

1953

The Doebner modification of the Knoevenagel reaction.

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BOSTON UNIVERSITY

GRADUATE SCHOOL

THESIS

THE DOEBNER MODIFICATION
OF THE KNOEVENAGEL REACTION

by

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SUBMITTED IN PARTIAL FULFILMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
MASTER OF ARTS

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ACKNOWLEDGEMENTS

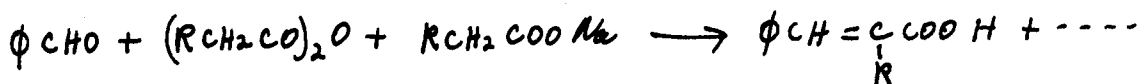
The author wishes to express his gratitude to his major professor, Dr. Walter J. Gensler, for his interest in this work and for the patience, helpfulness, and instruction received while working with him.

The author also wishes to thank Dr. Norman N. Lichtin, his second reader, for his helpful comments during the writing of this thesis, and Dr. George R. Thomas for his help and advice in the laboratory.

THE DOEBNER MODIFICATION OF THE KNOEVENAGEL REACTION

1. INTRODUCTION.

In 1868, Perkin⁴⁴ first described the synthesis of coumarin by heating the sodium salt of salicylaldehyde with acetic anhydride. In 1877, Perkin⁴⁵ described a synthesis of cinnamic acid by heating benzaldehyde, sodium acetate, and acetic anhydride. This general reaction, heating an aromatic aldehyde, an acid anhydride, and the sodium or potassium salt of the acid to form a chain and/or ring substituted cinnamic acid has become known as the Perkin reaction.



Although the reaction is of widespread use, there are two disadvantages; namely, high temperatures and long heating times are required.

In 1898, Knoevenagel³⁴ used malonic acid as the acid component and ammonia or a primary or secondary amine as the basic catalyst in alcohol as a solvent. Both time and temperature are decreased considerably; only two to four hours heating at 100° are required, as compared to five hours at 180° for the Perkin reaction. In addition, the yield is increased from Perkin's 50-70% to 70-80% in the case of cinnamic acid.

Although Verley⁵⁵ was the first to use pyridine in the modification of Knoevenagel's work,¹⁷ Doebner received credit for the innovation, because of his application of the reaction to many aldehydes. Doebner used pyridine as the solvent and a trace of piperidine as the catalyst, along with benzaldehyde and malonic acid. Reaction conditions are heating at 100° for only one or two hours; the yields are from 80 to 90%.



Although both the Knoevenagel reaction and the Doebner modification* (not to be confused with the Doebner reaction), are useful reactions with both aromatic and aliphatic aldehydes, (as compared with the Perkin reaction which yields very poor results with aliphatic aldehydes), the Doebner has one great advantage over the Knoevenagel reaction. The Doebner modification yields almost 100% α - β unsaturated acids, whereas the Knoevenagel reaction, conditions permitting, will yield a high percentage of β - γ as well as α - β unsaturated acids.⁷

The primary reason for the present study was to investigate the mechanism of the Doebner modification. To this end, the study was concerned with the reaction of methylmalonic acid and benzaldehyde under Doebner conditions.

The following section (section II) will deal with the mechanism of the Doebner modification. Section III will describe the problem and will treat the results of the work. Sections IV and V will present, respectively, a general and a detailed description of the experiments.

* For general discussions of the Doebner and Knoevenagel reactions, see references 3, 7, 19 and 30.

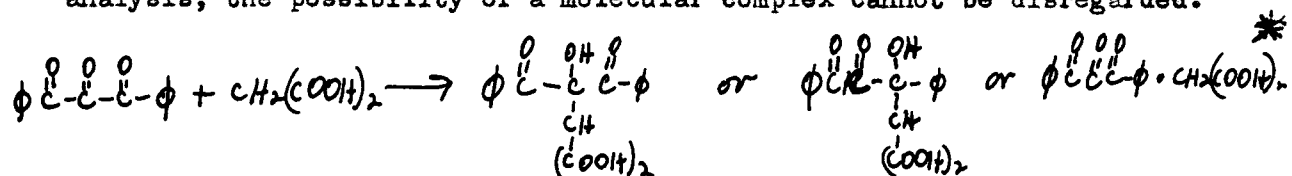
II. The Mechanism of the Doebner Modification.

At the outset, an important question which is recognized but not dealt with here concerns the form in which the malonic acid exists in the reaction medium. The state of the acid in the pyridine solution, whether undissociated acid, monoanion, or dianion is not known. Nor is the form known in which the malonic acid actually or preferentially reacts. However, because the nature of the malonic acid in the pyridine solution will not affect the arguments or conclusions in the present work, the form used in the equations below for the sake of convenience is the undissociated form. In the following discussion, the symbol B: represents any effective nucleophilic group; benzaldehyde is the carbonyl component in all cases; and the reverse reactions are neglected.

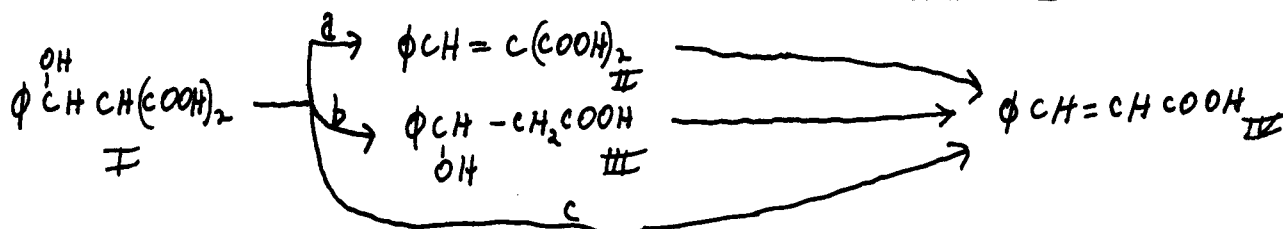
³
v. Auwers has outlined a plausible sequence of events for the Doebner process. This sequence, which begins with an aldol condensation and proceeds via one or more of three paths (i.e., paths a, b, or c, on page 4), is discussed in detail in the following paragraphs. A reasonable first step is an aldol condensation^{1,16,26,48} of malonic acid with benzaldehyde under the influence of a nucleophilic group, B:. According to this picture, the first compound formed is a β -hydroxy-benzylmalonic acid (I).¹⁸ Doebner suggested that a β -hydroxymalonic acid would be the first intermediate when he treated acrolein with malonic acid and observed no evolution of carbon dioxide; however, he failed to isolate the suggested (α -hydroxyallyl) malonic acid. $\left[\text{CH}_2 = \underset{\text{OH}}{\text{CH}} - \text{CH}(\text{COOH})_2 \right]$

There is, however, one possible example in the literature where

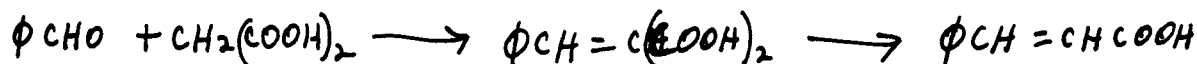
the β -hydroxymalonic acid has been isolated. Sharp and Hoffman⁵¹ treated 1,3-diphenylpropanetrione-1,2,3 with malonic acid and isolated the corresponding β -hydroxymalonic acid, although it was not known whether the malonic acid was attached at the 1-position or the 2-position. Analysis of the product fits the suggested intermediate. In as much as the only evidence bearing on this structure is the correct elementary analysis, the possibility of a molecular complex cannot be disregarded.



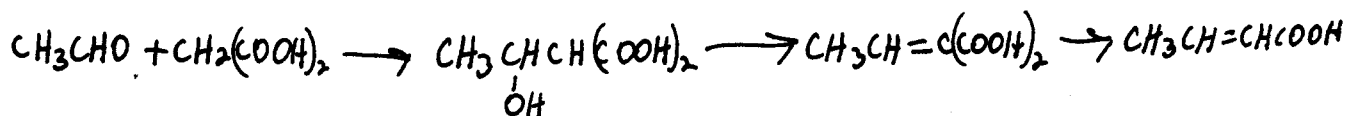
The β -hydroxy-benzylmalonic acid (I) may react further to furnish the final product, cinnamic acid (IV) by three paths, a, b, or c, as follows:



Reaction path a is the one frequently given as the reaction path in the Doebner modification. Whitmore⁵⁶ states that benzalmalonic acids (II) lose carbon dioxide readily under Knoevenagel conditions. Fieser²² in describing the Doebner process, formulates the reaction path as follows:



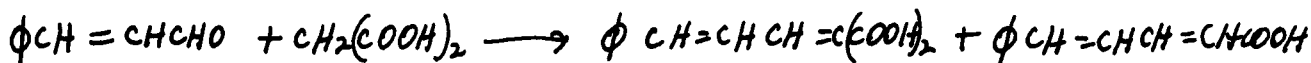
while Karrer³² suggests the following:



Noller⁴² and Hickinbottom²⁹ also suggest paths proceeding via the benzalmalonic acid.

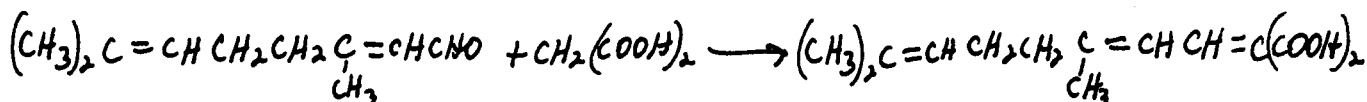
Indeed, the benzalmalonic acids or ethylidene malonic acids have
* THIS IS A SPECIAL CASE, BECAUSE OF THREE CONJUGATE KETO GROUPS.

been isolated in several cases. For example cinnamaldehyde, when treated with malonic acid under Doebner conditions, furnished 82% of condensation products, of which 56% was the dibasic acid and 44% was the monobasic acid.

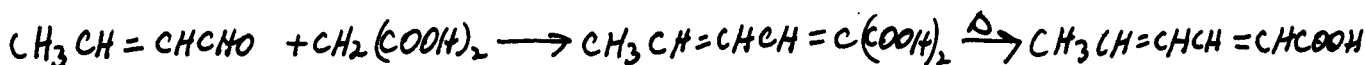


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Dutt, in considering the general case, states that the benzalmalonic acids are stable up to their melting points, (usually over 100°), but that they decarboxylate quite readily in the presence of pyridine at steam-bath temperature. Verley⁵⁵ isolated the corresponding ethylidene malonic acid when he treated citral with malonic acid.



Another example of an isolable ethylidene malonic acid is the case where crotonaldehyde and malonic acid were allowed to react at room temperature. A small amount of the dibasic acid was isolated, but when this acid was heated, it was converted to sorbic acid.⁴⁹



In two cases, 2-hydroxy-5-nitrobenzaldehyde and 3-methoxy-4-hydroxy-5-bromobenzaldehyde, only the corresponding benzalmalonic acids were isolated, and these could not be decarboxylated under the conditions of the experiment.^{43,41}

In the case with cinnamaldehyde mentioned above where a mixture of mono- and di-basic acids was obtained, prolonged heating of the reaction mixture increased the yield of the monobasic acid, but decreased the overall yield. If it could be shown generally that the decarboxylation of the benzalmalonic acid will not occur under Doebner conditions, as in

the case with 2-hydroxy-5-nitrobenzaldehyde, then path a can be eliminated altogether as a possibility. But if decarboxylation occurs readily under ¹⁹ Doebner conditions, as indicated by Dutt, then the only method to determine the importance of the decarboxylation of benzalmalonic acid is a quantitative comparison of the rate of this reaction and the rate of formation of cinnamic acid, starting with benzaldehyde and malonic acid.

The possibility that the benzalmalonic acid is not an intermediate ⁵⁵ in the Doebner process has been explicitly considered by Verley ³ and von Auwers. Verley believes that the unsaturated dibasic acid is formed in a process having nothing to do with the monobasic unsaturated acid ⁷ product. Boxer and Linstead, referring evidently to the unsaturated dibasic acid, state;

"It is by no means proved that the postulated intermediates can decompose with the necessary ease under the conditions of the reaction;..."

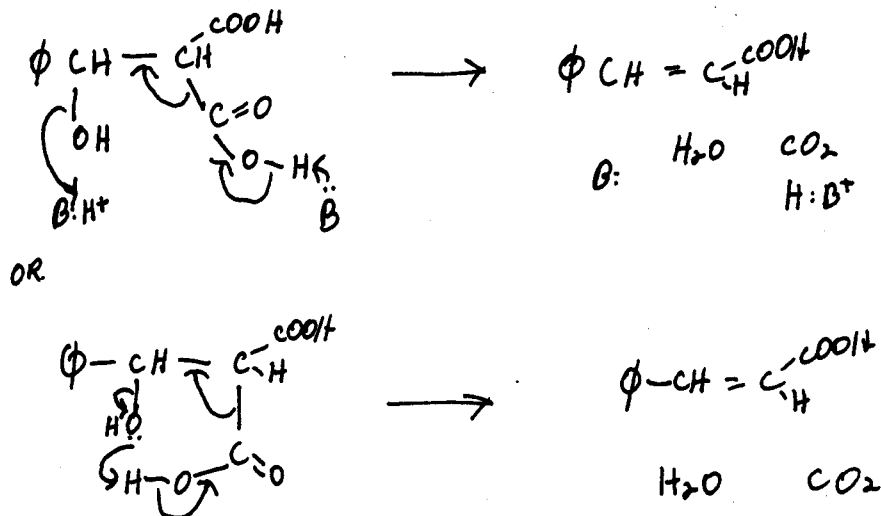
Another way to check the benzalmalonic acid as a possible intermediate is to determine the nature of the decarboxylation product; i.e., is the product cinnamic acid or cis-cinnamic acid? If it can be shown that the cinnamic - cis-cinnamic interconversion under Doebner conditions is negligible, and if the benzaldehyde - malonic acid product is different from the benzalmalonic acid decarboxylation product, then there would be another piece of evidence that benzalmalonic acid is not an intermediate in the Doebner process.

Path b requires that the β -hydroxymalonic acid lose carbon dioxide to form a β -^{HYDROXY}~~hydroxy~~ acid which in turn loses water to furnish the final product, the α - β unsaturated acid. The β -hydroxy acid might also be ³ formed by a mechanism proposed below. von Auwers has isolated the

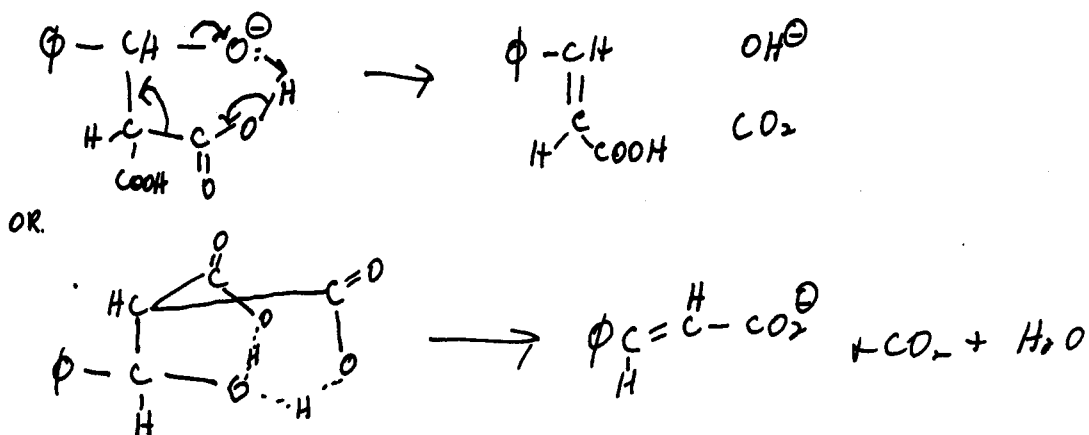
β -hydroxy acid as well as the unsaturated acid, in two cases and suggested that the two products were formed by two different mechanisms. If the β -hydroxy acid were to be prepared and subjected to Doebner conditions, and no unsaturated product were formed, then path b would be ruled out as a possible mechanism. However, if water were lost, and the unsaturated product obtained, then the results would show that the β -hydroxy acid is a possible intermediate in the reaction path. Again a quantitative comparison of the rate of dehydration and the rate of formation of the product from benzaldehyde and malonic acid could be the deciding factor in the determination of the importance of the β -hydroxy acid in the Doebner modification. Also, the nature of the dehydration product may be used as a check; i.e., is the product cinnamic acid or cis-cinnamic acid? If cinnamic acid is obtained in the Doebner reaction, whereas cis-cinnamic acid is obtained in the dehydration process, the hydroxy-acid is eliminated as an intermediate in the Doebner process.

(3)

Path c which is the one favored by v. Auwers, calls for a simultaneous loss of carbon dioxide ^{AND WATER} from the β -hydroxymalonic acid (I), and does not proceed through an isolable intermediate. A possible electronic mechanism might be

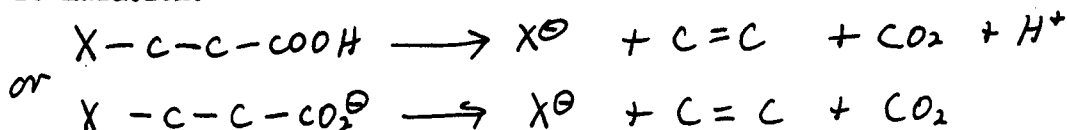


Another possibility is that actually no isolable compound may be formed from benzaldehyde and malonic acid. The reaction may proceed from the anion formed in the initial aldol condensation via simultaneous elimination of carbon dioxide and water as follows:



However, one of the above suggestions involves the elimination of hydroxide ion, which has never been reported in the literature, and the other suggestion involves the formation of a bicyclic intermediate which probably requires a large decrease in a high entropy of formation.

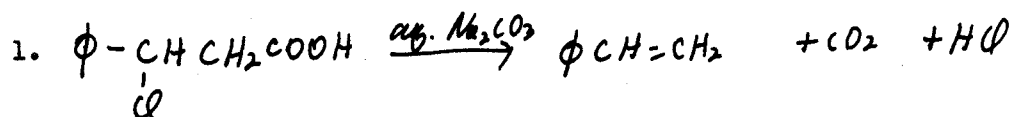
This type of simultaneous elimination of carbon dioxide and water (28) has been explicitly recognized by Hauser who generalizes in the formulation:



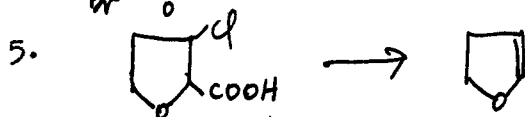
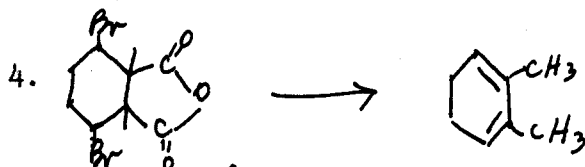
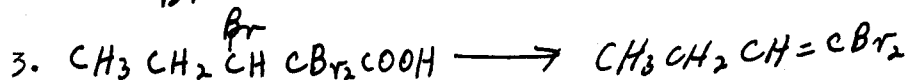
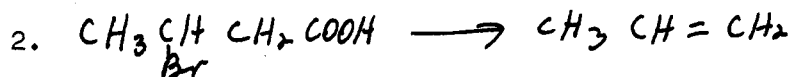
The following examples will illustrate the general process. It should be realized that the simultaneous loss of carbon dioxide and HX in most of these reactions has not been proved. However, the fact that in many cases in which X = halogen, the conditions employed for the elimination appear to be milder than those required for the corresponding two-step

process, is strongly suggestive of the simultaneity of the reaction. Also in some instances the two diastereoisomeric beta-substituted acids furnish the corresponding cis and trans olefins in a stereospecific manner.¹⁵ The possibility of a two-step process with decarboxylation as the first step is thereby excluded.

A. X = halogen



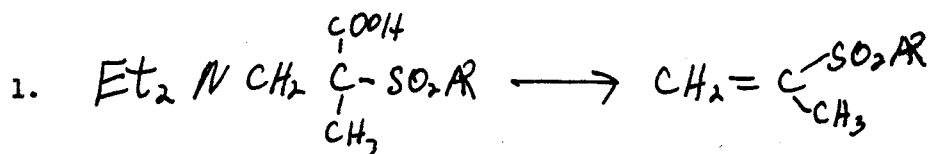
This type of reaction is recognized as a general method for the preparation of styrenes.²⁰ In at least one case, evidence for ~~salvolysis~~ ^{IONIZATION}₂₄ of the β -halogen as the first step has been presented.

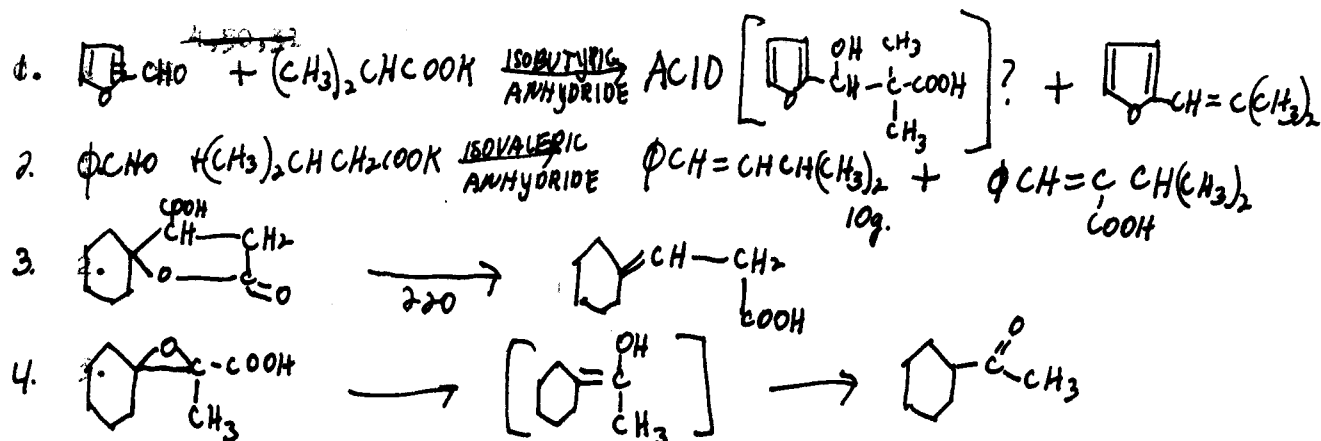
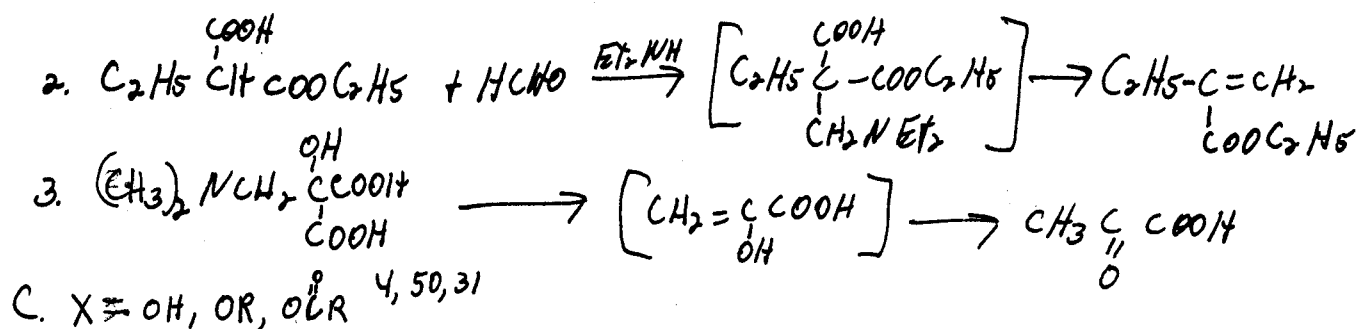


The list of examples of such reactions is long. The original literature should be consulted for the specific details.¹⁵ Reference 15 includes the above examples of this type of reaction with aliphatic compounds, as well as certain other special cases.

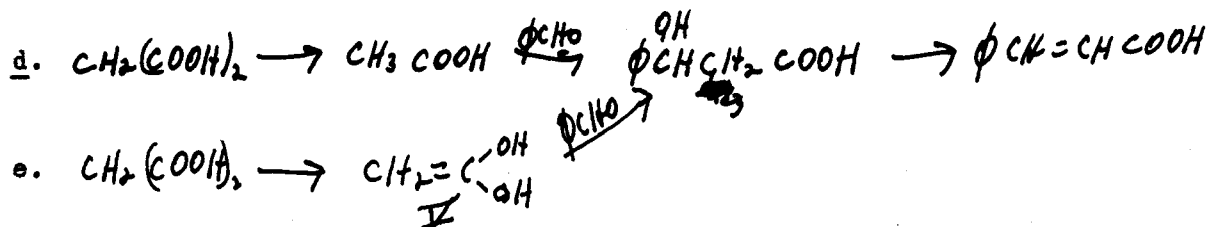
9, 37, 36

B. X = amino grouping





It may be mentioned at this point that proof that this type of simultaneous process must occur under certain structural circumstances in the Doebner process was the goal of the present study. There are, however, at least two possible reaction paths which have not been discussed as yet; namely the preliminary decarboxylation of malonic acid to acetic acid, where acetic acid is the condensing agent (path d), or where the condensing agent is a short lived enol or enolate anion (V) (path e). Verley proposed that "nascent acetic acid" (enolate anion?) was the reactive species.

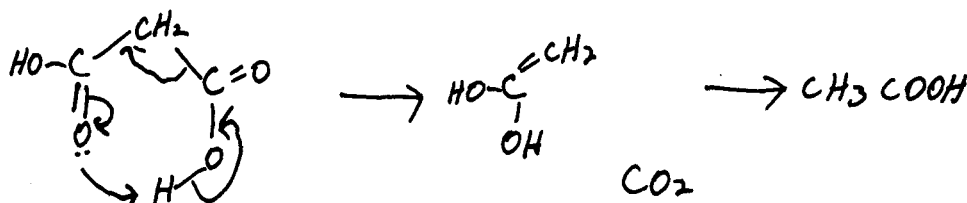


The importance of path d can be determined by replacing malonic acid with acetic acid in the Doebner process, and determining if any cinnamic acid is formed. Both d and e are subject to test of their importance by examining the behavior of the β -hydroxy acid in path b.

If either path d or e is the only possible reaction in the Doebner

process, then the formation and isolation of the unsaturated dibasic acids (eg. II) receives no explanation.

²⁵ Hall has shown that malonic acid decarboxylates ten times as fast as the monoanion and that the dianion is stable. ³³ King suggested that the decarboxylation proceeds through a hydrogen bonded group or zwitterion.

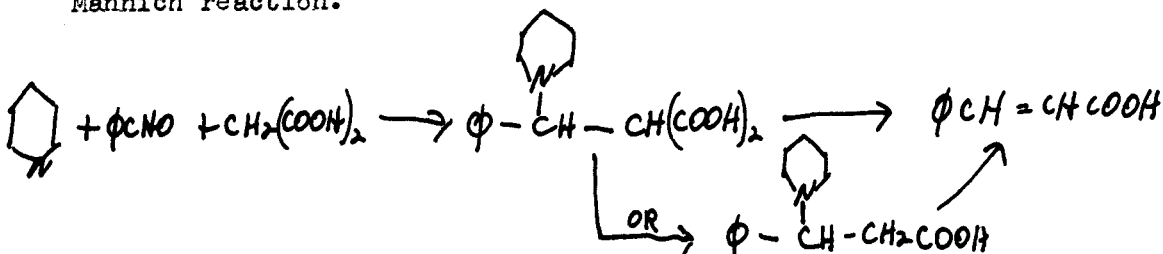


² Hammick et al showed the possibility of another zwitterion from a decarboxylation process, when they demonstrated that picolinic acid will react with a variety of cationoid reagents such as aldehydes, ketones, esters, etc.

Eg.



Still another possible reaction path is one where the basic catalyst actually condenses with the aldehyde and malonic acid, as in the Mannich reaction.

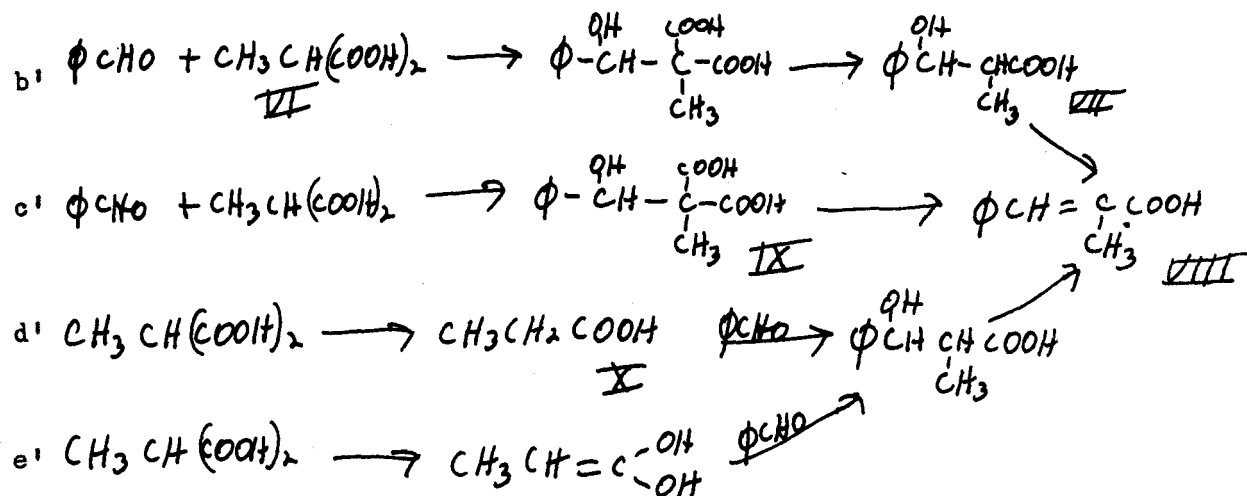


However, there is no case reported in the literature where a nitrogen-containing acid has been isolated from a Doebner process, unless of course, the aldehyde contained nitrogen. Moreover, tertiary amines have never been

known to react in a Mannich type reaction, but yet there are known cases where an aldehyde has condensed with malonic acid under Doebner¹³ conditions in the absence of any secondary or primary amines.

Section III The Problem, The Results, and The Conclusions

If instead of malonic acid, methylmalonic acid were used in the Doebner modification, reaction path a would no longer be possible, and only the following four paths need be considered.



The reaction path analogous to that mentioned on p.7, where the product is formed from a non-isolable intermediate, has been omitted for the reasons presented on p. 7. Path b' would be eliminated if α -methyl- β -hydroxy-hydrocinnamic acid (VII) did not yield α -methylcinnamic acid (VIII) when subjected to Doebner conditions. Paths d' and e' would also be eliminated by the same criterion. Path d' would also be eliminated if propionic acid (X) did not condense with benzaldehyde under Doebner conditions to yield α -methylcinnamic acid (VIII). Thus, if paths b', d' and e' could be eliminated, then path c', involving simultaneous dehydration and decarboxylation of intermediate IX, would likely be operative. The fact that this simultaneous process could operate in the case of methylmalonic acid would be strong presumptive evidence that it could also

operate in the case of unsubstituted malonic acid; and therefore, that the other mechanisms, especially that which proceeds through the benzal-malonic acid (path a), could no longer be accepted without question.

The paramount problem was to determine whether methylmalonic acid would react at all under Doebner conditions to furnish the desired product, α -methylcinnamic acid (VIII). Although certain monosubstituted malonic acids had been reported to condense with aldehydes under Perkin conditions, no examples of the Doebner process with monosubstituted malonic acids could be found in the literature. It is evident that this type of Doebner process at least has been considered before, for Johnson writes: "Neither the Doebner nor the Knoevenagel modification is used for alpha substituted cinnamic acids, as the requisite monosubstituted malonic acids are not readily accessible." (Ref. 30, p.235.) But it must be assumed now that the first part of this statement, which implies that the Doebner reaction actually has been used successfully with monosubstituted malonic acids, represents in fact an untried assumption to the effect that the process, if tried, would be successful. A request for elucidation of the above quotation addressed to Prof. Johnson has not been acknowledged.

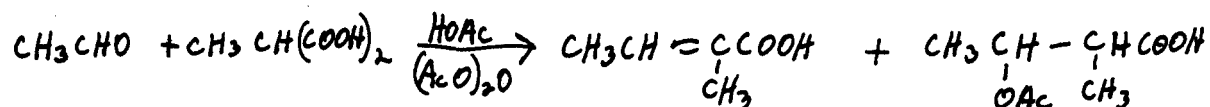
A brief and incomplete account of the condensations of methylmalonic acid with aldehydes under conditions resembling those used in the Perkin reaction is given below.

54

Stuart condensed the sodium salt of methylmalonic acid with benzaldehyde to form α -methylcinnamic acid in the presence of acetic anhydride. Breslow and Hauser, on repeating Stuart's work, found no condensation products at all. The explanation that Hauser gives is that there might have been some acetic acid present in the anhydride, therefore

some free methylmalonic acid. The methylmalonic acid, and not the salt as suggested by Stuart, was the condensing compound.

³⁹
Michael and Ross condensed methylmalonic acid with acetaldehyde, in the presence of acetic acid and acetic anhydride to form tiglic acid and α -methyl- β -acetoxybutyric acid.



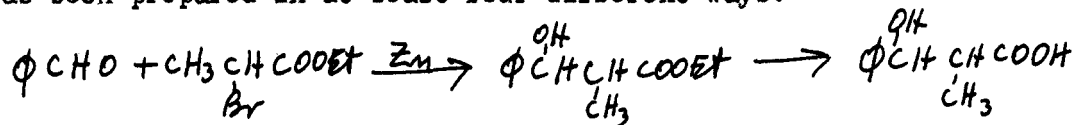
This would imply that the reaction path proceeds through a β -hydroxy acid, but Michael and Ross state that this is improbable. They suggest ³⁹ that the reaction proceeds through separate mechanisms. In the above paper, there are other examples of β -hydroxy acids formed by condensation of aldehydes and substituted malonic acids. These are isolated as the ⁴⁰ β -lactones (Meldrum lactones). Michael and Weiner condensed benzaldehyde and methylmalonic acid in the presence of acetic anhydride and a trace of sulphuric acid to form α -methyl- β -phenyl- β -propiolactone - α -carboxylic acid.

¹⁴
However, Davidson and Bernhard showed that Meldrum's lactone ($\text{(CH}_3\text{)}_2\text{C}-\underset{\text{O}-\text{C}=\text{O}}{\text{C}}-\text{CHCOOH}$), the investigation of which, along with other β -lactones, was the basis of Michael's ^{39, 40} work, had been assigned the incorrect structure, and that the true structure was not a lactone, but a cyclic diester. This proof tends to cast doubt upon Michael's β -lactones, and perhaps the only part of work which can be accepted as reliable is the formation of tiglic acid and the β -acetoxy compound.

Fortunately, in the present work, when the condensation of benzaldehyde and methylmalonic acid was attempted under Doebner conditions, the reaction did occur and did yield α -methylcinnamic acid and the planned

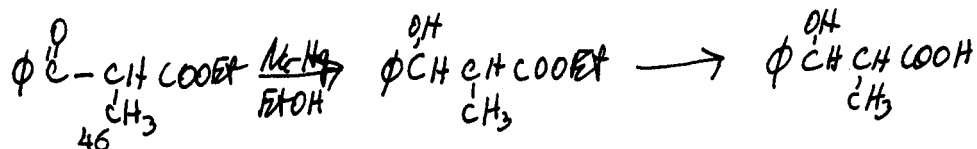
tests could therefore be carried out. Path d' was ruled out completely by direct test with propionic acid. Paths e' and b' were rendered unlikely by the results with α -methyl- β -hydroxy-hydrocinnamic acid. Therefore the conclusion was reached with certain reservations described below, that path c', the simultaneous elimination mechanism, is the most likely path. As a result of this present study, a definite question may be raised concerning the uncritical acceptance of the statement that an ethylidene malonic acid ($RCH=C(COOH)_2$) is a necessary intermediate in the Doebner process with malonic acid, and permissive evidence becomes available for the validity of path c', involving simultaneous loss of water and carbon dioxide for the malonic acid reaction.

Compound VII, α -methyl- β -hydroxy-hydrocinnamic acid is known and has been prepared in at least four different ways.



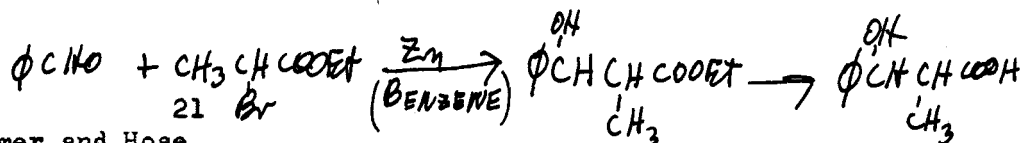
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I by Dain

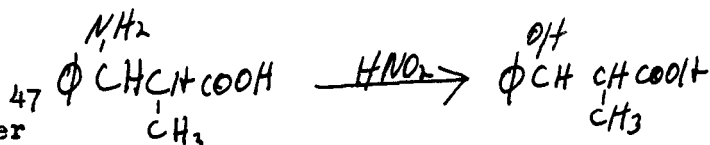


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II by Perkin



III by Farmer and Hose



IV by Posner

The melting point of the acid obtained from methods I, II, and IV has been reported as 95° . The reported m.p. of III is 77° . Application of method III in the present work afforded analytically pure material with m.p. $84.5-86$. Using this material, it was demonstrated that α -methyl- β -hydroxy-hydrocinnamic acid on exposure to Doebner conditions was not transformed into α -methylcinnamic acid, and therefore, as argued above, paths b' and e' are not tenable.

There is, however, a possible fallacy in this argument. α -methyl- β -hydroxy-hydrocinnamic acid may exist in two dl pairs and the variation in melting point may be due to an imperfect separation of the two pairs. The intermediate (VII) involved in the Doebner process with methylmalonic acid may not be the compound, m.p. $84.5-86^{\circ}$, actually synthesized and tested in this study, but might be instead the second diastereoisomer. If this were the case, as it indeed might be, then unfortunately the experiments carried out in the present work do not serve to rule out paths b' and e' conclusively. Realization of this situation forces a reservation on the conclusion reached in the above paragraph.

Although most of the work done in the present study was with methylmalonic acid, some work was done with phenylmalonic acid and ethylmalonic acid. There is no reason to believe that the behavior of ethylmalonic acid under Doebner conditions will differ much from that of methylmalonic acid. There is, however, evidence submitted in section V that phenylmalonic acid decarboxylates without condensing with benzaldehyde under Doebner conditions.

As a result of this investigation of the mechanism of the Doebner modification of the Knoevenagel reaction, an attractive method has been suggested for the production of α -methylcinnamic acids under conditions

milder than those of a typical Perkin reaction.

Development of optimum conditions and the extension to aliphatic aldehydes and/or other alkyl malonic acids remain for future study.

Further work on the actual mechanism of the Doebner process could involve isolation of each of the two pairs of isomers of the intermediate (VII), and subjecting each one to Doebner conditions. Use of ultra-violet ~~light~~^{spectroscopy} as an analytical tool for the determination of cinnamic acid in the reaction mixture would be useful in determining whether VII is an actual intermediate or not.

Section IV Discussion of Experimental Work

The reaction was carried out in a 100 c.c. round-bottomed flask with a reflux condenser equipped with a drying tube containing calcium chloride. (All glassware was equipped with standard tapered joints).

¹⁷
The classical Doebner modification calls for 1:1 ratio of benzaldehyde to malonic acid, pyridine as solvent, and a trace of piperidine, and heating on the steam bath. Since, however, both the inductive effect (electron-repelling behavior of the methyl group) and the statistical effect (only one active hydrogen) of methylmalonic acid, relative to malonic acid, would be working against the initial formation of the enolate anion which was expected to be the first step in the reaction path, it was decided to use harsher conditions and have the reaction proceed at reflux temperature.

The preliminary experiments used .02 moles each of aldehyde and methylmalonic acid, 10c. c. of pyridine, and two drops of piperidine. Yields were so low (of the order of 1% or less) that variations in reaction conditions were sought to increase the yield. It was found that the use of 20 drops of piperidine and a decrease in reflux time greatly increased the yield. Minor variations of these apparently key conditions failed to increase the yield appreciably.

In considering the length of reaction time as a factor in the yield, the maximum useful reaction time is given by the time required for the appearance of one mole of carbon dioxide per mole of methylmalonic acid, provided that it may be shown that the propionic acid (i.e., the decarboxylation product), is an unreactive species. This last proviso was shown to be true by direct experiment. Therefore it was a simple matter to measure the amount of carbon dioxide coming off after a given time of heating as

described under the decarboxylation experiments in section V. The decarboxylation experiments served as a guide to the length of time of heating in the preliminary experiments (see section V); no rate studies of decarboxylation were carried out under the conditions of the second set of experiments (where the amount of piperidine was 20 drops).

The identity of a product, whenever possible, was determined by means of a mixed melting point. However, since the purpose of the work was a study of the mechanism of the Doebner process, rather than a study of synthetic applications, little work was done with substituted malonic acids other than methylmalonic acid. However, it was shown that α -ethylcinnamic acid, (identified by its melting point), is produced in the reaction of benzaldehyde with ethylmalonic acid. In experiments with phenylmalonic acid, the decarboxylation product was identified by a mixed melting point with known phenylacetic acid. The product of the oxidation of benzaldehyde was identified by means of a mixed melting point with known benzoic acid. The product of the condensation of methylmalonic acid and benzaldehyde was identified by means of a mixed melting point with known α -methylcinnamic acid. The identity of the α -methyl- β -hydroxy-hydrocinnamic acid was determined by means of elementary analysis, since there was no unique melting point which could be used as identification. When, however, the hydroxy compound was subjected to Doebner conditions, it was identified by both elementary analysis and mixed melting point with starting material which had not been subjected to the conditions of the reaction. (see section V).

Concerning the α -methylcinnamic acid, the following quotation is
³⁰
 pertinent: "The acid obtained in this way (via Perkin reaction (ref.45) may melt at 81° or 74°, as α -methylcinnamic acid exists in two different crystalline forms. Both forms have the same configuration (trans C₆H₅: COOH) and give the same ester."

35

Li and Young reported the melting point of α -methylcinnamic acid as 82° .

The acid obtained in this work by means of the Perkin reaction melted at 74° when crystallized from ligroin, but melted at 81° when recrystallized from alcohol-water. (section V). A mixed melting point of Doebner product obtained from the second series' experiments and the 81° form of Perkin product showed no depression. The mixed melting point was 81° .

A method to determine the amount of unreacted benzaldehyde was sought. In view of the ease of oxidation of benzaldehyde to a product of useful melting point, benzaldehyde was oxidized by alkaline permanganate solution and the benzoic acid subsequently recovered. The identity of the product was determined by mixed melting point with known benzoic acid.

There are four methods of preparation of α -methyl- β -hydroxy-hydrocinnamic acid reported in the literature (see section III). Perkin first reported a melting point of $124-125^{\circ}$, but five years later, in a footnote to another paper, he stated that the original melting point was in error, and the true melting point was 95° . He gave no reason for the thirty degree difference in melting points. The melting point of the compound synthesized by Posner by an independent method agreed with that of Perkin. Dain, however, in 1898, and Farmer and Hose in 1933, both using the Reformatski reaction in the synthesis, got contradictory results; the former obtained a product, the melting point of which agreed with that of Perkin and Posner, but the latter obtained a product which melted at 77° . Farmer and Hose commented on the apparent difference between their compound and Dain's compound, but made no reference to the most likely reason for the difference, i.e., the separation or partial separation of the two possible diastereoisomeric compounds. The compound used in this study, synthesized by the method of

Farmer and Hose, had a melting point of $84.5-86^{\circ}$ after recrystallization from benzene-ligroin, and a melting point of $88.5-90^{\circ}$ when recrystallized from water. Both compounds were analytically pure.

When the α -hydroxy acid was subjected to Doebner conditions, similar to the experimental conditions used in the reaction of methylmalonic acid and benzaldehyde, the hydroxy acid could be recovered in 25% yield. Perhaps a better recovery of the starting material would have been effected had the isolation procedure been varied, (eg., a continuous ether extraction of the sodium carbonate washings after acidification for 24 or 48 hours), but it might very well be possible that dehydration could occur during the continuous extraction. It is pertinent to note, however, the relatively small amount of starting material used in this experiment.

The question might arise that α -methylcinnamic acid was actually formed from the hydroxy compound, but that it remained in the mother liquor from the crystallization of the hydroxy compound, and was, therefore, not detected. This is highly unlikely, as will be seen by a comparison of the solubilities. Dain ¹² reports that 100 parts of water will dissolve 4.66 parts of α -methyl- β -hydroxy-hydrocinnamic acid at 18° , whereas Conrad and Bischoff ¹¹ report that 100 c.c. of hot water will dissolve only 0.12g. of α -methylcinnamic acid.

Section V

Experimental*Pyridine

Technical and/or Eastman Kodak "White Label" pyridine was distilled in a Claisen flask over anhydrous barium oxide and the fraction boiling at 112-114° was collected and kept over potassium hydroxide pellets; the reported boiling point is 116° (27).

Ethyl Oxalate

Eastman Kodak "White Label" ethyl oxalate was dried over Drierite for 24 hours. After the Drierite was removed by filtration, the filtrate was distilled from a Claisen flask, and the fraction boiling at 181-182° was collected; the reported boiling point is 185.4°.(27)

Ethyl Propionate

Eastman Kodak "White Label" ethyl propionate was dried over Drierite for 24 hours. After the Drierite was removed by filtration, the residue was distilled from a Claisen flask, and the fraction boiling at 97-99° was collected; the reported boiling point is 99.1°.(27)

Benzaldehyde

The first batch was treated in the following manner; Eastman Kodak "White Label" benzaldehyde was dissolved in some petroleum ether (boiling point 30-60°), shaken twice with an equal volume of 5% aqueous sodium carbonate, dried over Drierite; the Drierite was removed by filtration, and the benzaldehyde was distilled from a Claisen flask with dry ("oil-pumped") nitrogen bubbling through a capillary. The fraction boiling at 175.5-177° was collected in a glass stoppered bottle which was covered with aluminum foil and flushed out with dry nitrogen after every use. The

* All melting points and boiling points are uncorrected. Semi-microanalyses were performed by Dr. Carol K. Fitz, 115 Lexington Avenue, Needham Heights 94, Mass.

reported boiling point is 179° . (27)

The second batch of benzaldehyde was obtained in the following manner: 100 c.c. of Eastman Kodak "White Label" benzaldehyde was dissolved in 50 c.c. of petroleum ether (boiling point $30-60^{\circ}$), shaken twice with two 50 c.c. portions of 5% sodium carbonate solution, and dried over Drierite. After the Drierite was removed by filtration, the petroleum ether was removed by vacuum distillation, and the flask containing the benzaldehyde was then sealed off under vacuum. The flask, still sealed, was then placed in a "dry-box", along with a file, Claisen flask, air condenser, heating mantle, and as a receiver, a bottle which had a rubber cap through which a syringe would be injected, thus permitting only a small amount (if any) of oxygen to be admitted to the benzaldehyde. The receiver was covered with aluminum foil to prevent light from entering the benzaldehyde. The "dry-box" was then sealed and evacuated to a pressure of 10 microns for sixteen hours. At the end of this time, tank-dry nitrogen, (containing less than 0.01% oxygen) was admitted into the box until the pressure reached one atmosphere. The flask was then opened, the benzaldehyde transferred to the Claisen flask, and distilled; again the fraction boiling at $175.5-177^{\circ}$ was collected. The receiver was allowed to stand uncovered in the "dry-box" to allow the benzaldehyde to cool. The flask was then covered and placed in the refrigerator.

* G. R. Thomas and N.N. Lichtin, Rev. of Sci. Inst., in press 1953

"Apparatus for Controlled Atmospheric Research".

G. R. THOMAS + N. N. LICHTIN, REV. OF Sci. INST., 23, 73F (1952)

~~* A description of the "dry-box" will be published soon in "The Review of Scientific Instruments."~~

Piperidine

Eastman Kodak "White Label" piperidine was refluxed for one hour with sodium, transferred to a Claisen flask, and distilled. The fraction boiling at 105-106° was collected over potassium hydroxide pellets and stored in the ice box. The reported boiling point is 106°. (27)

Methylmalonic Acid²³

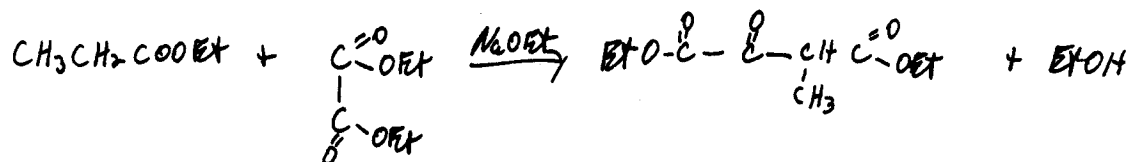
To a cooled solution of 15g. (.28 moles) of potassium hydroxide in 12 c.c. of water, 15 c.c. (.1 mole) of Mathieson and Co. diethyl methylmalonate (used as received) was added, and the mixture was refluxed on the steam bath until the two layers disappeared (approximately 24 hours). The mixture was allowed to cool, extracted once with ether to remove any unreacted ester, cooled in an ice bath, and acidified with 50 c.c. of 18% hydrochloric acid. The acidified solution was shaken with five 25 c.c. portions of ether. The ethereal solution was dried over Drierite, filtered, and the ether was evaporated on the steam bath. The residue crystallized and was recrystallized from benzene which was dried over sodium wire. The melting point was 122-124° with decomposition from 125° on; the reported melting point is 129°, 135°, and also reported as unreliable^{27,38}. The neutral equivalent (in water solution and phenolphthalein end point) was 122.8, whereas the theoretical is 118.

Repeated attempts at purification by recrystallization from benzene failed. The reason for this is that the boiling points of malonic ester, methylmalonic ester, and dimethylmalonic ester all lie within a two degree range³⁸ (198°, 196.5°, and 197° respectively) and the commercial material contains a mixture of the three esters. Since the free acids have very similar solubility properties, separation via crystallization, of the free

acids, obtained from saponification of a mixture of the esters would be very difficult.

Employing a qualitative test for active hydrogen atoms as a possible means of separation of the esters failed. ⁵³ To 5 c.c. of the commercial ester dissolved in 10 c.c. of 10% sodium ethoxide, 10 c.c. of 10% mercuric chloride in alcohol was added. A white precipitate settled out which was collected in a Buchner funnel and washed with two 20 c.c. portions of ether which was dried over sodium. Addition of concentrated hydrochloric acid to the white crystals evolved a good deal of heat, but extraction by two 20 c.c. portions of ether, followed by evaporation of the ether produced no ester.

Finally, methylmalonic ester was synthesized by means of an unambiguous path, through oxalylpropionic ester . ⁶

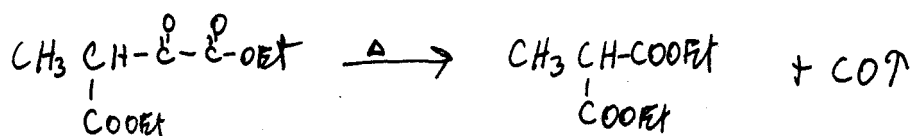


Twenty-three grams of clean sodium (1 mole) was powdered* in a one liter 3-necked flask under 100 c.c. of C.P. xylene which had been dried over sodium. The xylene was decanted and the sodium was washed twice with ether dried over sodium, then covered with 300 c.c. of dry ether. The flask was then equipped with a dropping funnel, a mercury seal stirrer, and a condenser. The stirrer was used throughout the reaction period. 67 c.c. of absolute alcohol (one mole) was admitted dropwise through the funnel (the addition took 2-3 hours) and the reaction allowed to proceed

*See L.F. Fieser, Experiments in Organic Chemistry, 2nd ed., D.C. Heath Co., Boston (1941) p. 385.

until no hydrogen was evolved. The flask was then placed in an ice bath and a mixture of 146g. of ethyl oxalate (one mole) and 102g. of ethyl propionate (one mole) was admitted to the ethereal suspension of sodium ethoxide, slowly enough so as not to permit refluxing the ether. The addition required 1-2 hours. The condenser was then placed in position for downward distillation, the stirrer and dropping funnel removed, and the ether removed by heating on the steam bath until a dark yellow scum formed on top of the reaction mixture. With no further heating the mixture was treated with 200 c.c. of 33% acetic acid and allowed to stand for 4-5 hours at room temperature with occasional shaking. This mixture was shaken with four 175 c.c. portions of ether. The combined ether portions were washed successively with 350 c.c. of water, two 200 c.c. portions of 10% sodium bicarbonate and finally 350 c.c. of water. The ether was then removed by distillation from a Claisen flask. (The ethereal solution was placed in a dropping funnel attached to the flask, and the flask placed on the steam bath). The steam was turned on, and the ethereal solution was added dropwise. After most of the ether was evaporated, the flask was heated on the steam bath and placed on the water pump for one hour to get rid of any ether and water present. The residue was distilled under vacuum in a Claisen flask, and the fraction boiling at 90-100°/2mm was collected. The reported boiling point is 114-116°/10mm.

The distillate was then refluxed at 180° on a heating mantle for two hours to eliminate carbon monoxide and to form methylmalonic ester.



After refluxing, the residue was distilled in a Claisen flask, and the fraction boiling at 190-192° was collected; the reported boiling point is 196°. The yield was 67g. (38%) overall.

This ester was hydrolyzed in the manner previously described for Mathieson's methylmalonic ester. The product was an acid of melting point 130-132° and neutral equivalent of 118; (The theoretical neutral equivalent is 118).

Ethylmalonic Acid

19c.c. (.1 mole) of Mathieson and Co. diethyl ethylmalonate (used as received), was added to a solution of 15g. (.28 moles) of potassium hydroxide and 12c.c. of water, and the mixture was refluxed on the steam bath until the two-phase mixture became homogeneous. This required approximately 24 hours. The mixture was shaken once with 15c.c. of ether to get rid of any unreacted ester. The mixture was then acidified with 50c.c. of 18% aqueous hydrochloric acid. The acidified mixture was extracted with five 25c.c. portions of ether; the ethereal solution was dried over Drierite, filtered, and the ether evaporated on the steam bath. The residue was crystallized once from benzene which was dried over sodium. The melting point was 108.5-109.5°. The reported melting point is 111.5°.

Phenylmalonic Acid

24g. (.1 mole) of Mathieson and Co. diethyl phenylmalonate (used as received), was treated in exactly the same way as above. The product gave a neutral equivalent of 180. (The theoretical neutral equivalent is 180). The melting point was 150-151°d. The reported melting point is 152-153°d.

α -Methyl- β -hydroxyhydrocinnamic Acid

The zinc used in this synthesis was treated in the following manner before use. Twenty mesh zinc was submerged in 5% hydrochloric acid for 5 minutes, washed successively with distilled water twice, absolute alcohol once, acetone once, and absolute ether twice, then placed in an oven at 100°⁵² for one hour.

12.4g. (.2g. atoms) of the activated zinc, 36.4g. (.2 moles) of Eastman Kodak "White Label" ethyl α -bromopropionate, (used as received), 20.4g. (.2 moles) of freshly distilled benzaldehyde and 75c.c. of benzene which was dried over sodium were refluxed for one hour on the steam bath; the reflux condenser was equipped with a calcium chloride drying tube. The mixture was then cooled in an ice bath, and poured into 200c.c. of ice cold 10% sulfuric acid. The aqueous layer was drawn off, and the benzene layer was washed successively with two 100c. c. portions of 10% sulfuric acid, one 200c. c. portion of 5% sodium carbonate, one 100c. c. portion of 5% sulfuric acid, and finally with 100c.c. of water. The combined acid and water washings were then extracted with two 100c.c. portions of ether. The combined ether benzene mixture was dried over Drierite, filtered and distilled from a Claisen flask on an oil bath. The fraction boiling at 141-143°/5mm. was collected as ethyl α -methyl- β -hydroxyhydrocinnamate. The reported boiling point is 157-158°/11mm.

The product, a yellow oil, was mixed with 30c.c. of 20% aqueous potassium hydroxide, with sufficient alcohol being added to give a homogeneous solution. The alkaline solution was allowed to stand at room temperature for 48 hours. At the end of this time, the alkaline solution was extracted with two 25c.c. portions of ether, cooled in an ice bath, and an

excess of 15% aqueous hydrochloric acid was added. An oil separated which was extracted with three 35c.c. portions of ether. The ethereal solution was dried over Drierite, filtered, and the ether distilled off. The yellow oily residue, which had been exposed to steam temperature for approximately one hour, would not crystallize, even upon long cooling in the ice box. The oil was then dissolved in 30c.c. benzene and extracted with 20c.c. portions of 5% sodium carbonate until the aqueous layer was alkaline. The combined alkaline layers were then washed once with 30c.c. of ether, then chilled and acidified with an excess of cold hydrochloric acid. Again an oil separated which was extracted with three 30c.c. portions of ether. The ethereal solution was dried over Drierite, filtered, and the ether evaporated off on the steam bath. The last trace of ether and/or benzene was removed by placing the flask in a vacuum desiccator along with a piece of paraffin wax and evacuating the desiccator by means of the water pump for one hour. The residue, a pale yellow oil, partially crystallized upon cooling, and was crystallized once from benzene-ligroin (boiling point 60-80°). The melting point was 84.5-86°. The reported melting point for this synthesis was 77°. The melting point of this compound from other syntheses^{12,46,47} was 95. (see page 14) The overall yield was 4g. (12%).

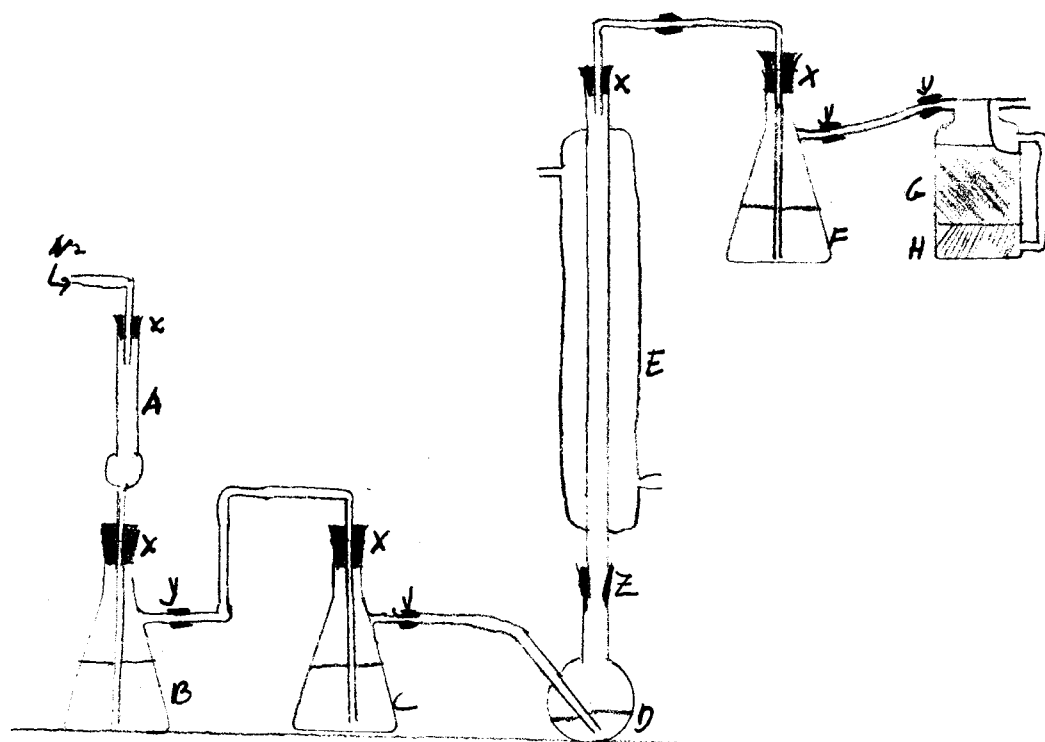
Analysis: Calculated for $C_{10}H_{12}O_3$: C, 66.7; H, 6.7.

Found: C, 66.6; H, 6.7%.

α -Methylcinnamic Acid

A mixture of 10.5g. (.1 mole) of freshly distilled benzaldehyde, 16g. (.12 mole) of propionic anhydride (used as received), and 10g. (.1 mole) of fused sodium propionate was heated with occasional shaking for 30 hours

in an oil bath at 130-135°. The warm mixture was poured into 250c.c. of water, stirred thoroughly, and neutralized by the addition of 10% sodium carbonate solution. The alkaline solution was then extracted with two 30c.c. portions of ether, and the aqueous portion was then warmed with 2g. of Norite (decolorizing carbon) and filtered while hot. The warm filtrate was poured, slowly, with stirring, into an excess of concentrated hydrachloric acid mixed with chopped ice. After the acid crystallized completely, it was collected by suction on a Buchner funnel, washed with several portions of water, and dried by pulling air through the cake on the funnel. The crude product was crystallized once from ligroin (boiling point 60-80°). The melting point was 73-74°. The reported melting point is 74° or 81°³⁰. When the acid was recrystallized from water, the melting point was 80-81°.



A. DRYING TUBE WITH ASCARITE

B. BARIUM HYDROXIDE

C. CONC. SULFURIC ACID

D. REACTION MIXTURE

E. CONDENSER

F. CONC. SULFURIC ACID

G. GAS CHAMBER WITH ASCARITE

H. " " " $MgClO_4$

X. RUBBER STOPPER

Y. RUBBER TUBING CONNECTION

Z. STANDARD TAPER (24/40) JOINT

DECARBOXYLATION APPARATUS.

Decarboxylation Experiments

A mixture of 2c.c. of benzaldehyde, 10c.c. of pyridine, 2 drops of piperidine, and a known weight of one of the three malonic acids, (corresponding to approximately the same number of moles of benzaldehyde), was placed in a 50 c.c. round-bottomed flask equipped with a sidearm, and treated in the following manner. Dry ("oil-pumped") nitrogen was passed slowly through a tube of Ascarite, a 250 ml. flask containing a concentrated solution of barium hydroxide, a 250 ml. flask containing concentrated sulfuric acid, and then into the sidearm of the reaction flask, below the surface of the mixture. The reaction mixture was refluxed gently on a heating mantle. The top of the reflux condenser (300 mm.) was connected to a 250 ml. flask containing concentrated sulfuric acid, and then into a 100 ml. gas drying tube which was filled with two-thirds Ascarite and one-third magnesium perchlorate. The magnesium perchlorate was used to absorb the water formed from the following reaction;



After heating for a given time, the flask was allowed to cool for 15 minutes, while nitrogen was still bubbled through the reaction mixture and condenser to flush out any carbon dioxide. The gas drying tube was weighed to ± 0.2 mg. before and after the experiment. This represented less than .1% of the weight of carbon dioxide evolved.

The following table gives the results of these experiments:

	<u>Temp.</u>	<u>Acid</u>	<u>Time of Heating</u>	<u>%CO₂</u> (a)
1.	120-130° (reflux)	Ethylmalonic	60 min.	90.5
2.	"	"	40 min.	96.5 (b)
3.	"	Methylmalonic	60 min.	98.4
4.	"	Phenylmalonic	15 min.	80.4
5.	"	"	20 min.	95.8
6.	"	"	25 min.	97.8
7.	"	"	3 hrs.	98.0 (c)

-
- (a). These figures are obtained from the ratio of the actual weight of carbon dioxide and the theoretical weight of carbon dioxide.
- (b). This run was carried out in an apparatus similar to the one described above, but there was no flask of sulfuric acid at the outlet of the reflux condenser.
- (c). Run #7 is a test for accuracy of the experiment, checking the fact that pyridine vapor does not carry over, and that as a semi-quantitative method, the experiment is effective.

Isolation of Product

The first series of experiments, including the decarboxylation experiments, was carried out in the following manner: 2 c.c. of benzaldehyde (from the first batch), an equimolar amount of the malonic acid, 10 c.c. of pyridine, and two drops of piperidine were refluxed on a heating mantle for one hour, cooled, and the mixture was dissolved in 50 c.c. of petroleum ether (b.p. 30-60°). The reaction mixture was then shaken with two 25 c.c. portions of 18% hydrochloric acid, and the combined acid washings were extracted with a 25 c.c. portion of ethyl ether which was added to the petroleum ether layer. The combined ethereal solution was

then shaken with 20 c.c. portions of 5% sodium carbonate until the aqueous washings were alkaline. The alkaline washings were extracted with a 25 c.c. portion of ether, cooled in an ice bath, and was acidified with an excess of 15% hydrochloric acid. The precipitate, if any, was then extracted with three 25 c.c. portions of ether; the ether was evaporated on the steam bath, and the residue was crystallized once from alcohol-water. After crystallization, the product was filtered on a sintered glass funnel and dried by pulling air through the cake of crystals. The yields of α -methylcinnamic acid (m.p. 80.5-82°) and α -ethylcinnamic acid (m.p. 103-104°) were of the order of one per cent. The reported melting points were 81° and 105°, respectively. No further work was done with ethylmalonic acid. In the case of phenylmalonic acid, the only product recovered from the alkaline portions was phenylacetic acid (m.p. 74-76°). The melting point of known phenylacetic acid was 75-77°, and the mixed melting point was 75-77°. The phenylacetic acid was recovered in 77% yield (1.6g).

The second series' conditions, (using benzaldehyde from the second batch), were very similar to those of the first. The changes made were an increase in the amount of piperidine, and a shortening of reflux time. Using methylmalonic acid:

	<u>Piperidine</u>	<u>Time</u>	<u>Temp.</u>	<u>Yield</u>	<u>M.P.</u>
1st series	2 drops	1 hour	130	1%	80.5-82°
2nd	" 20 drops	20 min.	130	41%	80.5-82°
"	" 30 drops	35 min.	130	41%	80-81.5°
"	" 20 drops	15 days	25-30	44%	80.5°

Increasing the mole ratio of methylmalonic acid (4.4g. = .04 moles) to benzaldehyde (2.1g. = .02 moles) and refluxing for 20 minutes failed to increase the yield. In fact, the yield of α -methylcinnamic acid (m.p. 80-81.5°) was slightly lower, approximately 39%.

Mixed melting points of α -methylcinnamic acid (from Perkin reaction) and products of the Doebner reaction were taken in the three experiments of the second series. The melting point of the Perkin product was 80-81°. The mixed melting point was 80.5-81.5°.

The Doebner Reaction with Propionic Acid

A. Determination of unreacted benzaldehyde.

The method of determining the amount of benzaldehyde left unreacted after the reaction was completed, was to follow reaction conditions exactly except that the alkyl malonic acid was omitted; i.e., 2 c.c. (2.1g.) of benzaldehyde, (from the second batch), 10 c.c. of pyridine, and 20 drops of piperidine were refluxed for twenty minutes, cooled, the reaction mixture dissolved in petroleum ether (boiling point 30-60°), washed successively with hydrochloric acid and sodium carbonate solution, as described previously. The remaining ethereal solution was heated on the steam bath, and the ether evaporated. To the residue was added 30 c.c. of 5% sodium hydroxide solution. 2 c.c. portions of 5% aqueous potassium permanganate were added, with shaking until a purple color persisted. The purple color was discharged by the addition of a few drops of ethanol, and the entire mixture was heated on the steam bath to a temperature of 60-70°, then filtered by suction to remove the manganese dioxide. The alkaline filtrate was then cooled and acidified with an excess of concentrated hydrochloric acid. The precipitate was extracted with three 25 c.c. portions of benzene and one 25 c.c. portion of ether. The benzene and

ether were then evaporated by heating on steam, and the residue was recrystallized once from water, and dried by suction on a Buchner funnel. The melting point was 119-120°. The reported melting point of benzoic acid is 121°²⁷. Yields on three successive runs were 2.25g., 2.42g., 2.40g. The theoretical yield is 2.41g. of benzoic acid from 2.1g. (2c.c.) of benzaldehyde.

B. Experiment with Propionic Acid

The reaction was carried out using 2 c.c. (.023 moles) of propionic acid, 2 c.c. of benzaldehyde, 10 c.c. of pyridine, and 20 drops of piperidine. Application of the isolation procedure as described for α -methylcinnamic acid furnished none of the desired product, α -methylcinnamic acid. Oxidation of the recovered benzaldehyde as described above yielded 2.42 g. of benzoic acid of melting point 119.5-121°. The melting point of known benzoic acid was 120-121.5°, and a mixed melting point was 120-121.5°. 2.42 grams represents a yield of 100% of the theoretical amount of benzoic acid from 2.0 c.c. (2.1g.) of benzaldehyde.

α -Methyl- β -Hydroxyhydrocinnamic Acid under Doebner Conditions

0.57 g. (0.003 moles) of α -methyl- β -hydroxy-hydrocinnamic acid was refluxed for 20 minutes with 5 c.c. of pyridine and 10 drops of piperidine. After the flask was cooled, the mixture was dissolved in 25 c.c. of petroleum ether (b.p. 30-60°), and washed with two 13 c.c. portions of 18% hydrochloric acid. The acid washings were extracted once with 15 c.c. of ethyl ether, which was added to the petroleum ether solution. The combined ethereal solution was then washed with two 20 c.c. portions of 5% sodium carbonate. The alkaline washings were extracted once with 20 c.c.

of ether, cooled in an ice bath, and acidified with an excess of cold concentrated hydrochloric acid. An oily suspension, rather than a precipitate was observed at this point. The oil was extracted with three 15 c.c. portions of ether, and the ether was evaporated on the steam bath. The oil was dissolved in a mixture of hot water and alcohol and placed in the ice box; only after long cooling did the product crystallize. The mixture was filtered, using a sintered glass funnel, and the crystals were dried by pulling air through the cake on the funnel. The melting point was $88.5-90^{\circ}$. When some of the original starting material was simply recrystallized from water and alcohol, its melting point changed from $84.5-86^{\circ}$ to $89-90^{\circ}$. A mixed melting point (of product which had been subjected to Doebner conditions, and product which had merely been recrystallized from water-alcohol), was $88.5-90^{\circ}$. The yield was 1.14g. (25%). The material recovered was analyzed.

Analysis: Calc. for $C_{10}H_{12}O_3$: C, 66.7; H, 6.7;

Found: C, 66.4; H, 6.7%.

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VII. Abstract of Thesis.

The mechanism of the Doebner modification of the Knoevenagel reaction has been assumed by many authors (see thesis) to proceed through an isolable intermediate, a benzalmalonic (or ethylidene malonic) acid, although there has not been any proof for this mechanism reported in the literature. The purpose of this work is an investigation of the mechanism of the Doebner modification.

In the body of the thesis (pp. 4 and 10), there are five possible paths presented for the reaction of benzaldehyde and malonic acid. The first three assume that malonic acid reacts as malonic acid, (or its monoanion or dianion), and that the initial product is a β -hydroxymalonic acid. From the initial condensation product, path a proceeds through benzalmalonic acid and yields cinnamic acid by loss of carbon dioxide, path b proceeds through β -hydroxyhydrocinnamic acid and yields cinnamic acid by loss of water, and path c yields cinnamic acid by means of a simultaneous loss of carbon dioxide and water. Paths d and e assume that malonic acid first decarboxylates to form acetic acid or its enol form, and then proceed via the hydroxy acid. If, however, methylmalonic acid were substituted for malonic acid, and if α -methylcinnamic acid were obtained as product, then path a would be impossible, and paths b', c', d', and e' would remain as likely reaction paths. (See page 13).

Path b' would proceed through a β -hydroxy acid and yield α -methylcinnamic acid by loss of water, and path c' would yield the product through simultaneous loss of carbon dioxide and water. Paths d' and e' would proceed via the hydroxy acid after preliminary decarboxylation to propionic acid or its enol form.

In the course of this work, it was shown that methylmalonic acid does condense with benzaldehyde under Doebner conditions to form α -methyl cinnamic acid. It was proven that propionic acid does not condense with benzaldehyde under Doebner conditions, thus ruling out paths d' and e', and it was demonstrated, with certain reservations, that α -methyl- β -hydroxy hydrocinnamic acid will not dehydrate to form the α - β unsaturated acid under Doebner conditions.

Since there is strong suggestive evidence for the Doebner modification with methylmalonic acid to proceed via a simultaneous elimination of carbon dioxide and water from the β -hydroxymalonic acid, then it is very possible that the same will hold true in the case of malonic acid, i.e., benzalmalonic acid is not a necessary intermediate in the Doebner modification with malonic acid.

Although the present work is an investigation of the Doebner reaction, it also suggests a pathway for the synthesis of alpha alkyl cinnamic acids from alkylmalonic acids. Under the conditions of the reaction, however, phenylmalonic acid was decarboxylated too rapidly to condense with benzaldehyde. Synthetic applications of this problem provide a fertile field for investigation in the future.