THE SYNTHESIS OF SOME LACTONES RELATED TO PODOPHYLLOTOXIN

by
Arthur Ellis Brown

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

1950

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

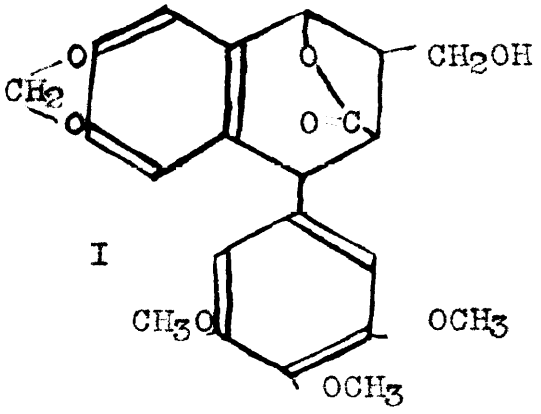
ACKNOWLEDGMENT

The author wishes to express his sincere appreciation of the interest and guidance of Professor Nathan L. Drake, which made this work possible.

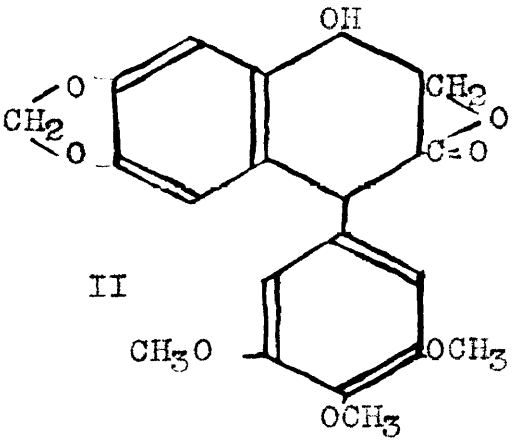
TABLE OF CONTENTS

INTRODUCTION

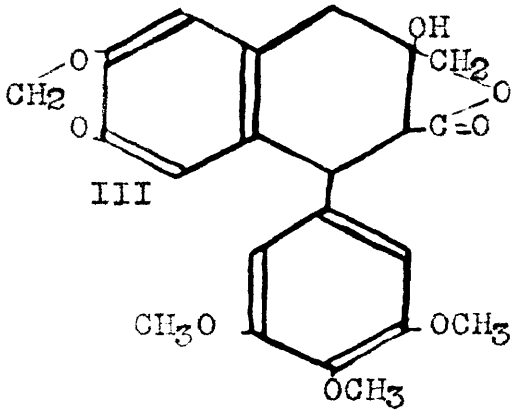
Podophyllotoxin is one of the compounds obtained from the rhizome extract of Podophyllum peltatum, and has been found damaging to cancerous cells.[1] Sterling[2] has reviewed the evidence on which Borsche and Spaeth based their suggestion that podophyllotoxin has the structure I, and picropodophyllin, an isomer occurring with it, and into which it is easily converted, the structure II. Recently Hartwell and Schrecker[3] have suggested that both substances have the structure II, the difference between podophyllotoxin and picropodophyllin being that of stereochemical arrangement. They also admit the possibility of III. In an effort to find similar compounds for cancer therapy, this investigation was undertaken to find a synthetic route to compounds of structure IV, the stripped open-chain analogue of I. Other synthetic work leading to compounds related to podophyllotoxin and to other naturally occurring phenolic compounds of the 1-phenyltetralin and 1,4-diphenylbutane series has been reported by Sterling[2] and Price[4]. Since there has been no previous approach to unsubstituted compounds similar to IV, reference will be made during the course of the discussion to the reactions which were deemed similar to those chosen for study.



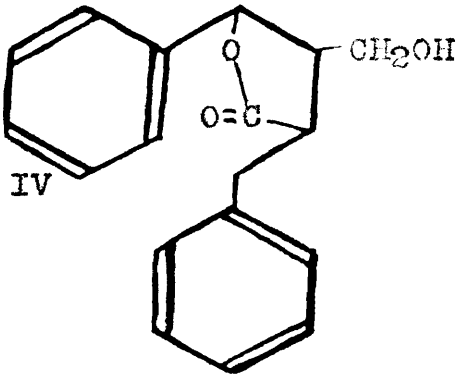
I



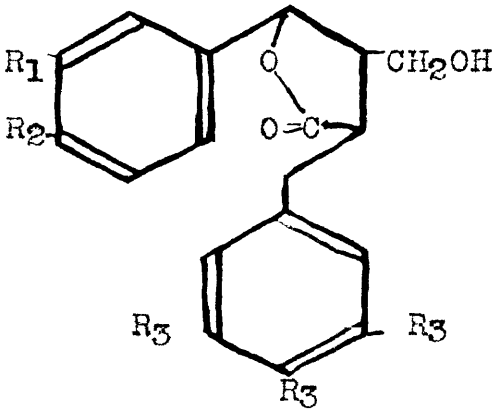
II



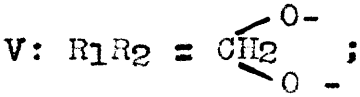
III



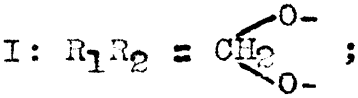
IV



V, VI, VII

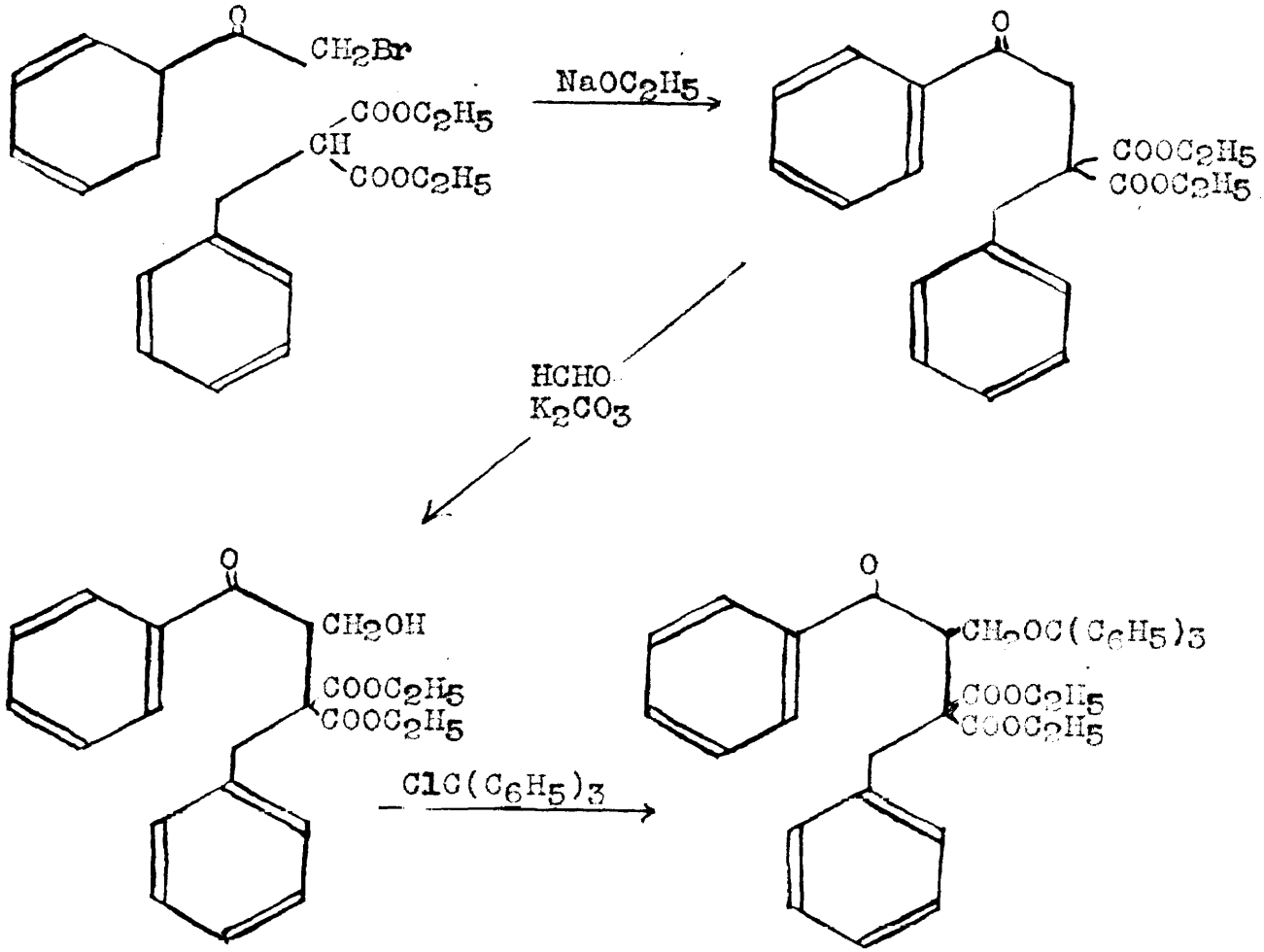
V: R_1R_2 =  ; R_3 = H

VI: R_1R_2 = H, H ; R_3 = OCH_3

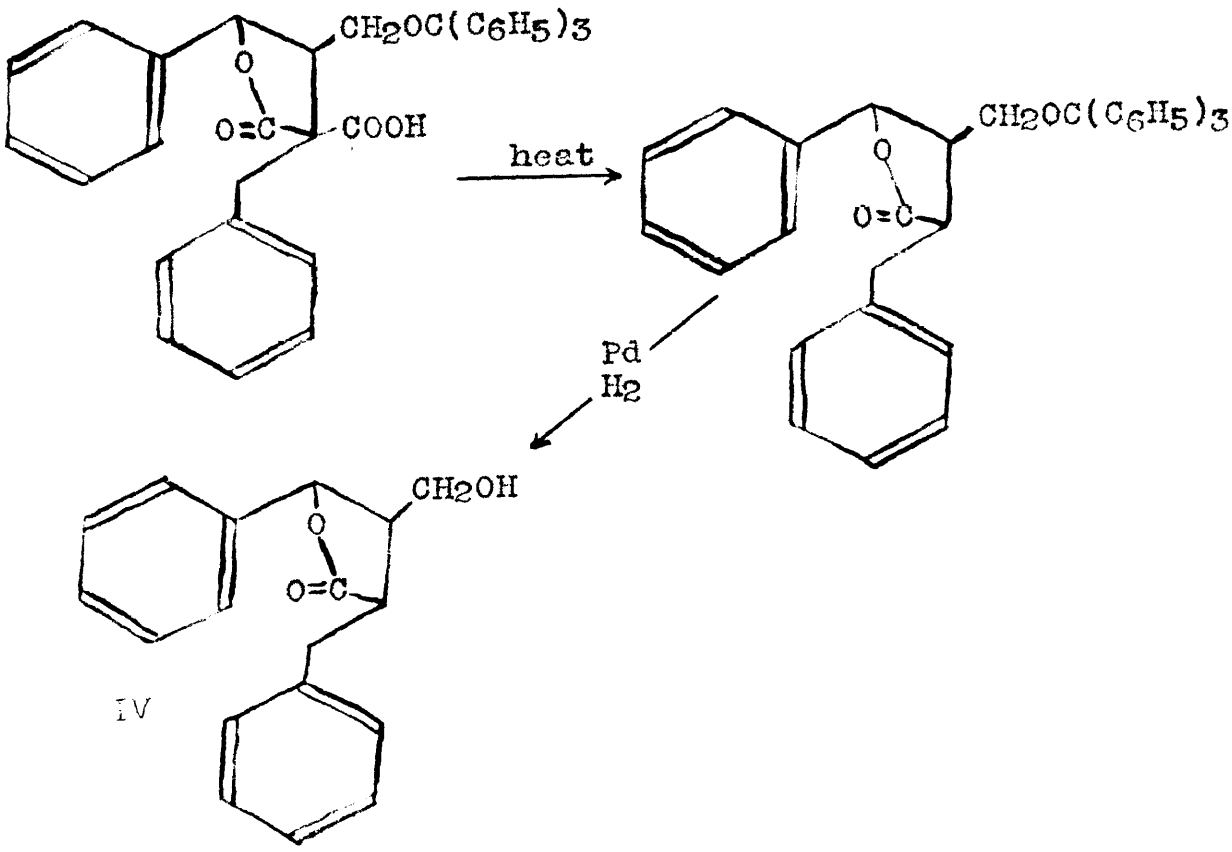
VII: R_1R_2 =  ; R_3 = OCH_3

DISCUSSION

An attempt was made to find a synthetic route to IV which would also apply to the preparation of V, VI, and VII. This entailed the avoidance of reactions which involved acid conditions suitable to the cleavage of the ether groups. With this in mind, the following reaction series was undertaken:



1. $Al(OCH(CH_3)_2)_3$
2. Saponification



IV

Ethyl benzylmalonate was prepared according to the procedure in Organic Syntheses[5] and the yields were found to be as reported (52-57%). However, it was found that the use of sodium hydride instead of sodium ethoxide as a base, in excess ethyl malonate instead of absolute ethanol as a solvent, cut down the time necessary for the reaction and increased the yield to 85%. The time spent preparing absolute ethanol and cutting sodium under oil was saved when sodium hydride was used, since the base is commercially available in a form suitable for use, an easily poured powder, and the reaction could be run at higher temperatures than those obtainable when ethanol was used.

The preparation of phenacyl bromide was also modified. Published directions[6] suggest that the crude product of the bromination, after being evaporated at low pressure to remove hydrogen bromide and the ether used as solvent, be washed with a mixture of petroleum ether and water, a purification process which leads to a strongly lachrymatory product that holds a large amount of water, making its use in the laboratory unpleasant and its suitability for malonic ester condensations questionable. If the crude brominated product is freed of solvent by lengthy (2 to 6 hours) evaporation under the diminished pressure obtainable with a water-pump, while a slight current of air is introduced by means of a capillary tube, and then washed thoroughly with water, it may be recrystallized from petroleum ether to yield hard flat plates that dry in air to a stable, almost non-lachrymatory product. The water that was held after the washing can be easily removed by decantation during the recrystallization.

The attempted preparation of ethyl benzylphenacylmalonate under the usual conditions, i.e. by the use of sodium ethoxide in alcohol solution, led to tarry products. Since ethyl phenacylmalonate can be easily made using the above conditions, it was decided that the lack of success involved the greater difficulty of introducing the second group onto the central carbon. Wallingford, Thorpe and Homeyer[7] reported success in the use of ethyl carbonate as solvent for the introduction of the second alkyl group. By using this solvent, and distilling out the ethanol formed

by the reaction of the sodium ethoxide with the ethyl benzylmalonate, the desired ethyl benzylphenacylmalonate was prepared. However, the difficulty in removing all of the solvent, a necessity before crystallization could be accomplished led to experiments involving the replacement of the ethyl carbonate with benzene. It was found that the sodio derivative of the benzylmalonic ester was soluble in benzene containing a slight excess of the ester. When the preparation was run using these solvents, the alcohol formed was easily removed as the benzene-alcohol azeotrope in a good fractionating column, and the benzene by fast steam distillation after the phenacylation. The resulting product could sometimes be crystallized directly, and sometimes had to be distilled in a molecular still before crystallization. The distillation was smooth, removing first the remaining excess benzylmalonic ester, and then the product as a clear, light yellow, viscous liquid that required only two or three crystallizations to be obtained pure. There remained a heavy red tarry residue which could not be purified.

The use of sodium hydride proved beneficial in this reaction also. The use of large volumes of benzene (about 7 - 8 liters per mole) was obviated by using excess ethyl benzylmalonate, in which the sodio derivative was much more soluble. In this case, in place of steam distillation, which was as expected very slow, the crude reaction mixture was extracted with water to remove inorganic and basic substances, and then subjected to rapid distillation under the pressure obtainable in ordinary distillation apparatus

with an oil diffusion pump. When the rate of distillation started to fall, the residue was transferred to a molecular still and distilled as above. One important difference was noted in the molecular distillation of the product obtained when the preparation was performed using sodium hydride instead of sodium ethoxide. If the heavy red residue in this reaction was subjected to slow molecular distillation, the desired product continued to distill, raising the yield from about 35% to about 55%.

Sodium hydride was used for the preparation of ethyl benzylacetoacetate also. When a procedure identical to that used to prepare ethyl benzylmalonate was used, ethyl benzylacetoacetate was obtained in 83% yield. Various workers have reported results in which they obtained this compound in yields of about 60% of the theoretical amount when the usual bases were used.

An attempt was made to make ethyl benzylcyanoacetate by the same method, but unlike the malonic and acetoacetic esters, ethyl cyanoacetate did not form a sodio derivative which was soluble in excess of the ester. The slurry became very viscous, and had to be diluted with absolute ethanol. After the ethanol had been added, no more sodium hydride could be added, since in the presence of alcohol sodium hydride is a good reducing agent for nitriles and esters. Unless a suitable solvent is found for this reaction, there is no advantage in using sodium hydride in place of sodium ethoxide.

In the preparations of ethyl benzylphenacylacetoacetate

and ethyl benzylphenacylcyanoacetate, sodium hydride was used in a procedure identical to that in which ethyl benzylphenacylmalonate was prepared. As a condensing agent for this type of reaction, sodium hydride seemed to have general application, giving higher yields, and facilitating manipulation in the laboratory through the use of smaller volumes; the preparation of large quantities of absolute alcohol was also unnecessary.

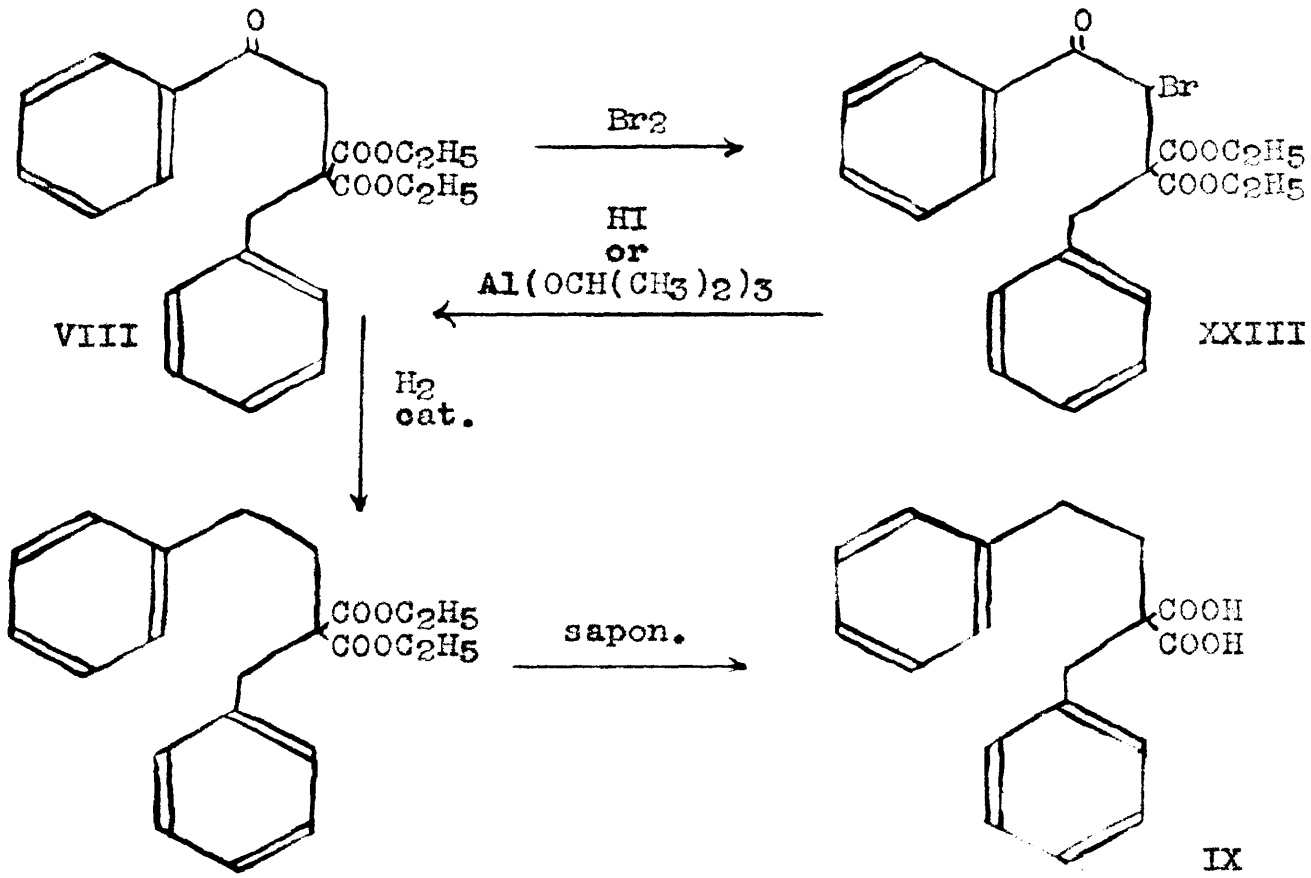
In the earlier preparations of ethyl benzylphenacylmalonate, it was noted that a large amount of ethyl benzylmalonate was recovered. Hence a preparation was attempted using a large excess of phenacyl bromide. After the strongly lachrymatory product was worked up, there were obtained only traces of the desired product, and most of the phenacyl bromide was recovered. It was discovered at this time that phenacyl bromide distills smoothly under pressures around one-half micron.

An attempted preparation of ethyl benzylphenacylmalonate from benzyl chloride and ethyl phenacylmalonate resulted only in the formation of tarry substances, presumably because there was more than one center of active hydrogens in the ethyl phenacylmalonate.

The preparation of derivatives of the carbonyl group of ethyl benzylphenacylmalonate proved to be difficult. The action of 2,4-dinitrophenylhydrazine yielded dark red resinous products, and semicarbazide did not react with the compound in aqueous alcohol or pyridine either at room temperature or when heated. Kues and Paal[8] reported

the action of hydrazine and hydroxylamine on diphenacylmalonic ester, and found either no reaction or, under strenuous reaction conditions, tars from which no pure substances could be obtained. Hydrazine with no solvent produced an immediate and vigorous reaction, but no products could be isolated from the tarry reaction mixture.

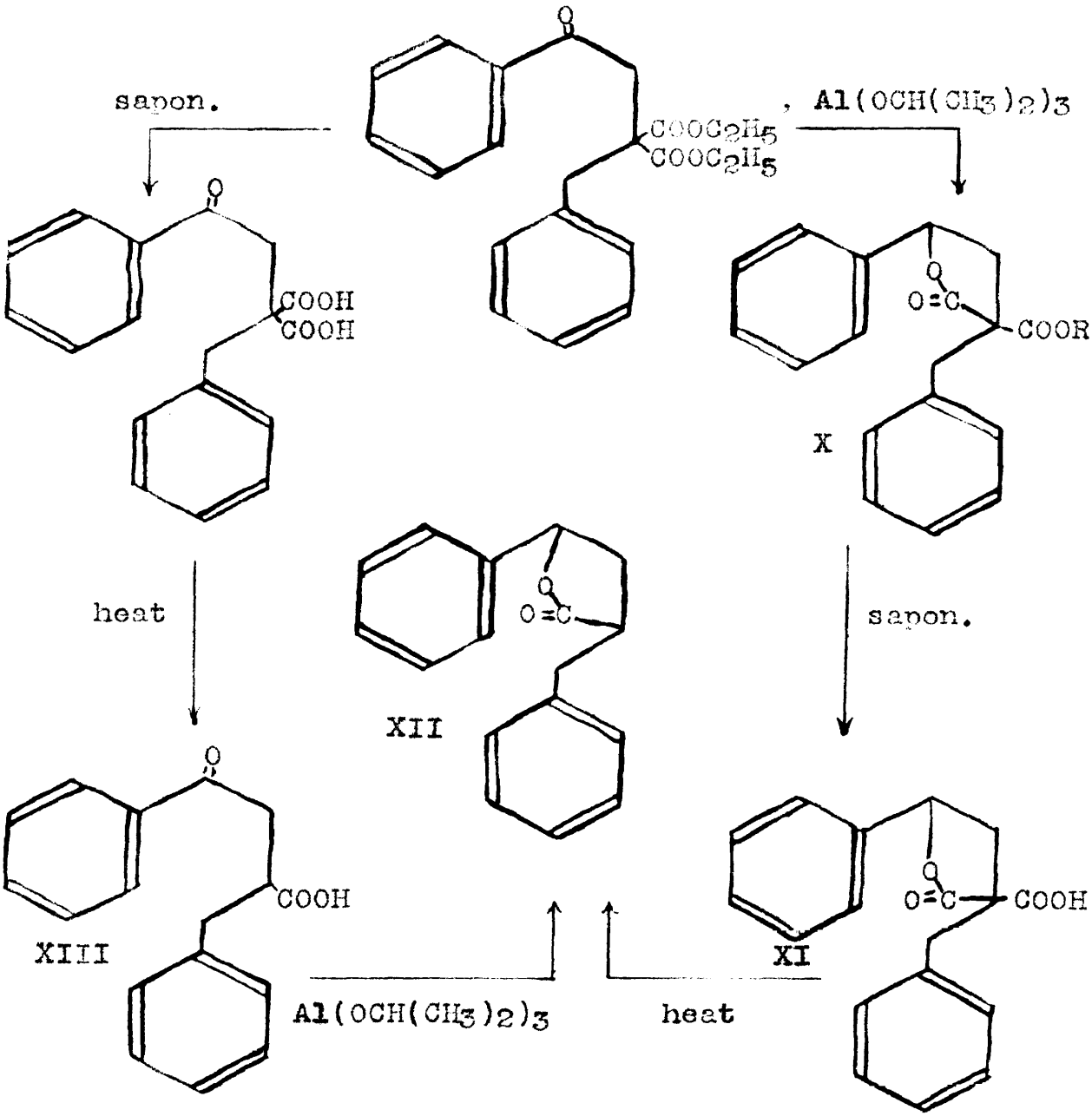
Ethyl benzylphenacylmalonate (VIII) reacted rapidly with bromine in boiling carbon tetrachloride solution, and



more slowly at room temperature after a short induction period. The product of this quantitative reaction contained one bromine atom whose lability was demonstrated by the reaction with hydriodic acid[9] to produce the original ester in quantitative yield, and by the reaction with aluminum isopropoxide, wherein the bromine was replaced with hydrogen to the exclusion of any carbonyl reduction. The final evidence for the structure was the reduction to ethyl benzylphenethylmalonate by hydrogen. Leuchs and Reinhart[10] prepared benzylphenethylmalonic acid (IX) by saponification of the ester produced by the reaction of ethyl malonate, phenethyl bromide and benzyl chloride. The catalytic reduction of ethyl benzylphenacylmalonate proceeded directly to the formation of ethyl benzylphenethylmalonate with no break in the rate of absorption of hydrogen at a point corresponding to the preparation of the substituted benzyl alcohol. Furthermore, when a reduction stopped because of insufficient catalyst, that part of the reaction mixture which was not the phenethyl compound was identified as starting compound.

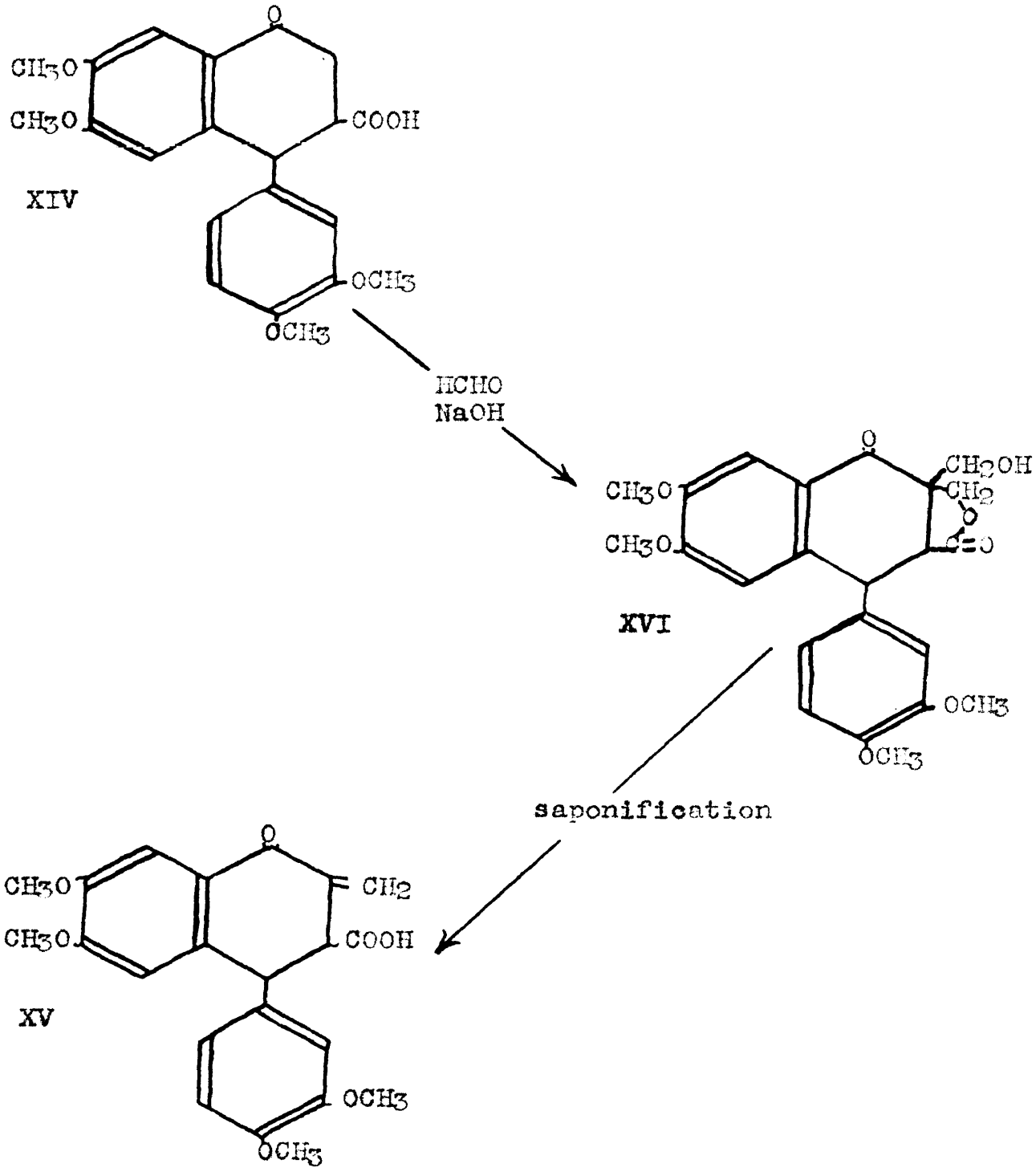
Although the keto group of ethyl benzylphenacylmalonate was reduced directly to a methylene group by catalytic hydrogenation, aluminum isopropoxide reduced the carbonyl with simultaneous lactonization, as is generally the case with gamma keto esters.[11] The product of this reaction (X) could not be crystallized, presumably because there was a mixture of esters from the partial transesterification, but saponification and subsequent acidification produced a crystalline compound, the malonic acid lactone (XI). Decarboxylation was readily accomplished by heating, and the resulting

lactone (XII) was easily recrystallized. If the original ethyl benzylphenacylmalonate was saponified, and the free acid heated, the monobasic keto acid (XIII) thus obtained yielded the same lactone (XII) when reduced with aluminum isopropoxide in isopropyl alcohol.



The possibility of the desired reaction of ethyl benzylphenacylmalonate with formaldehyde seemed questionable, since the review of Walker[12] reports experiments in which aryl alkyl ketones form methylol derivatives only with difficulty. The ease of reversal of the reaction and the fact that the use of other than very mild reaction conditions produce only complex products, were cited by Walker as the cause of the failure of the reaction; strong alkalies and heat can not be used. The optimum conditions, according to Walker, require shaking the ketone with anhydrous potassium carbonate and paraformaldehyde in anhydrous methanol. Under these conditions ethyl benzylphenacylmalonate failed to react.

Haworth and Sheldrick[13], however, succeeded in adding formaldehyde to a compound similar to ethyl benzylphenacylmalonate. When formalin and aqueous sodium hydroxide were allowed to react with 6,7-dimethoxy-1-(3,4-dimethoxyphenyl)-4-keto-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (XIV), two methylol groups entered in the three-position, one of them forming a lactone. Saponification removed one methylol group and dehydrated the other, producing a methylene compound, 6,7-dimethoxy-1-(3,4-dimethoxy-phenyl)-4-keto-3-methylene-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (XV). In the hope of obtaining a compound similar to XVI and blocking the free hydroxyl with the trityl group before removing the other methylol group, ethyl benzylphenacylmalonate was saponified, and the resulting acid subjected to the same reaction conditions as those used by Haworth and Sheldrick. Although their reaction went in good yield in a few hours, the malonic acid


O
CH3O
CH3O
COOH
OCH3
OCH3
HCHO
NaOH
CH2OH
CH2
C=O
saponification
CH2

XIV

XVI

XV

yielded only starting materials on standing as much as a week. On standing a month, the formaldehyde underwent a Cannizzaro reaction, removing sufficient alkali from the reaction mixture to precipitate the starting acid. The malonic acid was heated to decarboxylate it in order to start with an acid more nearly approximating that of Haworth and Sheldrick, but the same result was obtained with the monobasic acid.

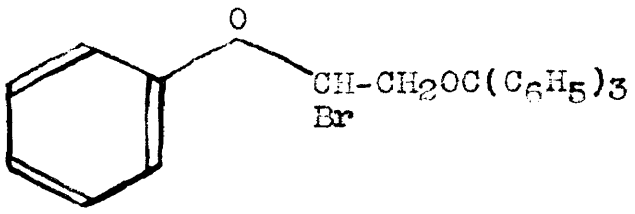
Since this route seemed to offer difficulties, it was thought that it might be possible to obtain a compound such as α-bromo-β-triphenylmethoxypropiophenone (XVII). This compound already contains the tritylated hydroxymethyl group, and might be condensed with ethyl benzylmalonate.

Trityloxyethyl chloride and bromide were prepared by heating the appropriate halohydrin with triphenylcarbinol and a trace of p-toluenesulfonic acid in benzene under reflux, using a Dean-Stark trap. Attempts were made to prepare Grignard reagents from these substances in the hope that the Grignard reagents could be added to benzoyl chloride to form the desired propiophenone. These attempts failed.

To approach from the other side of the carbonyl, β-cyanoethyl trityl ether was similarly prepared, and attempts were made to add phenylmagnesium bromide to the nitrile. This approach was discontinued when it was discovered that the conditions necessary to accomplish hydrogenolysis of trityl ethers far exceeded the limits that could be tolerated by compounds which would occur in later steps of the synthesis.

The first attempt to cleave such an ether involved the reaction of hydrogen with n-butyl trityl ether in ethanol in the

presence of palladium oxide. The reaction was carried out at room temperature and under two atmospheres pressure, but the product obtained proved to be the transetherified compound, ethyl trityl ether. Consequently a series of hydrogenolyses was attempted with ethyl trityl ether in cyclohexane, using palladium oxide, platinum (Adams') oxide, and platinum oxide which had been first shaken with hydrogen. When no reaction was observed at room temperature under pressures of one or two atmospheres, the pressure was raised to 1500 pounds per square inch; again there was no reaction. The use of Raney nickel under 2400 pounds pressure and at temperatures up to 118° when triethylamine (3 ml. per 100 ml. of solution) was added to decrease hydrogenation of the rings was not successful; starting



XVII

material was recovered. Van Duzee and Adkins[14] achieved the hydrogenolysis of ethyl trityl ether with Raney nickel at 175° and under 1500 pounds pressure, but the hydrogenolysis was accompanied by extensive hydrogenation.

Since benzyl ethers are known to cleave more rapidly[14], 2-cyanoethyl benzyl ether was prepared, but attempts to convert it to the acid, or to benzyloxypropiophenone resulted in the loss of benzyl alcohol and the production of polymers of acrylic acid or phenyl vinyl ketone.

The action of sodium benzylate on β-bromopropiophenone also produced phenyl vinyl ketone. It was thought that α,β-dibromopropiophenone could be converted to the unstable phenyl vinyl ketone, with the immediate addition of benzyl alcohol to form benzyloxypropiophenone. Kohler[15] removed the bromine atoms from α,β-dibromopropiophenone to form phenyl vinyl ketone, but found that when he worked in alcohol solution, there was considerable addition to form β-ethoxypropiophenone. If the phenyl vinyl ketone was boiled in ethanol with a trace of acid, larger amounts were formed. Potassium iodide was the agent preferred by Kohler to remove the bromine. However, when these reaction conditions were followed, substituting benzyl alcohol for ethanol, loss of benzyl alcohol from any addition product occurred, and only the polymer from phenyl vinyl ketone could be obtained. Leslie and Henze[16] prepared butoxypropiophenone by adding butyl alcohol to acrylonitrile in the presence of a trace of strong base, hydrolyzing the resultant nitrile to the acid, converting the acid to the acid chloride, and treatment of the acid chloride with diphenyl cadmium. However, their β-butoxyethyl phenyl ketone decomposed into the alcohol and phenyl vinyl ketone if they attempted to distill it under pressures above one millimeter. An attempt parallel to that of Leslie and Henze failed after the nitrile was hydrolyzed. Efforts to purify the acid or to convert it to the acid chloride, so that it might be purified in that form by distillation, were unsuccessful.

Rehburg, Dixon and Fisher[17] added various straight-chain, olefinic, and branched alcohols to methyl acrylate to form β-

alkoxypropionic esters, but were unable to add tertiary butyl alcohol. Other similarities between tertiary butyl and benzyl alcohols have been noted. The addition of benzyl alcohol to acrylonitrile in the presence of a trace of alkali is accomplished in good yield[18].

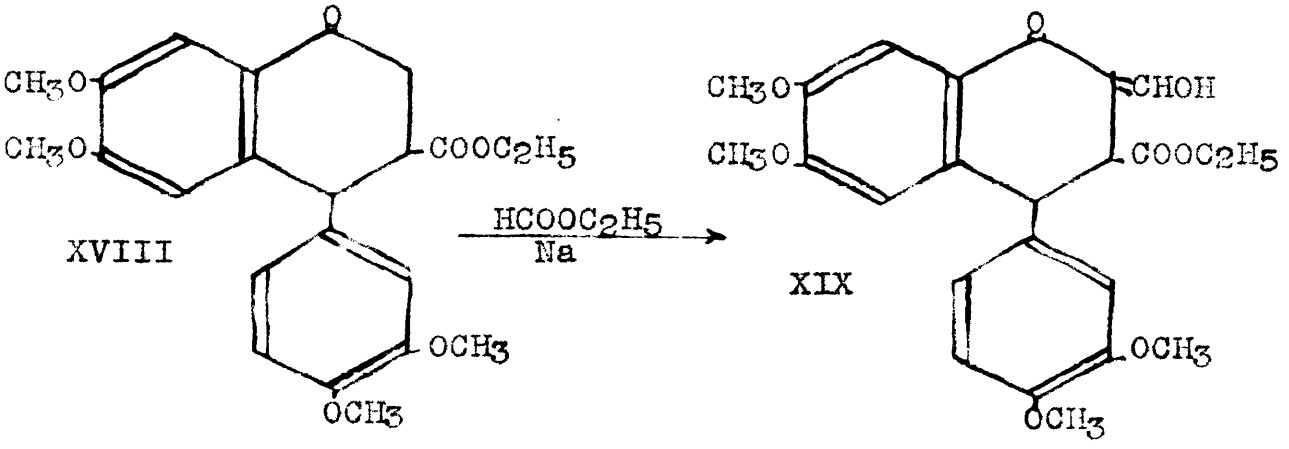
These approaches to the synthesis having failed, attention was turned to the brominated benzylphenacylmalonic ester. It was hoped to replace the bromine with cyanide, reduce the carbonyl and lactonize to avoid the problems associated with a β-keto acid, and then to hydrolyze the nitrile to the acid, and reduce to the methylol compound by way of the acid chloride. The reaction with potassium cyanide in aqueous alcohol yielded a crystalline product which was shown by analysis to contain no nitrogen. Other attempts in anhydrous media and in various solvents and at various temperatures either produced the same compound, no reaction, or extensive decomposition. Analysis indicated a bimolecular ether involving an oxygen atom in excess of those in the original bromo compound, but extensive structure determinations were not pursued, since it was apparent that this route would not yield the desired end-product. It is interesting to note the apparent stability of the bromo compound to acid hydrolysis. A sample was dissolved in concentrated sulfuric acid and poured into water. An alkaline wash of the precipitate thus obtained, on acidification, produced only a faint cloudiness, representing an amount of material too small to be weighed. The solid left undissolved after the alkali treatment represented almost quantitative recovery of the starting material. Prolonged heating under reflux with

aqueous sulfuric acid containing sufficient ethanol to wet the solid also produced no hydrolysis.

Although examples of the use of α-bromoketones for the Reformatsky reaction are relatively scarce, an attempt was made to prepare the zinc derivative of the bromo ester. Prolonged heating with either 200 mesh zinc or zinc-copper alloy turnings produced no zinc derivative.

Attention was then turned back to methods of introducing a carbon atom directly in the proper position on the carbon skeleton. A suitable reaction appeared to be that of ethyl formate in the presence of alkali.

There are many examples of this type of reaction in the literature, some of them on compounds very similar to ethyl benzylphenacylmalonate. For instance, Haworth and Sheldrick[19] treated 2-carbethoxy-6,7-dimethoxy-1-(3,4-dimethoxyphenyl)-4-keto-1,2,3,4-tetrahydronaphthalene (XVIII) with ethyl formate and sodium wire for 12 hours in benzene and obtained in good yield the corresponding 3-hydroxymethylene compound (XIX), stable enough to be recrystallized.



Claisen[20] operated on 1-methylcyclohexanone with amyl formate and obtained a crystalline product which he dried in air. Birch and Robinson[21] prepared 2-hydroxymethylene-trans-1-decalone and were able to distill it at low pressure. After the hydroxymethylene group was blocked with methylaniline and an angular methyl group introduced, they boiled the substance in excess 10% hydrochloric acid for 30 minutes to remove the aniline. Boiling with 20% sodium hydroxide was required to remove the hydroxymethylene group which survived the acid treatment. Johnson and Posvic[22] prepared the same hydroxymethylene decalone but blocked the aldehyde by converting it to the enol ether; the overall yield was 93%. They reported that the enol ether was stable under nitrogen, but decomposed in air in a few days. In contrast to these cases where the action of ethyl formate produced compounds stable enough to be handled, stored, distilled or recrystallized, Prelog and Geyer[23] prepared the formyl derivative of cyclopentadecanone. Although they were able to use mineral acid to precipitate the hydroxymethylene ketone from the alkaline extract, the product was unstable even as a crystalline solid, and resinified on recrystillization even from low boiling petroleum ether. Haworth and Kelly[24] reported that the methylene groups of 1,2-dibenzoylethane are unreactive, and will give no reaction with formalin, ethyl formate, or ethyl oxalate.

A further complication is the decomposition of ethyl formate into ethanol and carbon monoxide, catalyzed or caused by sodium ethoxide. The mechanism of this decomposition was the subject of some dispute[25], but the end result is the

destruction of one of the reagents in the formylation by another necessary reagent. It was found in this investigation that the decomposition of ethyl formate does not occur at an appreciable rate at the boiling point of ethyl formate. At intermediate temperatures the decomposition is appreciable but not rapid. For instance, at 45° there was a major part of the original ester present after 12 hours, in a reaction started with 15 g. of ethyl formate in 250 ml. of benzene, although the evolution of gas was easily visible.

Early attempts to prepare the hydroxymethylene derivative of ethyl benzylphenacylmalonate were unsuccessful, due largely to the low temperatures employed. Almost all of the formylations reported were carried out at room temperature or lower, and it was presumed that higher temperatures would result in the destruction of the ethyl formate. It is believed that in those cases where higher temperatures were used in this investigation, this destruction of the reagent caused failure of the reaction. Later, a reaction was started at ice temperatures, and was left to warm up to room temperature. However, after the ice-bath had melted, the resulting water-bath was warmed by the magnetic stirrer to approximately 40°, so that the reaction was maintained at that slightly elevated temperature during the course of the reaction. Furthermore, all of the reactions in the literature were run for 12 hours or less, while with ethyl benzylphenacylmalonate a longer time seems advantageous. When the above reaction mixture was worked up, a large quantity of alkali soluble material was present, and it was thought to be the required hydroxymethylene compound.

The alkaline form was soluble in water and insoluble in organic solvents. The soft solid precipitated by acid from the alkaline solutions was soluble in organic solvents.

When it was thus found that an elevated temperature was necessary for the formylation, an attempt was made to circumvent the difficulty occasioned by the decomposition of the ethyl formate by adding small quantities over a period of time. When the temperature was held at 50-60°, three additions of ethyl formate at 6-hour intervals sufficed to keep the reaction supplied with that reagent, and a formyl compound was obtained in good yield.

The use of isopropyl formate in place of ethyl formate resulted in the improvement that the reaction proceeded at room temperature with no apparent decomposition of the formate. The reaction required a longer time with isopropyl formate than with ethyl formate, approximately 48 hours being required.

The addition of cupric acetate solution to either the aqueous solution of the sodio derivative or the neutral alcoholic solution precipitated a copper compound that was soluble in organic solvents. If the supposed hydroxymethylene compound was dissolved in ether, and the ether solution shaken with cupric acetate solution, the ether phase became green, and a solid could be obtained from it on evaporation. This green copper derivative could not be crystallized. Chromatographic adsorption on alumina from carbon tetrachloride solution produced a clear green filtrate that left a hard brittle glassy green solid on evaporation. A slight amount of yellow brown color remained high on the column. When the

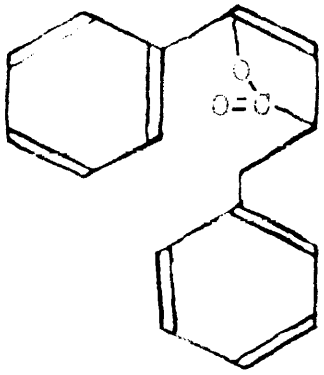
copper compound was dissolved in ethyl ether instead of carbon tetrachloride and chromatographed, the green color was completely discharged, and the filtrate was light brown and contained aluminum. Hence the apparent purity of the green glass from the carbon tetrachloride chromatography became questionable. Analysis of this green glass agreed fairly closely with that of a sample of freshly precipitated compound prepared in methanolic solution; however, the analysis indicated a copper content far higher than that calculated for the copper chelate derivative of the expected keto-aldehyde. Catalytic hydrogenation of the copper derivative removed the copper, and the original copper compound could be regenerated by the addition of cupric acetate solution.

Klason[26] used β-naphthylamine hydrochloride to separate α-lignosulfonic acid, a compound with an aldehyde group, from other substances present in sulfite liquors. In separate tests, he determined that β-naphthylamine hydrochloride reacted with all the aldehydes that were available to him, and with none of the ketones. Hence it was thought that this amine might be used to separate the hydroxymethylene compound from the reaction mixture. The soft solid obtained by acidification of the alkaline extract of the formylation reaction mixture was dissolved in alcohol and treated with an aqueous solution of β-naphthylamine hydrochloride. When sufficient was added to induce turbidity, and the flask allowed to stand, some yellow crystals were deposited which melted over a wide range. Recrystallization did not produce a pure product. A sample was dissolved in absolute ethanol and passed through a

column of alumina. The yellow filtrate deposited yellow needles on evaporation. A portion of this yellow precipitate was sublimed under a pressure of 0.1 micron. Analysis and melting point showed this substance to be di-β-naphthylformamidine. From this fact it appeared that the formyl group had at one time been present in the molecule, but had suffered cleavage during or after the reaction with the naphthylamine.

In the earlier formylations, before it was discovered that a slightly elevated temperature was required, alkaline extraction of the benzene reaction solution yielded very little if any material on acidification, and when the neutral benzene solution was evaporated, a residue was left which was thought to be recovered starting material. When this residue was boiled with petroleum ether (the solvent from which the ethyl benzylphenacylmalonate was recrystallized), the residue did not dissolve, but changed from oil to crystalline material. It could be recrystallized from ethanol, and analysis showed it to be much higher in carbon content than the starting material. Saponification equivalents gave results that varied according to the concentrations of reagents used and according to the length of time of heating for the saponification. The only structure for which the analysis agreed seemed an improbable one: an enol lactone from which one of the carbethoxy groups had been lost. The same compound (XXIV) was obtained, along with the free acid derived from it, when ethyl benzylphenacylmalonate was heated with alkali under anhydrous conditions in the absence of ethyl formate. Saponification and subsequent acidification of this compound confirmed its structure

by converting it to benzylphenacylacetic acid, known from the decarboxylation of the malonic acid, in almost quantitative



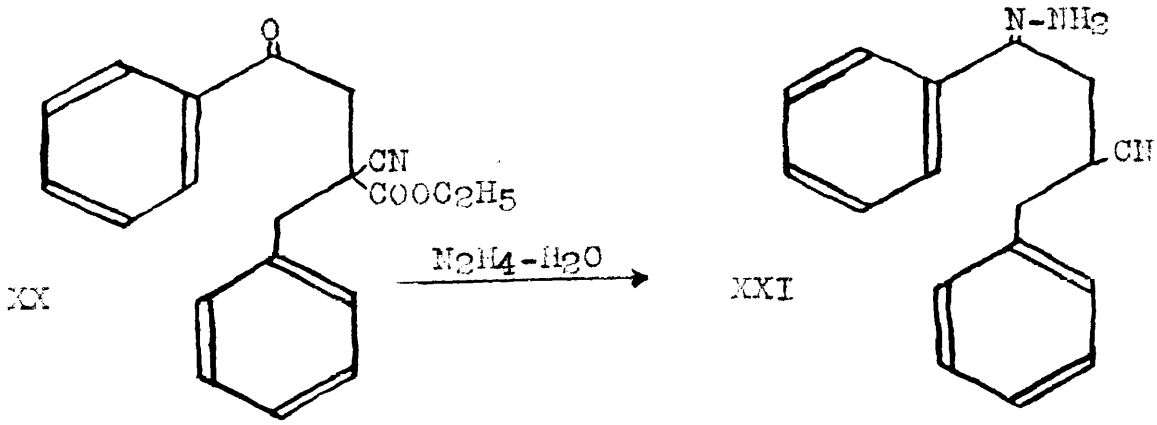
XLIV

yield. Attempts to convert the keto acid to the lactone by boiling with acetic anhydride or by boiling in benzene with toluenesulfonic acid failed.

Decarbethoxylation under alkaline conditions is not common, and the mechanism for it is thought to be similar to the ketone split of acetoacetic ester. In the case under investigation, enolization of the keto group provides a second unsaturated carbon in the beta position to the carbethoxy group, and the accumulation of negative substituents is sufficient to increase instability to the point of cleavage. Since ethyl benzylphenacylmalonate is stable when not in the presence of alkalies and can be heated well above its melting point without decomposition, it is apparent that only a small proportion of it is in the enol form. It is likely that the energy released in the transesterification involved in the lactonization provides sufficient impetus to expel the carbethoxy group. Once lactonization has occurred, there is no longer the equilibrium between keto and enol forms, and the beta unsaturation is fully operative. Whether the enol lactonization and decarbethoxylation on the one hand, and the

introduction of the formyl group on the other, are competitive reactions or successive reactions can now be determined. If the latter is the case, the active carbon will be alpha to the ester carbonyl and an aldehyde group in that position can not enolize to form the copper chelate. If the formyl group is introduced first, on the carbon alpha to the keto group, and then there is enolization and lactone formation, there will be no hydrogen left and the aldehyde group can not enolize to form the copper chelate. The copper salts of benzylphenacylmalonic acid, benzylphenacylacetic acid, benzyl-β-hydroxy-β-phenethylmalonic acid lactone, and benzoic acid were prepared, and their properties compared with those of the apparent copper chelate compound. There was no similarity, and since the properties of the latter do indicate a copper chelate type of compound, it must be concluded that the formylation reaction is competitive to the enolization. If the chelate is to be formed, there must be a hydrogen alpha to the aldehyde; this requirement excludes the enol lactone structure. No explanation is available for the resistance of the aldehyde to hydrogenation, and the structure of the formyl compound and its cupric derivative can not be definitely stated. It may be that two distinct compounds were formed, the separation of which was not accomplished.

Ethyl benzylphenacylcyanoacetate (XX) was prepared and heated with hydrazine hydrate. The compound formed contained no oxygen and its analysis showed it to be the hydrazone of β-benzoyl-α-benzylpropionitrile (XXI). No intermediates could be isolated and hence it appears likely that the loss



XX XXI

of the carbethoxy group occurs rapidly, simultaneously with the formation of the hydrazone. When ethyl benzylphenacylacetoacetate was treated with 2,4-dinitrophenylhydrazine under acid conditions, no such loss occurred, and the simple 2,4-dinitrophenylhydrazone was formed. The presence of base to promote enolization is thus clearly necessary to the loss of the carbethoxy group. The failure of the attempted conversion of the benzylphenacylacetic acid to the enol lactone under the influence of boiling acetic anhydride represents another example of the necessity of base for enolization.

When ethyl benzylphenacylmalonate was heated in benzene with ethyl orthoformate and sodium hydride, two products were formed in approximately equal quantities: the same enol lactone obtained before, and a compound which by its analysis was the enol lactone with a diethyl acetal group attached. Again the problem arose of locating the acetal group. If the formation of the lactone occurred first, it is unlikely that the orthoformate attacked the carbon alpha to the keto group. In the formylation reaction, evidence

indicates that the attack by ethyl formate occurred prior to enolization of the keto group, since that enolization would prevent the enolization of the aldehyde to form the chelate. The changes that took place after the introduction of the formyl group are not understood, and may involve, as suggested above, the competitive formation of a separate compound. In the orthoformate reaction, no such mutual exclusion exists. The enolization of the keto group is in no way prevented by the presence of the acetal group alpha to the ketone. Since the formyl group does enolize, it can not be on the carbon alpha to the carboxyl. If the analogy is valid, the acetal group is probably on the carbon alpha to the keto group. However, since the formation of the enol lactone would not prevent the entry of the acetal group, it may be alpha to the carboxyl. An attempt to hydrolyze the acetal showed it to be surprisingly resistant to acid hydrolysis. This phenomenon may be related to the lack of aldehyde reactions of the formyl group, except chelation. By analogy again, this evidence tends to show that the acetal is alpha to the keto group. If the hydrolysis were accomplished under more strenuous conditions, it is unlikely that it would prove the structure. Since hydrolysis, followed by oxidation would produce a β-keto acid in one case and a malonic acid in the other, the decarboxylation that would very probably occur would produce the same compound in both cases.

If, however, the enol lactone portion of the molecule were opened by saponification, aluminum isopropoxide

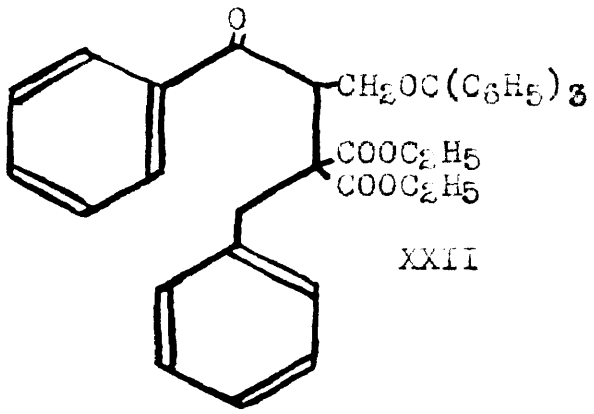
reduction would form the saturated lactone. The acetal would then form a stable aldehyde on hydrolysis, and oxidation would produce a stable acid if the acetal had been originally alpha to the keto group. If it had been alpha to the carboxyl group, the above reactions would produce the lactone acid (X) and this approach would be shown to be valueless.

The course of future work toward the synthesis of the desired structure should proceed in three directions. The acetal above has already been discussed, and if the acetal group is shown to be on the carbon alpha to the keto group, conversion to the acid of the saturated lactone could be followed by reduction to the methylol group by way of the acid chloride.

A second approach worth investigating involves the brominated ethyl benzylphenacylmalonate. The bromine might be able to be replaced by the ethinyl group with sodium acetylide. If the other active hydrogen of the ethinyl group caused difficulties by reaction with isopropoxide to precipitate the aluminum salt during the reduction, sodium methylacetylide could be used. Such a compound could be reduced by aluminum isopropoxide, decarboxylated as before, and the ethinyl group cleaved to methylol by partial hydrogenation, oxidative cleavage, and reduction.

The third approach involves α-benzoyldiethylacetal, the preparation of which is described[27] and which is said to react like the acetyl acetic esters. Reports in the literature and results of this investigation indicate that

that β-triphenylmethoxypropiophenone would produce a compound (XXII) that would suffer extensive hydrogenation before



XXII

hydrogenolysis of the ether bond could be accomplished. It has also been shown that β-benzyloxypropiophenone is unavailable for subsequent condensation with ethyl benzylmalonate.

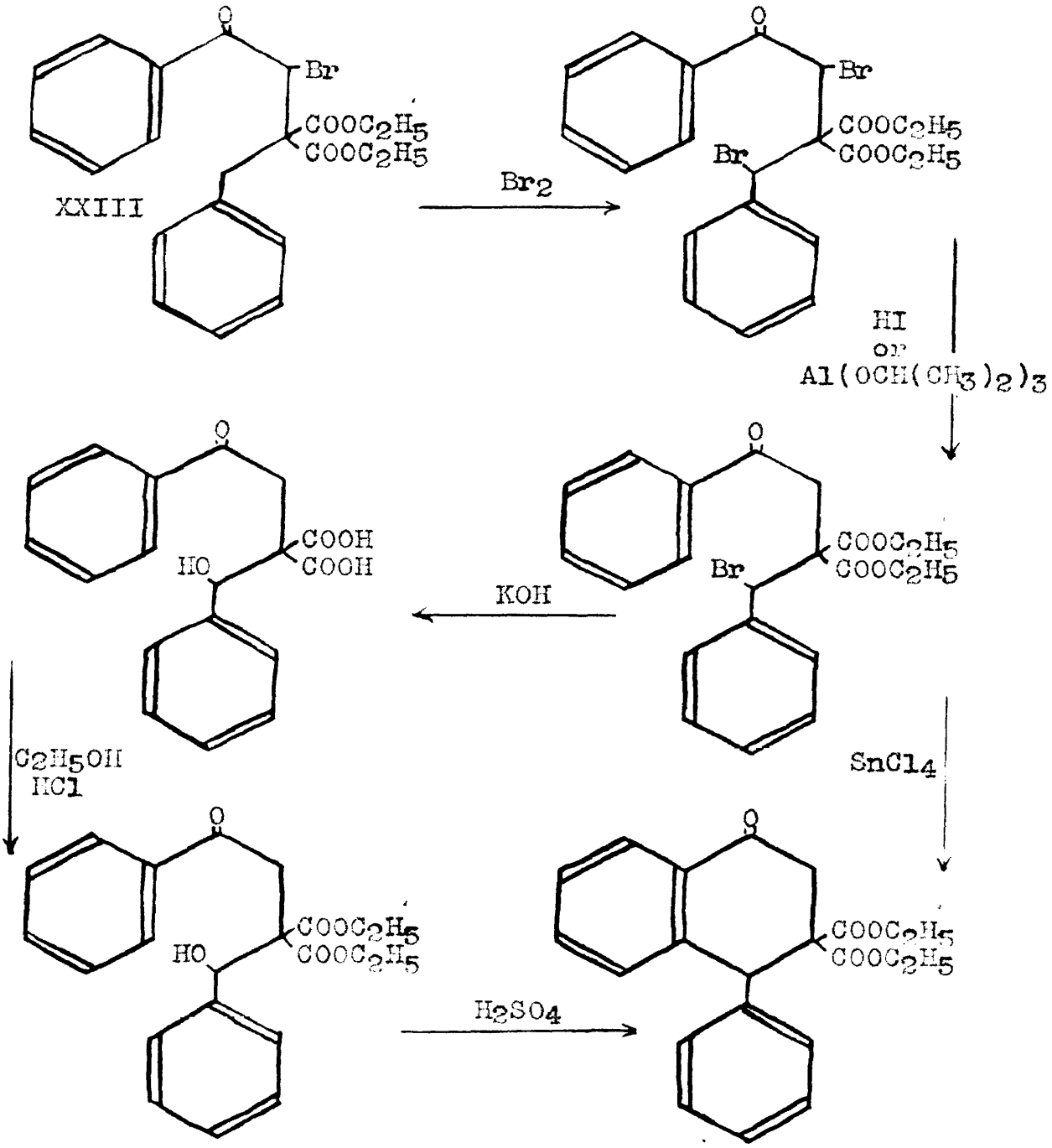
In view of the problems associated with the formylation, it would be useful to be able to make a compound of the same type as XXII, where the trityloxymethyl group of that compound is replaced with another group more amenable to mild reagents. It is thought that the β-keto acetal above may be able to provide that type XXII compound, and would provide the remainder of the necessary carbon skeleton with a stable side-chain already present in the proper position, if it, like acetoacetic ester, could be condensed with ethyl benzylmalonate. The acetal group should be more tractable than the previous ether group. By the application of aluminum isopropoxide reduction which has been shown to be effective in reducing the γ-ketones and closing the lactone ring, the desired lactone would be formed, leaving only the acetal group susceptible to gentle acid cleavage, to be

followed by reduction. The problems inherent in the β-keto-aldehyde structure, which led to difficulties in the formylation reactions, would thus be avoided.

Similarly, a compound such as ethyl β-benzoyl-α-benzyl-succinate would probably form the desired γ-lactone rather than the much more improbable β-lactone if subjected to the same aluminum isopropoxide reduction. Saponification of the resulting lactone ester would produce a stable lactone acid instead of the unstable lactone acid (XI) obtained from the malonic ester. This group could then be reduced to the methylol through the acid chloride. If the ketone were left intact, saponification would probably cleave the β-keto ester.

A comparison of the work of Haworth and Sheldrick with the results of this investigation, both with regard to the acid (XIV) and the ester (XVIII), shows that benzylphenacylacetic acid and its esters did not react in a manner that was to be expected. Whether it is because of the substituents on the rings of Haworth's and Sheldrick's compounds, or because of the closed versus the open ring structure, can probably be determined by operating with such substitution present. Closing the ring without the substitution is a more difficult matter, but could be accomplished by further bromination of the already brominated ethyl benzylphenacylmalonate. The benzyl hydrogens should brominate fairly readily, and it has been demonstrated that the bromine alpha to the ketone is readily removed by hydriodic acid. An internal Friedel and Crafts reaction

could then be employed. Removal of the bromine and replacement with hydroxyl is also to be considered, the ring then to be closed under acid conditions, but without as drastic a reagent as those usually employed in the former reaction. The bromo malonic ester (XXIII) can be dissolved



in concentrated sulfuric acid and recovered unchanged. Such is the stability to acid.

With the series of compounds used in this investigation, the direct introduction of the formyl group in the presence of alkali is not practical, in view of the reaction which the ethyl benzylphenacylmalonate underwent in the presence of alkali. There is no doubt that the formyl group entered the molecule somewhere, but in view of the ease with which the ketone enolized and transesterified the ester portion of the molecule, it is extremely unlikely that the reaction took place in the manner anticipated. The extreme instability of the compound obtained in the formylation toward all the reagents with which it was treated has prevented its characterization.

It has also appeared that β-benzyloxypropiophenone is too unstable to be brominated so that it could be condensed with ethyl benzylmalonate, if, indeed, it is capable of existence. If α-bromo-β-triphenylmethoxypropiophenone were successfully condensed with ethyl benzylmalonate, the ether could not be cleaved under conditions that would not cause extensive damage elsewhere through hydrogenation.

It has been found that sodium hydride is a useful condensing agent to introduce the phenacyl group in the alpha position of various activated hydrocinnamic esters, and useful also in simple malonic ester condensations.

The γ-keto esters are readily reduced by aluminum isopropoxide to the corresponding alcohol, with simultaneous lactone formation. In the case of the malonic ester, saponification and acidification produced the lactone acid, and

not the hydroxy dibasic acid, and the lactone acid was easily decarboxylated to the simple lactone. Such ease of lactone formation should preclude other side reactions of either the hydroxyl or the acid group, such as anhydride formation with succinic esters.

EXPERIMENTAL

All melting points are corrected. A figure in preceding parentheses indicates the temperature at which the first softening or sintering occurred. Melting points were determined in capillary tubes in a stirred bath heated so that the temperature rise was at the rate of two degrees per minute.

All pressures below 5 millimeters were read on a McLeod gauge.

The author wishes to express his gratitude to Mrs. Mary H. Aldridge and Mr. Byron Baer, who performed the microanalyses reported here.

Ethyl Benzylmalonate

To a 100-ml. three-necked flask containing 50 ml. of ethyl malonate and fitted with a thermometer immersed in the liquid, a magnetic stirrer, a dropping funnel, and a drying tube charged with calcium sulfate, was added 2.4 g. (0.096 mole) of sodium hydride* in small portions. The reaction mixture was stirred constantly. The reaction was exothermic, and each addition of sodium hydride was made only after the material previously added had reacted, leaving a clear solution.

When all of the sodium hydride was introduced, 12.8 g. (0.101 mole) of benzyl chloride was added dropwise through the addition funnel, the temperature being maintained at 100° for

* The sodium hydride used in these experiments was of 95% assay.

12 hours after all of the benzyl chloride was added. After 12 hours a drop on moist test paper showed a neutral reaction. A few drops of glacial acetic acid were added, and sufficient water was added to coagulate the finely dispersed sodium chloride. The slightly yellow solution was decanted from the sodium chloride and subjected to distillation at reduced pressure. After the excess ethyl malonate distilled at 38°/.05 mm., the product was collected at 94°/.05 mm. and weighed 20.2 g. (84%).

Ethyl Benzylacetoacetate

A 1000-ml. three-necked flask fitted as above was charged with 500 ml. of ethyl acetoacetate. Following the above procedure, but using 25 g. (1 mole) of sodium hydride and 130 g. (1.03 mole) of benzyl chloride, there was obtained 208 g. of crude ethyl benzylacetoacetate which on redistillation gave 182g. (83%) of pure ester, which distilled at 131°/3 mm.

Phenacyl Bromide

Acetophenone (50 g., 0.42 mole) and 50 ml. of absolute ether were stirred in a three-necked flask in an ice bath, 0.5 g. of anhydrous aluminum chloride was added, and 67 g. (0.42 mole) of bromine was added dropwise at the rate of 1 ml. per minute. After the addition of the bromine was complete, the solution was transferred to a suction flask fitted with a capillary reaching to the bottom, and solvent was evaporated at room temperature under diminished pressure for several hours. The solid resulting was stirred with water, filtered, and washed several times with water. The solid crystal mass was stirred with 600 ml. of 60-80° ligroin at 50°, and the supernatant so-

lution separated from the aqueous phase remaining. On cooling, the solution deposited 67 g. (30%) of hard crystals whose size depended on the rate of cooling. The melting point was 49 - 50°.

Ethyl Benzylphenacylmalonate (VIII)

Method A. In a 5-l. round-bottomed flask fitted with an addition funnel and connected to an efficient fractionating column, ethyl alcohol was dried by distillation with benzene. Eight grams (0.34 atom) of sodium was then added and allowed to dissolve. Dry benzene was added and the excess alcohol was distilled off. Ninety-six grams (0.385 mole) of ethyl benzylmalonate was added to the sodium ethoxide suspension, and the ethanol formed was distilled off as the benzene-alcohol azeotrope. The distillation required about 12 hours, and left a clear slightly yellow solution. Benzene was added to keep the volume equal to three liters. To this solution of sodio derivative was added through the addition funnel over a period of 12 hours 66 g. (0.33 mole) of phenacyl bromide dissolved in benzene. The solution was heated under reflux for 12 hours, during which time it became quite cloudy. At the end of this time, the odor of phenacyl bromide could not be detected over the hot reaction mixture, and heating was discontinued.

Without further treatment, the mixture was subjected to rapid steam distillation, using an 18-inch Vigreaux column. The benzene was rapidly removed, and distillation was discontinued when the temperature at the head of the column rose to nearly 100°. The residue was washed with water, and

the organic layer was placed in a 500-ml. flask and subjected to distillation under low pressure. When the recovered ethyl benzylmalonate stopped distilling, the residue was transferred to a Hickman still and subjected to molecular distillation. At a pressure of 0.1 micron a short forerun of ethyl benzylmalonate was collected at a bath temperature of 80°. The transition from forerun to product was best observed by chilling the condensing surface of the still with ice-water. At that temperature the product was extremely viscous, a drop requiring several seconds to sever itself from the drip tip and recover; on the other hand the forerun dripped readily from the tip under these conditions. The product distilled smoothly at a bath temperature of 100°, and left a red residue.

The product from the distillation was recrystallized from 10 ml. of 60-80° petroleum ether per gram of product, and weighed 46 g. (36%). The substance melted at 74.6 - 76.4°.

Method B. A 300-ml. three-necked flask was fitted with a reflux condenser, a mercury-sealed stirrer, and an addition funnel. It was charged with 37 g. (0.149 mole) of ethyl benzylmalonate and 100 ml. of dry benzene, and the solution was heated to reflux. While the solution was stirred, 2.5 g. (0.1 mole) of sodium hydride was added gradually, giving a clear solution. A solution of 18 g. (0.09 mole) of phenacyl bromide in benzene was added dropwise, and the reaction mixture was heated under reflux, with stirring, for 12 hours.

Worked up as above, the reaction yielded 18.0 g. of product (55% of the theoretical amount).

Calculated for $C_{22}H_{24}O_5$	6.57 % H	71.72 % C	S.E.184
Found	6.62	71.85	variable
	6.59	71.67	

mg. sample	7.372	7.903
mg. H_2O	4.366	4.658
mg. CO_2	19.410	20.754

Ethyl Benzylphenacylacetoacetate

In a 300-ml. round-bottomed flask fitted with a magnetic stirrer and a reflux condenser with drying tube, were placed 22 g. (0.1 mole) of ethyl benzylacetoacetate and 100 ml. of dry benzene. The solution was heated to reflux temperature and 2.2 g. (0.088 mole) of sodium hydride was added gradually. The solution became slightly darker. When all of the sodium hydride had reacted, a solution of 20 g. (0.1 mole) of phenacyl bromide in 70 ml. of dry benzene was added dropwise, producing an exothermic reaction. The reaction mixture was heated under reflux overnight. At the end of this time, no smell of phenacyl bromide was detected. The reaction mixture was cooled, extracted with water, and the benzene solution dried with anhydrous sodium sulfate and evaporated. Molecular distillation gave about 0.3 g. of the original ester at a bath temperature of 60° and under a pressure of 0.2 micron. The viscosity of the distillate then increased suddenly, and the product distilled, slightly yellow, at a bath temperature of 85°. The temperature could be raised to 140° without increasing the pressure. The viscous product weighed 18 g. (53%) and did not crystallize.

Calculated for $C_{21}H_{22}O_4$	6.55 % H	74.53 % C
Found	6.53	75.67
	6.70	75.81

mg. sample	6.7612	6.5589
mg. H_2O	3.9453	3.9285
mg. CO_2	18.7459	18.2215

Ethyl Benzylphenacylcyanoacetate (XX)

A solution of 35 g. (0.1725 mole) of ethyl benzylcyanoacetate in 300 ml. of dry benzene was heated under reflux while 2.5 g. (0.1 mole) of sodium hydride was added in small portions. To the clear light yellow solution resulting was added a solution of 17.25 g. (0.086 mole) of phenacyl bromide in benzene. This produced a vigorous reaction although no precipitation of sodium bromide was observed. The reaction mixture was heated under reflux overnight. It was then washed with water until no more color was extracted. At the point in the washing where the pH dropped to approximately neutral, a very stable emulsion occurred, consisting of a portion of the benzene layer in all of the water layer. The benzene solution was dried and evaporated by dropping it into an evacuated flask heated in an oil bath held at 150°. When the excess ethyl benzylcyanoacetate was distilled off under reduced pressure, the residue crystallized. It was recrystalliz ed from ethanol, and yielded 13.5 g. (50%) of product which melted at (93.3) 93.7 - 94.4°

Calculated for $C_{20}H_{19}O_3N$	5.96 % H	74.74 % C	4.36 % N
Found	6.01	74.38	4.60
	6.29	74.98	4.68

mg. sample	6.3321	5.9943	3.563	3.482
mg. H_2O	3.4028	3.3690		
mg. CO_2	17.2588	16.4543		
ml. N_2			0.153	0.144
pressure			760	762
temperature °C.			30	29.5

Hydrazone of β-benzoyl- α-benzylpropionitrile (XXI)

A solution of 3 g. (0.009 mole) of ethyl benzylphenacylcyanoacetate and 0.8 g. (0.014 mole) of 85% hydrazine hydrate in 15 ml. of 95% ethanol was warmed overnight on a steam cone, yielding 0.6 g. of crystalline material which was soluble in benzene, chloroform, and insoluble in ethanol, ligroin, and ethyl acetate. In mixtures of solvents the compound showed a negligible temperature coefficient of solubility. The crystals were repeatedly washed with hot absolute and 95% ethanol; they melted at (208.2) 208.8 - 211.6°.

Calculated for $C_{17}H_{17}N_3$		6.51 % H	77.53 % C	15.96 % N
Found		6.28	77.85	15.56
		6.37	77.98	15.35
mg. sample	6.3230	6.6212	3.929	3.879
mg. H_2O	3.5486	3.7374		
mg. CO_2	18.0380	18.9194		
ml. N_2			0.550	0.540
pressure			760	759.5
temperature °C.			30	29

2,4-Dinitrophenylhydrazone of Ethyl Benzylphenacylacetoacetate

To a solution of 0.2 g. (0.01 mole) of 2,4-dinitrophenylhydrazine and 1 ml. of concentrated hydrochloric acid in 25 ml. of methanol was added 0.45 g. (0.013 mole) of ethyl benzylphenacylacetoacetate in 10 ml. of methanol. The solution was stirred at room temperature. After 10 minutes the solution became red, and after an hour a precipitate was observed. It was collected on a filter and weighed less than 0.01 g.; it melted gradually from 82 - 126°. The filtrate was stirred another 10 hours, after which a yellow-orange precipitate was present. This, when filtered and dried, weighed 0.35 g. and melted at (148) 153.8 - 155.8°. The filtrate was stirred fur-

ther, and deposited a further crop of crystals. On recrystallization from boiling methanol, the precipitate was not wholly soluble, although the major portion of it dissolved rapidly. When the suspension was filtered and the filtrate cooled, crystals were obtained. Recrystallization from methanol gave a product which melted at 157.5 - 157.7°.

Calculated for $C_{27}H_{26}O_7N_4$		5.05 % H	62.54 % C	10.81 % N
Found		5.31	62.45	10.28
		5.27	62.74	10.21
mg. sample	6.4140	5.9455	3.084	2.959
mg. H_2O	3.0470	2.7985		
mg. CO_2	14.6775	13.6636		
ml. N_2			0.287	0.275
pressure			758	761.5
temperature °C.			30.5	30.5

Benzylphenacylmalonic acid

To a solution of 1.6 g. (0.04 mole) of sodium hydroxide in 150 ml. of absolute ethanol was added 7.35 g. (0.02 mole) of ethyl benzylphenacylmalonate. On standing at room temperature the solution turned slightly yellow as the sodium salt of the acid precipitated. After standing for 12 hours, water was added to make 250 ml. of clear solution. After being stirred with decolorizing charcoal, the solution was filtered, made acid to litmus with hydrochloric acid, and treated similarly with charcoal again. The solution was then warmed to 70° and water was added until permanent cloudiness appeared. The volume of the solution was about 500 ml. The solution was stirred until crystallization was well started, and then cooled in an ice bath. Filtering gave 5.4 g. (75%) of product which decomposed at 181°. All attempts to recrystallize gave a less pure product.

The calcium salt was precipitated, filtered and washed with acetone. The salt was suspended in ether, and concentrated hydrochloric acid was added. The ether layer was separated, washed with water, dried, and carefully evaporated. The acid crystallized in clumps of needles, which melted at (154.4) 155.0 - 157° with decomposition.

Calculated for $C_{18}H_{16}O_5$	5.16 % H	69.22 % C	N.E.156
Found	5.36	68.45	157
	5.69	68.86	
	5.52	68.44	

mg. sample	7.386	5.673	7.704
mg. H_2O	3.536	2.887	3.875
mg. CO_2	18.527	14.314	19.317

Benzylphenacylacetic acid (XIII)

The decarboxylation of the malonic acid above was carried out in a testtube suspended in a melting point bath. The testtube contained 3.12 g. (0.01 mole) of benzylphenacylmalonic acid, and was heated carefully to 170° so that only a small part of the bottom of the tube was heated. Otherwise the evolution of gases carried material above the heated zone. After the reaction had subsided, the tube was lowered further so that the material which had been carried to the walls of the tube would also be heated. The small amounts of material thus situated did not react vigorously enough to carry the material further. The reaction was considered to be finished when no further effervescence could be observed. The product was recrystallized from 50% acetic acid and weighed 2.60 g. (97%). It melted at (173.3) 174.0 - 174.7°.

Calculated for $C_{17}H_{16}O_3$	6.01 % H	76.10% C	N.E. 268
Found	6.24	76.20	268
	6.17	76.02	

mg. sample	9.716	8.621
mg. H_2O	5.423	7.753
mg. CO_2	27.129	24.014

Ethyl Benzylphenacylacetate

Anhydrous hydrogen chloride was passed into a solution of 2.7 g. (0.01 mole) of benzylphenacylacetic acid in 100 ml. of absolute ethanol at 0° until the solution was nearly saturated. After 4 hours the solution was evaporated under reduced pressure, the residue taken up in benzene and water, and the benzene solution washed with sodium bicarbonate solution several times. After being dried with anhydrous sodium sulfate, the benzene solution was evaporated to dryness under reduced pressure, leaving a colorless oil which crystallized after standing several days. Recrystallization from 30-60° ligroin yielded 2.8 g. (94%) of ester which melted at (48.9) 49.2 - 49.5°.

Calculated for $C_{19}H_{20}O_3$	6.80 % H	77.00 % C
	6.95	77.20
	6.92	77.20

mg. sample	6.520	6.900
mg. H_2O	3.884	4.266
mg. CO_2	17.686	19.519

p-Phenylphenacyl Benzylphenacylacetate

One gram of benzylphenacylacetic acid was neutralized in 10 ml. of ethanol with sodium hydroxide solution. There were added 4 drops of 0.3 N hydrochloric acid, 1 g. of p-phenylphenacyl bromide, and ethanol to make 50 ml. Solid was still present. The mixture was heated under reflux for 1 hour, cooled, and the crystals separated by filtration. Recrystallization from ethyl acetate gave a product which melted at (149.8) 150.4 - 150.7°.

Calculated for $C_{31}H_{26}O_4$	5.37 % H	80.50 % C
Found	5.84	80.66
	5.92	80.43

mg. sample	8.123	7.217
mg. H_2O	4.261	3.816
mg. CO_2	24.011	21.270

Benzyl-β-hydroxy-β-phenethylmalonic acid lactone (XI)

Ethyl benzylphenacylmalonate (3.68 g., 0.01 mole) was dissolved in 250 ml. of 1 M aluminum isopropoxide in isopropyl alcohol, and solvent was distilled very slowly through an efficient fractionating column for 1 week. At the end of this time reduction was complete. The solution was evaporated to dryness under reduced pressure, and the residue, dissolved in ether, washed with sodium hydroxide solution. Evaporation of the ether produced an oil which could not be crystallized. The addition of alcoholic sodium hydroxide produced a white precipitate on standing overnight at room temperature. Water was added and the alcohol was distilled off through a column. The aqueous solution was cooled, acidified with hydrochloric acid, and extracted with chloroform. The chloroform extract was dried with anhydrous sodium sulfate and evaporated to dryness. After standing about 2 weeks, the oil crystallized. Recrystallization from 60-80° ligroin gave 2.3 g. (78%) of lactone acid which melted at (113.0) 114.2 - 115.5 with decomposition.

Calculated for $C_{18}H_{18}O_4$	5.44 % H	72.96 % C
Found	5.69	73.54
	5.79	73.11

mg. sample	7.170	6.982
mg. H_2O	3.647	3.605
mg. CO_2	19.269	18.730

Ethyl Benzyl- α-bromophenacylmalonate (XXIII)

A solution of 36.8 g. (0.1 mole) of ethyl benzylphenacylmalonate in 100 ml. of carbon tetrachloride was heated to reflux in a 500-ml. round-bottomed flask, and 16.0 g. (0.1 mole) of bromine was added dropwise. Each drop was decolorized as it hit the surface and the solution remained colorless until practically all of the bromine had been added, when it assumed a reddish color. The solvent was distilled off under reduced pressure (the red color distilled with the solvent) and the remaining solid was recrystallized from alcohol. There was obtained 42.5 g. (95%) of white solid which melted at (114.5) 115.2 - 116.2°.

When this bromination was run at room temperature, the reaction proceeded more slowly, and the product precipitated; the reaction mixture set to an almost solid slush.

Calculated for $C_{22}H_{23}O_5Br$	5.18 % H	59.07 % C	17.87 % Br
Found	5.48	59.00	17.86
	5.46	58.95	17.82

mg. sample	8.645	9.268	5.854	4.300
mg. H_2O	4.231	4.521		
mg. CO_2	18.689	20.020		
mg. AgBr			2.457	1.801

Hydriodic Acid Reduction of Ethyl Benzyl- α-bromophenacylmalonate

A solution of 0.447 g. (0.001 mole) of ethyl benzyl- α-bromophenacylmalonate in 40 ml. of warm 95% ethanol was treated with approximately 0.4 g. (0.0024 mole) of potassium iodide and 2 ml. of syrupy phosphoric acid, and maintained at 50° overnight, tightly stoppered. The iodine in the solution was titrated with 0.1 N sodium thiosulfate, and required 19.5 ml. 0.00195 equivalent). Further heating produced no more iodine.

When cooled, the solution precipitated 0.36 g. of white crystals which melted at (73.8) 74.1 - 75.3°. A mixed melting point with ethyl benzylphenacylmalonate showed no depression.

Aluminum Isopropoxide Reduction of Ethyl Benzyl-α-bromophenacylmalonate

Ethyl benzyl-α-bromophenacylmalonate (0.45 g., 0.001 mole) was dissolved in 10 ml. of 1 M aluminum isopropoxide in isopropyl alcohol (0.03 mole) and heated under reflux for 2 hours. The solution was cooled, 2 ml. of concentrated sulfuric acid in 20 ml. of water was added, and the alcohol was distilled out, together with the acetone formed, through an efficient fractionating column. The distillate was caught in 50 ml. of 2 N hydrochloric acid containing 0.001 mole of 2,4-dinitrophenylhydrazine. The precipitate was filtered into a Gooch crucible, washed with 2 N hydrochloric acid, and then with water until free of chloride ion. The crucible was dried at 100° and weighed. The precipitate weighed 0.2110 g. (0.000899 mole), showing that this amount of reducing agent had reacted.

The aqueous acid solution from which the acetone and alcohol were distilled was washed with chloroform until colorless (3 ml.). The resulting solution was then titrated with standard silver nitrate solution, using a modified[29] Mohr method. The titration required 0.000902 mole, indicating that 90.2% of the bromine originally present had been removed by reduction.

The agreement, 3 parts per thousand, between the amount of bromine removed and the amount of reducing agent oxidized, indicated that there was no carbonyl reduction.

Catalytic Reduction of Ethyl Benzylphenacylmalonate

A solution of 0. 37 g. (0.001 mole) of ethyl benzylphenacylmalonate in 80 ml. of 96% ethanol was shaken with hydrogen with various catalysts. When platinum oxide was used, the catalyst was always first reduced by shaking with hydrogen. Both platinum oxide and Raney nickel were used at room temperature and pressure, but the barium-copper-chromium-oxide was used as indicated. The products were either ethyl benzylphenacylmalonate (A) or ethyl benzylphenethylmalonate (B), except Run No. 7 which produced a brown oil from which no pure substances could be isolated.

Run No.	g.	Cat.	equiv. H_2 absorbed	Products	Remarks
1	0.1	PtO_2	1.5	1 part A, 3 parts B	
2	0.4	PtO_2	2	B	10 minute induction period.
3	2	Ni(R)	2	B	A added in solution
4	2	Ni(R)	2	B	A added solid.
5	2	Ni(R)	2	B	3 ml. $(C_2H_5)_3N$ added. Slow.
6	1	BaCuCrO	--	A	1500 p.s.i., 125°, 2hrs.
7	1	BaCuCrO	--	--	2000 p.s.i., 135°, 3hrs.

The ethyl benzyl-β-phenethylmalonate was identified by saponification and acidification to give benzyl-β-phenethylacid, which melted at 152 - 153.2°. The literature reported a melting point of 153°.

α-Benzyl-γ-phenyl-γ-butyrolactone (XII)

Method A. Benzylphenacylacetic acid (2.68 g., 0.01 mole) was dissolved in 20 ml. of 1 M aluminum isopropoxide in isopropyl alcohol and heated under reflux for 2 days with occasional slow distillation of the acetone formed. At the end of this time, no more acetone was present in the distillate. Dilute hydrochloric acid was added and the alcohol was removed

by distillation. The resulting suspension of oil in water was extracted with chloroform, the extract dried with magnesium sulfate and evaporated at the water pump. The syrup resulting was distilled in a molecular still under a pressure of 0.1 micron with a bath temperature of 100°, giving a clear white distillate. When seeded, the distillate crystallized. Recrystallization from ethanol gave 2.3 g. (91%) of lactone which melted at (79.1) 79.6 - 80.6°.

Calculated for $C_{17}H_{16}O_2$	6.39 % H	80.92% C
Found	6.66	81.22
	6.48	81.06

mg. sample	6.262	7.143
mg. H_2O	3.732	4.127
mg. CO_2	18.637	21.218

Method B. A small sample of the lactone acid (XI) was heated in a testtube at 150°; the product was dissolved in hot alcohol, and crystallized by scratching and cooling. When recrystallized from alcohol, the substance proved to be identical with the lactone from the above reduction.

Attempted Addition of Formaldehyde to Ethyl Benzylphenacylmalonate

Ethyl benzylphenacylmalonate (7.40 g., 0.02 mole), 0.60 g. (0.02 mole monomer) of paraformaldehyde, and 0.30 g. (0.0021 mole) of anhydrous potassium carbonate were placed in an Erlenmeyer flask with 15 ml. of dry methanol and a magnetic stirrer. The flask was closed with a stopper and stirred for 14 days. At the end of this time the contents of the flask were poured into 100 ml. of 2 N hydrochloric acid. The white precipitate formed was filtered, washed with water, and recrystallized from ethanol. It proved to be starting material.

Attempted Addition of Formaldehyde to Benzylphenacylmalonic acid

An aqueous solution of 3.12 g. (0.01 mole) of benzylphenacylmalonic acid, 10 ml. of 2.5 N sodium hydroxide solution, and 8 ml. (0.1 mole) of 37% formalin was allowed to stand at room temperature for 40 hours. Acidification produced a cloudiness that later deposited as crystals. Further acidification precipitated more crystals, which when filtered and dried in air until the smell of formaldehyde was no longer apparent, weighed 3.0 g. They melted with vigorous evolution of gas at 160° giving a solid that melted at 173 - 174°. A mixed melting point with the original malonic acid demonstrated that the product was starting material, recovered in good yield.

Attempted Addition of Formaldehyde to Benzylphenacylacetic acid

A solution of 2.7 g. (0.01 mole) of benzylphenacylacetic acid, 10 ml. of 2.5 N sodium hydroxide solution, and 8 ml. of 37% formalin was allowed to stand stoppered for 5 weeks at room temperature. A heavier liquid phase was observed. It was taken up in ether, dried and evaporated under diminished pressure. but could not be crystallized. With no solvent it remained as a hard clear almost colorless glass. Treatment with 2,4-dinitrophenylhydrazine in alcoholic solution yielded only a trace of the 2,4-dinitrophenylhydrazone of formaldehyde, identified by melting point, mixed melting point and analysis. A test of the original aqueous phase left after the extraction with ether showed it to be only slightly alkaline, about pH 8.

2-Chloroethyl Triphenylmethyl Ether

A solution of 8.05 g. (0.1 mole) of ethylene chlorohydrin,

26.0 g. (0.1 mole) of triphenylcarbinol and 0.05 g. of p-toluenesulfonic acid in 75 ml. of benzene was heated under reflux with a Dean-Stark trap until no more water was being collected. The theoretical amount of water was obtained. The solution was cooled while being stirred. If the solution was not stirred, the crystals adhered very strongly to the walls of the flask. The crystals were filtered and recrystallized from petroleum ether. The product weighed 22.7 g. (70%) and melted at 131.1 - 131.8°. The benzene filtrate contained more product, but was not worked up.

Calculated for $C_{21}H_{19}OCl$	5.93 % H	78.13 % C	10.98 % Cl
Found	6.04	78.35	10.79
	5.95	78.24	10.92

mg. sample	7.331	6.732	4.918	7.004
mg. H_2O	3.958	3.582		
mg. CO_2	21.048	19.298		
mg. AgCl			2.144	3.091

Since this work was done the preparation of this compound from triphenylmethyl chloride and the chlorohydrin in pyridine, with a melting point of 130 - 131°, has been reported.[28]

2-Bromoethyl Triphenylmethyl Ether

This compound was made as described above for the preparation of the 2-chloro compound. It was obtained in nearly theoretical yield although exact measurements were not made. The white crystals melted at 127.0 - 127.8°.

Calculated for $C_{21}H_{19}OBr$	5.21 % H	68.67 % C	21.76 % Br
Found	5.43	69.02	22.22
	5.58	68.94	22.34

mg. sample	6.3874	5.9540	7.980	5.098
mg. H_2O	3.1022	2.9721		
mg. CO_2	16.1543	15.0412		
mg. AgBr			4.166	2.680

2-Cyanoethyl Triphenylmethyl Ether

This compound was made as described above for the 2-chloro compound, except that toluene was used instead of benzene for the reaction medium, and toluene was used in place of petroleum ether for the recrystallization. The compound melted at (167.2) 169.2 - 170.5°.

Calculated for $C_{22}H_{19}ON$		6.11 % H	84.31 % C	4.47 % N
Found		6.22	84.31	4.93
		6.49	84.57	5.05
mg. sample	6.1724	6.3783	4.480	3.467
mg. H_2O	3.433	3.6155		
mg. CO_2	19.0702	19.7677		
ml. N_2	0.203	0.162	0.203	0.162
pressure			766	765
temperature °C.			34	35

Attempted Hydrogenolysis of n-Butyl Triphenylmethyl Ether

Two grams of n-butyl trityl ether in 100 ml. of absolute ethanol were shaken with 0.05 g. of palladium oxide for 5 hours under hydrogen at 35 p.s.i. The catalyst was filtered off and the filtrate treated with water until cloudy. After standing for 5 days, the solution deposited crystals. After being recrystallized from alcohol, the product melted at 80.7 - 81.6° and weighed 0.6 g. The remainder was an oil that could not be crystallized, and was considered to be starting material and butanol. A mixed melting point with an authentic specimen of ethyl trityl ether showed no depression.

Attempted Hydrogenolysis of Ethyl Triphenylmethyl Ether

A solution of 20 g. (0.069 mole) of ethyl triphenylmethyl ether in cyclohexane was shaken with hydrogen at room temperature and 20 p.s.i. pressure, using successively palladium oxide, platinum oxide, and platinum oxide that had first been

reduced with hydrogen. No absorption of hydrogen took place.

The same solution was shaken with reduced platinum oxide at room temperature under 1500 p.s.i. No reaction took place. When Raney nickel was used at a temperature of 115° and under a pressure of 2300 p.s.i., no reaction took place, and starting material was recovered in good yield.

Reaction of Benzyl Alcohol with Methyl Acrylate

A solution of 0.1 g. (0.00435 atom) of sodium in 10 ml. of benzyl alcohol was added with stirring and cooling to a solution of 8.8 g. (0.1 mole) of methyl acrylate and 3 ml. of benzyl alcohol so that the temperature did not rise above 40°. The reaction mixture was allowed to stand for 2 days. Distillation under reduced pressure gave 11.4 g. of a clear distillate whose boiling point, even with careful fractionation, rose gradually and steadily from 56 - 137° under 100 microns pressure. Repeated fractionation did not achieve any separation. Saponification at room temperature with alcoholic sodium hydroxide yielded a substance soluble in aqueous alkali and precipitated by mineral acids. The product was insoluble in chloroform and melted over 500°. Reprecipitation continued to give the same gummy material which could not be purified sufficiently for identification.

Reaction of Sodium Benzylate with β-Bromopropiophenone

A benzene solution of 4.25 g. (0.02 mole) of β-bromopropiophenone was added to 15 ml. of benzyl alcohol in which 0.46 g. (0.02 atom) of sodium had been dissolved. The reaction mixture was stirred for 4 hours, filtered, and distilled under

reduced pressure. After the benzene was removed, the benzyl alcohol was removed at room temperature at a pressure of .1 - .5 micron. The residue was dissolved in alcohol, and cooling precipitated a white solid. The precipitate was only partially soluble in a fresh portion of alcohol, and the solution thus obtained deposited a precipitate on cooling. This process was repeated, each time producing less of a white solid which melted to a viscous liquid at 115 - 130°. This behavior was consistent with that of phenyl vinyl ketone.

Reaction of α,β-Dibromopropiophenone with Benzyl Alcohol and Potassium Iodide

To 35 ml. of benzyl alcohol at 100° containing 8.3 g. (0.05 mole) of potassium iodide was added 5.84 g. (0.02 mole) of α,β-dibromopropiophenone. An immediate red color developed. The reaction mixture was stirred and kept at 100° for 2 hours, then cooled and poured into excess thiosulfate solution. The organic layer was extracted with ether, dried and returned to the reaction flask to which 2 drops of sulfuric acid had been added. After standing overnight, the reaction mixture was heated to 90° to expel the ether. The iodine color was discharged by stirring with thiosulfate solution, and the organic layer was separated. The organic layer amounted to 35 ml. and consisted presumably of benzyl alcohol and products. It was subjected to distillation under diminished pressure. After the benzyl alcohol was collected, the boiling point rose gradually, distilling a small amount of material and leaving a tarry residue in the still pot, probably the polymer from phenyl vinyl ketone.

Attempted Transetherification of β-Ethoxypropiophenone

A solution of 2.55 g. (0.014 mole) of β-ethoxypropiophenone, 3.1 g. (0.028 mole) of benzyl alcohol, and 0.077 g. (0.00045 mole) of p-toluenesulfonic acid in benzene to make 112 ml. was heated under reflux for 4 hours. No ethanol formed could be detected, and the starting products were recovered by distillation under diminished pressure.

Reaction of Ethyl Benzyl-α-bromophenacylmalonate with Potassium Cyanide

A solution of 4.46 g. (0.01 mole) of ethyl benzyl-α-bromophenacylmalonate was heated under reflux with 1.0 g. (0.015 mole) of dry potassium cyanide in absolute alcohol for 12 hours. At the end of this time the suspension of white solid was filtered hot to remove the potassium bromide, and the filtrate chilled in ice. A precipitate formed slowly; it was removed by filtration and weighed 0.75 g. When recrystallized from 60% ethanol, it melted at (69.8) 70.2 - 71.2°.

When the reaction was carried out in 95% ethanol, a larger yield of material was obtained, which when recrystallized as above melted at (75.0) 75.2 - 76.2°.

The use of 75% ethanol as solvent and the direct fusion at 135° of the reactants without any solvent resulted in the formation of tars from which traces of starting materials could be isolated, along with traces of the same compound obtained above. When glycerol or dioxane was used as solvent, most of the starting material was recovered unchanged.

Calculated for $C_{44}H_{46}O_{11}$	6.18 % H	70.38 % C	24.00 % OC_2H_5
Found	6.43	70.53	23.75
	6.50	70.35	23.69

mg. sample	7.874	7.531	4.906	5.115
mg. H_2O	4.524	4.576		
mg. CO_2	20.351	19.414		
ml. thiosulfate			12.68	12.06
N of thiosulfate			0.01224	0.01338

Attempted Reformatsky Reaction with Ethyl Benzyl- α-bromophenacylmalonate

Using thoroughly dry apparatus, a solution of 4.47 g. (0.01 mole) of ethyl benzyl- α-bromophenacylmalonate in absolute ether was stirred and heated under reflux with 7.1 g. (0.1 mole) of zinc alloy (8% copper). There was no apparent reaction after 12 hours. The ether was replaced by toluene and the heating was continued for 36 hours. There was again no reaction. The addition of paraformaldehyde caused no change, and the polymer sublimed into the condenser.

Reaction of Ethyl Formate with Ethyl Benzylphenacylmalonate

A suspension of dry alcohol-free sodium methoxide was prepared by dissolving 4.6 g. (0.2 atom) of sodium in dry methanol, evaporating the solution to dryness, heating for 2 hours at low pressure in an oil bath at 200°, and then distilling in 250 ml. of dry benzene. Ethyl benzylphenacylmalonate (17.5 g., 0.0475 mole) and about 18 g. of dry ethyl formate were added. The suspension, which acquired a yellow color when the ketone was added, was stirred at about 40° for 44 hours, at the end of which time the reaction mixture was a clear red solution.

The solution was cooled to 10°, transferred to a separatory funnel, and treated with 60 ml. of ice water. It was agitated with a stream of nitrogen and allowed to settle. Three layers were formed: the lower aqueous layer, a middle dark red oily layer, and the upper benzene layer. The two lower phases were

separated from the upper layer, and the benzene layer was washed three times with cold 0.1 N sodium hydroxide solution which had been swept with nitrogen. The aqueous extracts were combined, washed with ether, and poured slowly into a slush of ice and concentrated hydrochloric acid. The gummy precipitate formed was taken up in ether. On one occasion the gummy precipitate turned partially crystalline when treated with ether, but the substance could not be reprecipitated when once in solution. When the solvent was evaporated carefully after being dried with anhydrous sodium sulfate, the residual oil had a sharp smell similar to that observed after a parallel preparation of 2-hydroxymethylene-1-decalone.

Attempted Alkylation of Formylation Product

The oil obtained above was heated under reflux with stirring with 250 ml. of dry acetone, 14 g. (0.1 mole) of anhydrous potassium carbonate and 17 g. (0.1 mole) of isopropyl iodide for 15 hours. The reaction mixture was evaporated to dryness under diminished pressure and the residue was taken up in ether and water. The ether phase was washed twice with sodium hydroxide solution, dried, and evaporated at room temperature, leaving approximately 1 ml. of a red oil. The oil was stirred and scratched with 60 ml. of 30-60° ligroin, and stored under nitrogen in the refrigerator for 2 days. There was no apparent reaction or change, and other attempts to induce crystallization met with failure.

Attempted Reduction of Alkylated Formylated Product

The ligroin solution from the above experiment was

evaporated under reduced pressure and the residual oil was dissolved in isopropyl alcohol containing excess aluminum isopropoxide. Slow distillation through a good column yielded some acetone. After 40 hours no more acetone was formed. The solution was cooled, and poured into ice and sodium hydroxide solution. The organic layer was washed twice with 10% sodium hydroxide solution and then evaporated. The alkaline extracts on acidification showed no precipitate. The organic residue could not be purified.

Saponification of Reduced Product

The organic residue directly above was dissolved in alcoholic sodium hydroxide, and on standing at room temperature a few hours deposited a large mass of soft solid, as in the saponification of ethyl benzylphenacylmalonate. Benzene was added, and careful fractionation removed the alcohol as the azeotrope. The benzene suspension was extracted three times with water, and the aqueous extract acidified. The resulting oil was extracted with ether, but the hard clear glass obtained on evaporation could not be crystallized, and no pure products could be isolated.

Copper Derivative of Formylated Product

An aqueous solution of the sodio derivative of the formylated product was treated with a saturated aqueous solution of cupric acetate. A green precipitate was formed; it was filtered off with difficulty, since it was gelatinous and soft. It could be reprecipitated from aqueous ethanol, but was not crystalline. After reprecipitation the filtration was easier, and

the product was solid. Various samples from different preparations melted gradually over a five to ten degree range from 140° to 175°.

A solution of the formylated product in ether was shaken with a saturated aqueous solution of cupric acetate. The ether phase took on the characteristic green color of the copper derivative, which could be obtained from it on evaporation.

To a solution of the formylated product in either methyl or ethyl alcohol was added dropwise a saturated solution of cupric acetate in water. Although filtration left most of the product in the filtrate, a fine precipitate was separated which melted at (143) 152 - 156° with decomposition.

Analysis: 5.02 % H 35.85 % C 14.97 % CuO

A solution of the copper derivative in carbon tetrachloride was passed through a chromatographic column packed with activated alumina. A yellow-brown area at the top remained while the green remained lower in the column. Passage of more carbon tetrachloride made the separation of the two colors less distinct, but chloroform made the separation sharp again, and eluted the green color, leaving the yellow-brown band at the top of the column. Evaporation of the filtrate yielded a hard dark green glass which melted from 167 - 175° with decomposition.

Analysis:	5.12 % H	63.39 % C	13.65 % CuO
	5.08	63.56	13.68

A solution of the copper derivative in absolute ether was passed through an alumina column. The copper was completely removed, and the filtrate contained aluminum.

Hydrogenation of Copper Derivative

A solution of 8 g. of copper derivative in 150 ml. of 95% ethanol was shaken with platinum oxide and hydrogen at room temperature and pressure. The green color was discharged. Since the catalyst apparently became poisoned and fresh platinum oxide had to be added, the volume of hydrogen absorbed by the compound could not be determined. The catalyst was removed by filtration, and the slightly yellow filtrate was evaporated under diminished pressure. The residue was taken up in ether and washed with 0.1 N sodium hydroxide, an amount of alkali approximately equivalent to the amount of copper derivative being required. Addition of cupric acetate solution to this slightly alkaline extract produced the original copper derivative.

Attempted Benzylation of Formylated Compound

A solution of 1.2 g. of copper derivative in 30 ml. of ether was shaken with 30 ml. of 25% sulfuric acid. The blue aqueous layer was drawn off, and the yellow-brown ether layer was dried with anhydrous sodium sulfate and evaporated, leaving 0.8 g. of oil. This oil was dissolved in 8 ml. of ethanol containing 0.1 g. of sodium hydroxide, and 0.3 g. (0.0024 mole) of benzyl chloride was added. There being no apparent reaction, the solution was warmed briefly on a steam cone and let stand for 24 hours. Dilution with water, followed by extraction with ether and evaporation under diminished pressure, yielded 0.7 g. of a red oil from which no pure substance could be obtained.

Attempted Benzylation of Copper Derivative

A solution in dry benzene of 0.83 g. of copper derivative and 0.30 g. (0.0025 mole) of benzyl chloride was allowed to stand overnight. A small amount of brown precipitate was filtered off, and the solution was heated under reflux for 20 hours. A water insoluble precipitate was filtered off, and the filtrate examined for products. When the benzyl chloride was removed, only dark tarry products remained, from which no pure substances could be isolated.

Reaction of β-Naphthylamine with Formylated Product

An alkaline solution of the formylated compound from 0.025 mole of ethyl benzylphenacylmalonate was poured into a solution of 5 g. (0.035 mole) of β-naphthylamine and 17 ml. of concentrated hydrochloric acid in 150 ml. of ethanol. Water was added until the solution became cloudy. After standing for 90 minutes the yellow precipitate which had formed was filtered. Recrystallization twice from 95% ethanol gave a product that melted gradually in the neighborhood of 220° with decomposition.

Calculated for $C_{33}H_{31}O_5N$	5.99 % H	75.98 % C
Found	5.77	75.33

mg. sample	7.249
mg. H_2O	3.740
mg. CO_2	19.220

A sample of this product was boiled with 100 ml. of benzene containing 6 ml. of absolute ethanol. The suspension was filtered hot, but when the filtrate was cooled, there was no precipitate. The clear yellow solution was reheated to boiling and evaporated partially at the boiling point, producing

a precipitate which was collected and dried.

Analysis	5.55 % H	75.39 % C
mg. sample	4.068	
mg. H_2O	2.013	
mg. CO_2	10.940	

A sample of the product from alcohol above was dissolved in absolute ethanol (0.1 g. in 500 ml.) and passed through a column of activated alumina. Cautious evaporation of the filtrate yielded yellow needles. When sublimed at a bath temperature of 140° and under a pressure of 0.2 micron, the product melted at (176.6) 177.5 - 178.4°. The literature lists the melting point of di-β-naphthylformamidine as 186°.

Calculated for $C_{21}H_{16}N_2$	5.44 % H	85.10 % C
Found	5.70	85.92
	5.79	86.06

mg. sample	6.0777	6.1621
mg. H_2O	3.0960	3.1928
mg. CO_2	19.1557	19.4514

Other attempts of purify the compound resulted is oils, tars, or low melting solids.

Reaction of Alkali with Ethyl Benzylphenacylmalonate

Ethyl benzylphenacylmalonate (3.68 g., 0.01 mole) was dissolved in 250 ml. of thiophene-free benzene and treated with 0.25 g. (0.01 mole) of sodium hydride. The suspension was heated under reflux for 5 hours, cooled, and poured into ice water. Hydrogen was evolved. The benzene layer was washed with water until the washings were no longer alkaline, dried with anhydrous sodium sulfate and evaporated on a steam cone. The flask containing the residue was evacuated briefly to remove the last traces of benzene, and the residue was then boiled

with 60-80° ligroin, which converted the oily residue to crystals. The suspension was filtered hot, and the solid, which weighed 2.2 g., was recrystallized from 80 ml. of 95% ethanol. Precipitation was very slow from this dilute solution; a more concentrated solution (20 ml.) formed an almost solid slush. Recrystallization four times yielded white crystals of melting point (154) 155.0 - 156.0°.

Calculated for $C_{17}H_{14}O_2$	5.64 % H	81.58 % C
Found	5.80	80.99
	5.90	80.99

mg. sample	7.629	7.912
mg. H_2O	3.952	4.170
mg. CO_2	22.639	23.480

β-Benzoyl-α-benzylpropionic acid enol lactone (XXIV)

Dry, alcohol-free sodium methoxide (0.2 mole) was suspended in dry benzene, and 18.4 g. (0.05 mole) of ethyl benzylphenacylmalonate and 16 ml. of dry ethyl formate were added. The suspension was stirred for 22 hours at room temperature. It was then chilled and extracted with dilute sodium hydroxide solution and water. Since the ethyl formate did not react at room temperature, the extraction removed only a very small amount of material. The benzene solution remaining was evaporated to an oil on a steam cone. The residue was boiled with 60-80° ligroin, a treatment which converted the residue to crystals. The suspension was filtered hot, and the filtrate on cooling deposited only small amounts of an oily material. The precipitate obtained from the hot filtration was recrystallized three times from 95% ethanol, yielding 8.5 g. of white fluffy needles which melted at (158.7) 159.1 - 159.5°.

Calculated for $C_{17}H_{14}O_2$	5.64 % H	81.58 % C
Found	6.03	81.65
	6.13	81.57

mg. sample	6.3195	5.9918
mg. H_2O	3.4046	3.7841
mg. CO_2	18.9077	17.9088

Saponification of β-Benzoyl-α-benzylpropionic acid enol lactone

The enol lactone of β-benzoyl-α-benzylpropionic acid (0.25 g., 0.001 mole), was heated with 15 ml. of 0.1 N sodium hydroxide solution (0.0015 mole) and 15 ml. of 96% ethanol for an hour. The solution was allowed to stand and cool overnight. It was then evaporated under reduced pressure to dryness. When 15 ml. of water was added, a slightly turbid solution was formed. After the turbidity was removed by filtration, the solution was acidified slowly with stirring by adding dropwise 20 ml. of 0.1 N hydrochloric acid. The crystalline slurry was chilled overnight in the refrigerator. Filtration and drying at 60° under reduced pressure yielded 0.25 g. (94%) of white crystals which melted at (171.0) 172.6 - 173.3°. A mixed melting point with an authentic specimen of benzylphenacylacetic acid (XIII) melted at 172.8 - 174.3°.

α- or β-Aldehydo-β-benzoyl-α-benzylpropionic acid enol lactone diethylacetal

Ethyl benzylphenacylmalonate (18.4 g., 0.05 mole), 7.4 g. (0.05 mole) of ethyl orthoformate, and 1.25 g. (0.05 mole) of sodium hydride were placed in a flask with 250 ml. of dry thiophene-free benzene and heated under reflux for 12 hours. The mixture was cooled and extracted with water until neutral, and the benzene solution was dried and evaporated on a steam cone. The residue left after the evaporation, when boiled with 60-80° ligroin, was partially changed to crystals of β-benzoyl-α-benzylpropionic acid enol lactone (1.0 g., 0.004 mole). The

filtrate, on cooling and slow evaporation, deposited large clumps of crystals. Recrystallization from 60-80° ligroin yielded 2.7 g. (0.0076 mole) of product which melted at (104.7) 104.9 - 105.5°. The remainder of the starting material was recovered as benzylphenacylacetic acid on acidification of the alkaline extract.

Calculated for $C_{22}H_{24}O_4$		6.86 % H	74.98 % C	25.57 % OC_2H_5
Found		7.06	75.08	25.89
		7.03	75.18	25.80
mg. sample	6.3594	6.4798	3.903	3-049
mg. H_2O	4.0240	4.0741		
mg. CO_2	17.5668	17.8477		
ml. thiosulfate			13.10	10.20
N of thiosulfate			0.01027	0.01027

LITERATURE CITED

1. Belkin, M., Federation Proceedings, 6, 308 (1947)

2. Sterling, John D., Jr., "The Synthesis of Intermediates Leading to Anticarcinogenic Compounds." Thesis, University of Maryland, College Park, Maryland (1949)

3. Hartwell, J. L., and A. W. Schrecker, paper presented before the American Chemical Society, Philadelphia meeting, April 10, 1950.

4. Price, E. H., "The Chemistry of Podophyllotoxin." Thesis, University of Maryland, College Park, Maryland (1949)

5. Organic Syntheses, 21, 99 (1941)

6. Organic Syntheses, Coll. Vol. II, 480 (1943)

7. Wallingford, V. H., M. A. Thorpe, and A. H. Homeyer, J. Am. Chem. Soc., 64, 580 (1942)

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

9. Meyer, K. H. and P. Kappelmeier, Ber. 44, 2718 (1911)

10. Leuchs, H. and F. Reinhart, Ber. 57, 1203 (1924)

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

12. Walker, J. F. Formaldehyde. New York: Reinhold Publishing Company, 1944, p. 159

13. Haworth, R. D. and G. Sheldrick, J. Chem. Soc. 159, 289 (1941)

14. Van Duzee, E. M. and H. Adkins, J. Am. Chem. Soc. 57, 147 (1935)

15. Kohler, E. P., Am. Chem. J. 42, 375 (1909)

16. Leslie, R. E. and H. R. Henze, J. Am. Chem. Soc. 71, 3480 (1949)

17. Rehburg, C. E., M. B. Dixon and C. H. Fisher, J. Am. Chem. Soc. 68, 544 (1946)

18. Utermohlen, W. P., Jr., J. Am. Chem. Soc. 67, 1505 (1945)

19. Haworth, R. D. and G. Sheldrick, J. Chem. Soc. 147, 636 (1935)

20. Claisen, L., Ann. 281, 331 (1894)

21. Birch, A. J. and R. Robinson, J. Chem. Soc. 1944, 501

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

23. Prelog, V. and U. Geyer, Helv. chim. Acta 28, 1677 (1945)

24. Haworth, R. D. and W. Kelly, J. Chem. Soc. 151, 1645 (1937)

25. Adickes, F. and G. Schäfer, Ber. 65, 950 (1932)

26. Klason, P., Ber. 63, 1981 (1930)

27. Nelles, J., U. S. Patent No. 2,091,373 (Aug. 31, 1937)

28. Castorina, G., Farm. sci. e tec. 4, 45 (1949)

29. Meldrum, W. B. and J. C. Forbes, J. Chem. Ed. 5, 205 (1928)

VITA

Name: Arthur Ellis Brown

Permanent Address: 222 West Price Street, Linden, New Jersey

Degree to be conferred; date: Doctor of Philosophy, 1951

Date of birth: June 19, 1918

Place of birth: West Grove, Pennsylvania

Secondary Education: Westtown School, Westtown, Pennsylvania

Collegiate Institutions attended	Dates	Degree	Date of Degree
Haverford College	1936-1940	A.B.	1940
University of Pennsylvania	1940-1942		
University of Maryland	1946-1950	Ph.D.	1951

Positions held:

Chemist; Eastern Regional Research Laboratory, Philadelphia, Pennsylvania. 1942

Graduate Assistant, Research Assistant, Research Fellow: University of Maryland. 1946-1950

Chemist: General Aniline and Film Corporation, Linden, New Jersey. 1950