklett,
and Block's (8) condensation product of m-hydroxybenzoic acid.
A similar procedure for the lactone of 6-hydroxymethyl-1,
3-benzodioxan-8-methyl-5-carboxylic acid might lead to Buehler,
Slack, Shirley, Sanguinetti, and Frey's (10) known lactone of
6-hydroxymethyl-1,3-benzodioxan-5-carboxylic acid.

3)   The alkaline permangante oxidation of 3-hydroxy-6-
methylphthalide should also be attempted.

4)   Buehler, Powers, and Michels' (7) 3-hydroxyphthalide
should be condensed with formaldehyde and sulphuric acid
in an attempt to obtain a dioxane ring by Borsche and
Berkhout's (6) method.

5)   Since m-hydroxybenzoic acid and 5-hydroxy-o-toluic
acid gave the simple phthalide and dioxanylphthalide
structures, 3-hydroxy-p-toluic acid should do the same
under proper conditions. Anderson (1) was only able to
isolate from the condensation of the latter compound,
the dioxanylphthalide structure.

6)   A study of the properties of phthalide and their
application to substituted phthalides may lead to interest-
ing derivatives. In some of the cases, it may lead to
the confirmation of the structures of condensation
products.

Richter (35) and Hessert (19) reported that boiling
hydriodic acid in the presence of phosphorus has been
successful in converting phthalide into o-toluic acid.
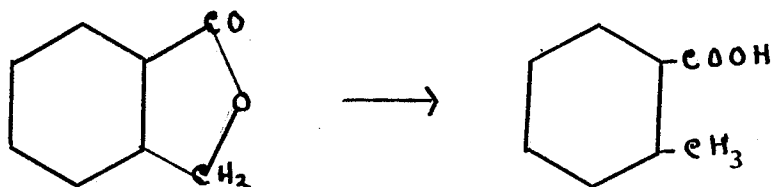
Other reduction methods may also provide means of identify-
ing phthalide structures.

The treatment by Hessert of phthalide with boiling
aniline led to the formation of an imide-type of compound.
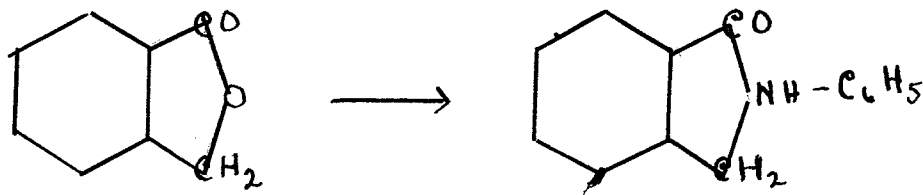
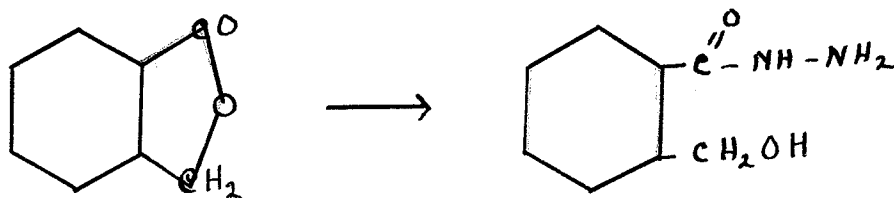By the action of hydrazine on phthalide Teppema (44) was able to obtain the hydrazide of the hydroxyacid.

Similar compounds were derived from 5-bromophthalide and 5-aminophthalide. The latter phthalides might be prepared by the Fritsch (17) method. The above mentioned reaction with hydrazine could form a different compound by a condensation involving a liberation of water as illustrated in the preceding suggestion with aniline. Alkaline hydrolysis of this possible intermediate stage should lead to the previously mentioned hydrazide. Other derivatives with phenylhydrazine might be prepared.

7)   King and King (22) reported that 3, 4, 5, trimethoxyphthalide condensed with sodium ethoxide and ethyl oxalate to give ethyl-3, 4, 5-trimethoxyphthalidyl glyoxylate.
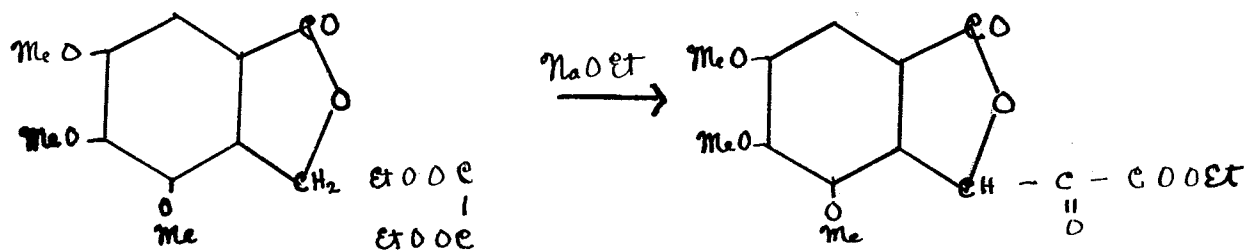
This is an indication that the phthalide ring may have
an active methylene group.

8)   Condensation of suitable aromatic acids with β-β'-
-dichloroethylether may lead to chloroethylation and
possible lactone formation.

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