THE CONDENSATION OF CARBONYL GROUPS WITH ACTIVE METHYLENE GROUPS

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

1949

ACKNOWLEDGMENT

The author wishes to thank Dr. Ernest F. Pratt who suggested this investigation for his constant encouragement and enthusiastic direction. Generous financial support from the Research Corporation is sincerely appreciated.

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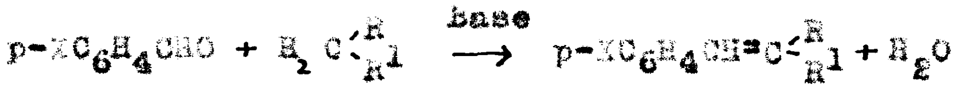
HISTORICAL INTRODUCTION

The purpose of this investigation was to study the condensation of carbonyl compounds with compounds containing active methylene groups. It consists of two parts, the first being mainly a study of the ability of various groups to activate a methylene compound and the second being a study of the formation of aromatic rings by the condensation of α-dicarbonyl compounds with o-phenylenediacetic acid.

The Knoevenagel reaction occurs between an aldehyde or ketone and an active methylene compound in the presence of various organic bases or ammonia. Sometimes a complex catalyst, an organic acid and an organic base, is used. The general equation is:

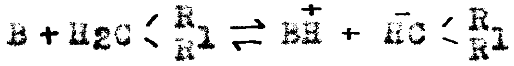


$$p\text{-}XC_6H_4CHO + H_2C{<}^{R}_{R^1} \xrightarrow{\text{base}} p\text{-}XC_6H_4CH{=}C{<}^{R}_{R^1} + H_2O$$

where R and R^1 are activating groups. In this work the R and R^1 groups studied were $-CN$, $-COCH_3$. $-COC_6H_5$. $-COOC_2H_5$. $-C_6H_5$. $-NO_2$. $-CONH_2$. and $-SO_2C_6H_5$. The X- was $-H$, $-OCH_3$, $-Cl$, or $-NO_2$. Catalyst and kinetic studies were also made which yielded further insight into the reaction mechanism.

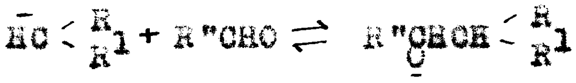
The reaction was carried out in boiling benzene in the presence of piperidine and caproic acid as the catalysts. As the water was formed it was distilled off with the benzene and collected in an automatic liquid separator, the benzene being returned to the reaction mixture. The course of the reaction was easily followed by reading the increase in volume of water with time.

Early work on the mechanism has been summarized by Kohler and Corson[1] who demonstrated that enolization of the aldehyde or ketone was not a necessary step in the reaction. More recent studies have been reviewed by Arndt and Eistert[2] and by Kuhn and coworkers[3]. The mechanism for the base catalyzed Knoevenagel reaction which is most widely accepted today was originally stated by Lapworth[4] and by Hann and Lapworth[5]. The first step is activation of the methylene compound by the base, yielding an anion as follows:

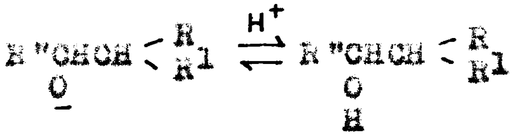
(1) 

$$B + H_2C<{R \atop R^1} \rightleftharpoons \overset{+}{BH} + \overset{-}{H}C<{R \atop R^1}$$

Then the anion adds to the carbonyl compound forming the ion of the aldol:

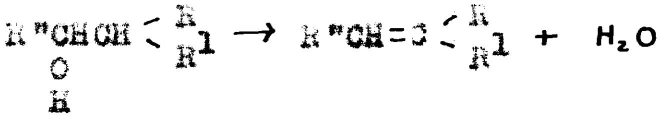
(2) 

$$\overset{-}{H}C<{R \atop R^1} + R''CHO \rightleftharpoons R''\underset{\underset{-}{O}}{C}HCH<{R \atop R^1}$$

(3) 

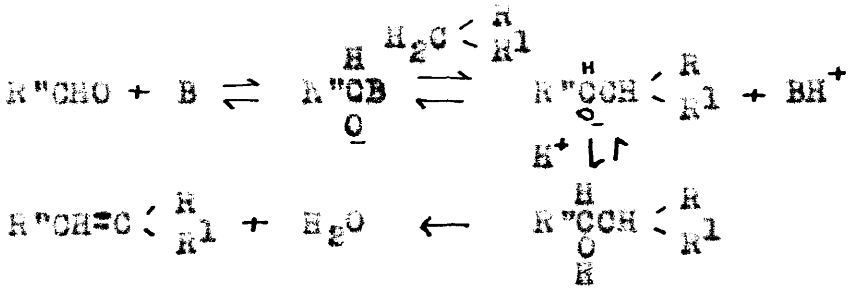
$$R''\underset{\underset{-}{O}}{C}HCH<{R \atop R^1} \overset{H^+}{\rightleftharpoons} R''\underset{\underset{H}{O}}{C}HCH<{R \atop R^1}$$

The final step is elimination of water from the aldol intermediate:

(4) 

$$R''\underset{\underset{H}{O}}{C}HCH<{R \atop R^1} \rightarrow R''CH=C<{R \atop R^1} + H_2O$$

In a recent review of the mechanism Watson[6] presents the possibility that the basic catalyst might attack the carbonyl compound rather than the methylene component forming a complex ion which then adds to the methylene compound:



$$R''CHO + B \rightleftharpoons R''\overset{H}{\underset{O^-}{C}}B \xrightleftharpoons{H_2C<^{R}_{R^1}} R''\overset{H}{\underset{O^-}{C}}CH<^{R}_{R^1} + BH^+$$

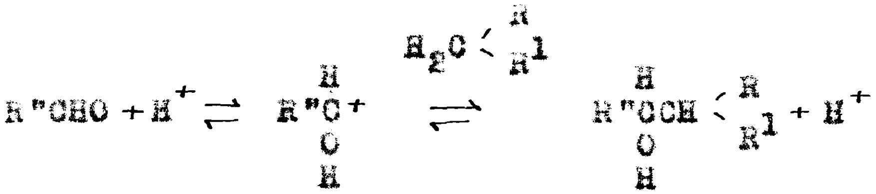
$$H^+ \downarrow\uparrow$$

$$R''CH{=}C<^{R}_{R^1} + H_2O \longleftarrow R''\overset{H}{\underset{\underset{H}{O}}{C}}CH<^{R}_{R^1}$$

However, this view is not generally accepted at present.

There have been numerous basic catalysts used for this reaction. In his original work Knoevenagel[7] used ammonia, primary amines such as methyl amine, and secondary amines such as piperidine. Later it was demonstrated by Hann and Lapworth[5] that tertiary amines also could be used. This evidence refuted the original mechanism of Knoevenagel[7] that the carbonyl compound first formed a Schiff's base with a primary or secondary amine and the Schiff's base then reacted with the methylene compound, eliminating the amine. Boxer and Linstead[8] studied the reaction of numerous amines and also showed conclusively that the action of tertiary amines was not due to impurities of primary amines.

It has been shown by Hauser and Breslow[9] that acidic as well as basic reagents may catalyse the aldol condensation, including the Knoevenagel and Perkin types. They carried out the condensation of benzaldehyde with malonic ester in the presence of BF_3 and obtained a good yield of benzalmalonic ester. The mechanism involved in condensations effected by acidic reagents is thought to proceed via activation of the electron accepting component, aldehyde or ketone, rather than of the electron donating component. It involves the formation of a coordination complex such as:



$$R''CHO + H^{+} \rightleftharpoons R''\overset{H}{\underset{\underset{H}{O}}{C}}{}^{+} \xrightleftharpoons{H_2C<^{R}_{R^1}} R''\overset{H}{\underset{\underset{H}{O}}{C}}CH<^{R}_{R^1} + H^{+}$$

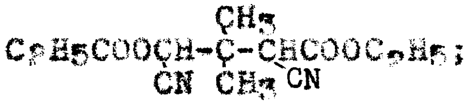
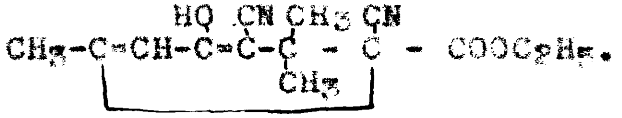
Another example of acid catalysis was the use of p-toluenesulfonic acid in the condensation of ethyl acetoacetate and butyraldehyde[10]. However only a 28% yield of product was obtained as compared with 81% when piperidine was used.

It has been shown[3] that at least a small amount of acid should be present when catalysis is effected by an amine. When piperidine was added to pure crotonaldehyde there was no condensation, but when the aldehyde had undergone slight autooxidation the reaction proceeded readily.

The first extensive work on the use of salts and of amides as catalysts was carried out by Cope[11] in a study of the condensation of ketones with cyanoacetic esters. For this type of reaction excellent yields were obtained using piperidine acetate, ammonium acetate, ethylenediamine diacetate, or acetamide in glacial acetic acid. For the mixture of ester, ketone and catalyst he used as solvent glacial acetic acid; as water was formed during the reaction it was removed by slow distillation. He found that the salts were superior to the free bases in catalytic activity. These results were explained on the basis that salts furnish both acid and base. The first step of the mechanism as discussed above may be acid or base catalyzed, but it is better catalyzed by base. On the other hand, the dehydration step which is also acid or base catalyzed is more strongly catalyzed by acid.

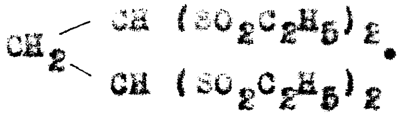
There are many examples in the literature of the condensation of active methylene compounds and carbonyl compounds. In a publication of 1904 Knoevenagel[12] reviewed the large number of compounds which had been prepared since 1893 by his method. The aldehydes, including all types, aliphatic and aromatic, saturated and unsaturated, were condensed with a wide variety of active methylene compounds such as the acetoacetic ester and malonic ester types, acetylacetone, cyano esters, nitromethane and phenylnitromethane. Somewhat later condensation with ketones[13] were also reported.

Cyclic ketones and ethyl cyanoacetate were condensed by Harding, Haworth, and Perkin[14]. Also a large number of cyclic ketones were condensed by Vogel[15].

In the condensation of excess acetone with ethyl cyanoacetate Gardner and Haworth[16] showed that the reaction in piperidine differed from that with sodium ethoxide as the catalyst. With piperidine the product is  $C_2H_5COO\underset{CN}{CH}-\overset{CH_3}{\underset{CH_3}{C}}-\underset{CN}{CH}COOC_2H_5$; with sodium ethoxide it is the cyclic compound,  $CH_3-C=CH-\overset{HO}{C}=\overset{CN}{C}-\overset{CH_3}{\underset{CH_3}{C}}-\overset{CN}{C}-COOC_2H_5$.

Ken and Thorpe[19] formed nitrogen heterocyclics by condensing cyanoacetamide with ketones having two secondary carbon atoms adjacent to the carbonyl.

Worall[18] used aromatic aldehydes and nitromethane to prepare a series of unsaturated nitro compounds. Kotz[19] condensed a methylene compound activated by two sulphone groups, $C_2H_5SO_2CH_2SO_2C_2H_5$, with formaldehyde. He obtained


$CH_2\begin{matrix} CH(SO_2C_2H_5)_2 \\ CH(SO_2C_2H_5)_2 \end{matrix}$. Kohler and Potter[20] attempted also to use a sulphone; they tried to condense benzaldehyde with methyl p - tolyl sulphone but obtained only a low yield of α, β unsaturated sulphone which was difficult to separate from a variety of other products.

Another example of the scope of the Knoevenagel reaction is to be found in a recent publication[21] in which cinchonaldehyde was condensed with a variety of methylene compounds, including in addition to the usual types mentioned above, cyclohexanone and acetophenone as active methylene compounds. A recent book[22] dealing with organic cyanogen compounds contains an extensive review of the literature on the condensation of aldehydes and ketones with nitriles containing an active methylene group.

Cope[23] reported an improvement on earlier work[11], described above, for the condensation of ethyl cyanoacetate and ketones. According to this procedure the ketone, ester, ammonium acetate and acetic acid were refluxed in benzene in a flask fitted with a constant water separator. As the reaction was refluxed the water formed was distilled off with the benzene into the separator. The mixture was refluxed until the formation of water ceased.

Recently Mowry[24] studied the condensation of malononitrile with variously substituted acetophenones. He used acetic acid and ammonium acetate as catalyst and employed Cope's method of distilling the water formed into a liquid separator. Since some of the acetic acid collected in the aqueous layer of the separator, the volume of water exceeded the theoretical requirement for the condensation by approximately 20%. As a result the reaction could not be followed accurately and only the time for total reaction was determined.

In view of the satisfactory results obtained in these laboratories in following etherification[25] and alkylation[26] reactions by a distillation method it was decided to attempt to modify Cope's method so that the reaction rate of the Knoevenagel reaction could be accurately determined. If this could be accomplished then the method could be applied to the determination of the relative ability of various groups to activate a methylene compound as well as to the study of the order of the reaction. Information of this nature is valuable both for theoretical and synthetic considerations and only very little of such information has previously been obtained.

DISCUSSION

PRELIMINARY STUDIES

The standard apparatus which was used in all experiments was similar to that of Draper[25]. It consisted of a one liter flask fitted with a thermometer well and a water separator which was calibrated in tenths of a milliliter to a total volume of five milliliters. The water separator held a reflux condenser equipped with a calcium chloride drying tube. All connections were ground glass. A "Glas-Col" heater was used with a "Variac" set at 80 volts for benzene; this was the highest voltage which would not cause flooding of the condenser. The thermomoters used were checked against Bureau of Standards thermometers. Barometer readings were taken but usually variations in atmospheric pressure did not affect the reflux temperature significantly. Readings of the water volume were taken every five minutes or at some other convenient time intervals depending on the speed of the reaction.

In the standard procedure used for all experiments, except where otherwise stated, one-eighth of a mole of active methylene compound was mixed with the desired amount of piperidine and caproic acid and this mixture was diluted with benzene to a total volume of 250 ml. in a volumetric flask. Another 250 ml. volumetric flask was filled with benzene and a volume equal to the calculated volume of the benzaldehyde which was to be added later was pipetted off. The total solution was poured into the liter flask and the water separator was filled with solvent. The solution was refluxed to remove any superficial water which usually amounted to not more than 0.05 ml. One-eighth of a mole of freshly distilled benzaldehyde was added to the hot solution. Zero time was taken as the time of addition of the aldehyde. Reflux was continued until the volume of water in the liquid separator was essentially constant.

Upon completion of the reaction the solution was washed three or four times with sufficient 10% sodium carbonate solution to remove all the caproic acid and piperidine. The solution was then washed with water and finally with a 5% acetic acid solution. A large amount of the solvent was distilled off at atmospheric pressure, the remainder at reduced pressure, and the product was isolated by distillation under reduced pressure or by crystallization.

A combination of acid and base was chosen as the catalyst. The basic component was piperidine but instead of acetic acid a higher boiling aliphatic acid was found to be preferable. Acetic acid distilled over and collected in the aqueous layer to some extent, causing an error in the volume readings. When caproic acid was used, the water layer was found to be free of acid. Since caproic acid is cheap and commercially available, it was used for these experiments although other aliphatic acids may be equally effective.

On the basis of preliminary experiments an important system for intensive study was chosen. This consisted of diethyl malonate as the active methylene compound and benzaldehyde as the carbonyl compound. It was found that ketones such as cyclohexanone and diethyl ketone did not react with malonic ester under the standard conditions. Straight chain aliphatic aldehydes, for example heptaldehyde, underwent the aldol as well as Knoevenagel condensations so that it was difficult to isolate a single pure reaction product from the mixture; consequently they were unsuitable for kinetics work. Aliphtic aldehydes branched at the alpha carbon such as 2-ethylbutanal and 2-ethylhexanal proved to be equally as good as benzaldehyde. The theoretical volume of water was evolved smoothly and 76% and 80% yields of pure product, respectively, were isolated.

Since ethyl groups are electron releasing as compared with the hydrogen atom, the alpha hydrogen of these branched chain aldehydes is less labile than the alpha hydrogens in the straight chain aldehydes. For this reason these branched chain aldehydes undergo the aldol condensation much less readily than the straight chain aldehydes. It was felt, however, that benzaldehyde was a more widely used aldehyde than either of these branched chain compounds.

It was found that both benzene and toluene were suitable as solvents. When a mixture of piperidine and caproic acid was refluxed in benzene or toluene, there was no evidence of a reaction. When, however, o-xylene was tried as a solvent, water was evolved as the result of amide formation occurring to an appreciable extent between piperidine and caproic acid at this higher temperature, 144°C. A pure product identified by analyses as N-caproyl piperidine was isolated in a 40% yield. This compound had previously been prepared by the reaction of piperidine and caproyl chloride[27]. Further study of the distillation method for making amides is planned in these laboratories.

There are certain limitations and sources of error in the distillation method for carrying out and following the Knoevenagel reaction. Only solvents which boil below about 125° can be safely used because of the side reaction just discussed. It is not possible to use piperidine without at least an equivalent amount of acid present because the piperidine will distill over with the water. The acid must be non-volatile or insoluble in water. The reactants and products also must not be very volatile or water soluble. The temperature of the reaction usually varies somewhat. For the 20% to 60% portion of the reaction it was constant to within ±0.3°.

There are numerous advantages to this method of studying the reactions. The constant removal of water forces the reaction to completion. It has been shown[11] that it is a reversible reaction. When methyl-1-methyl-heptylidene cyanoacetate was heated with an equivalent amount of water in the presence of piperidine acetate for five hours at 125°, a 20% yield of methyl hexyl ketone was obtained and 70% of the unsaturated ester was recovered. Another important advantage is that the process is a simple and rapid one and does not require analysis of samples at regular intervals.

CATALYST STUDIES

A series of experiments were carried out to determine the effect on the reaction rate of varying the acid strength, piperidine ; caproic acid ratio, and the total concentration of catalyst.

Since Breslow and Hauser[9] found that acid catalysts such as BF_3 promoted the condensation of benzaldehyde and diethyl malonate it was decided to determine whether caproic acid alone would bring about any reaction. It was found, however, that no water was evolved over a period of several hours when caproic acid was the only catalyst. This result is not surprising considering the much greater ability of BF_3 to act as an acid, or as an electron acceptor according to the Lewis definition.

When the condensation of benzaldehyde with ethyl cyanoacetate in the presence of p-toluene sulfonic acid as a catalyst was tried, 42% of the theoretical amount of water was formed. This result is comparable with that obtained by Cope[10] in the similar condensation of aldehydes with ethyl acetoacetate.

At the other extreme it is well known that piperidine alone is an effective catalyst although according to Kuhn[3] at least a trace of acid must be present. It was not possible to use piperidine alone in these experiments since it is so volatile; therefore tri-n-butylamine was tested, but no water was evolved. When this amine was used together with caproic acid as a catalyst there was likewise no reaction.

Piperidine used with chloroacetic acid, a much stronger acid than caproic, gave approximately 86% of the theoretical amount of water; the half-reaction time was 495 minutes. About 0.3% of the chloroacetic acid was found in the water layer in the separator causing a slight error in the volume reading.

Piperidine with caproic acid gave 100% of the calculated volume of water and an 80% yield of pure benzalmalonic ester was isolated. The half-reaction time was about 75 minutes.

A study of the acid : base ratio of the catalyst was carried out using one-eighth of a mole each of benzaldehyde and malonic ester with one-sixteenth of a mole of piperidine. The amount of acid was varied so that the acid : base ratio was 1:1, 2:1, 4:1, and 8:1. No check run was made at the highest ratio, but satisfactory agreement was obtained when each of the other experiments was repeated. The results are summarized in Table I. As the acid content increased the half-reaction time increased and reaction rate constants decreased.

TABLE I

The Effect of Varying the Acid : Base Ratio

Ratio[a] Acid: Base	Half Reaction Time (Min.)	k (min.$^{-1}$ x 10^{-3})						
		30%	40%	50%	60%	70%	80%	Average
1:1	63	11.04	11.19	11.19	11.06	10.87	9.99[b]	11.07
2:1	75	9.82	9.92	10.02	10.07	9.95	9.61	9.90
4:1	114	6.07	6.12	6.18	6.08	5.99	5.89[b]	6.09
8:1	150	4.77	4.71	4.68	4.58	4.54	4.55	4.64

[a] 0.0625 mole piperidine used

[b] omitted from average

These reaction rate constants as well as those given subsequently were calculated in the following manner. Experimental results of percent reaction completed were plotted versus time giving a smooth curve. An enlarged graph was plotted of the values between 20% and 80% reaction completed. Unavoidable variations often appear over the first and last 20% of the reaction. During the first 20% of the reaction the system is establishing equilibrium. During the latter part of the reaction deviations due to the presence of slight amounts of impurities in the reactants become relatively more serious. Errors in reading the volume of water collected are also more serious during the first and last portions of the reactions.

Time intervals were read off from the larger graph at 20%, 30%, 40%, 50%, 60%, 70% and 80%. Taking the time at 20% as zero time, the reaction rate constants were calculated using the first order reaction equation:

$$k = \frac{2.303}{t} \log \frac{a}{a-x}$$

where a is the concentration at zero time and a-x is the concentration at any time t. It can be seen from Table I that the constants check fairly well, indicating that the reaction follows first order kinetics under these conditions. At the conclusion of this series of experiments it was decided to use an acid : base ratio of 2:1 in all subsequent standard experiments.

The results bear out the statement made by Hammett[28] that the catalytic effect of piperidine in the presence of acid increases with decreasing acidity. He claims that this suggests that the base piperidine and not its conjugate acid, piperidinium ion, is the catalyst. Although the catalysis may be effective only in the presence of some acid, a strong acid or a large amount of a weak acid represses the activity of the piperidine markedly as found above. In the condensation of diethyl malonate and formaldehyde in alcohol solution with various organic bases as catalysts, Welch[29] found that the reaction rate constant was inversely proportional to hydrogen ion concentration.

It has been suggested at various times that the dehydration step might be the determining factor in the overall rate. If this were so, it would seem, in contrast with the above results, that an increase in acid strength should increase the rate of reaction since, as pointed out by Cope[11], this dehydration is more strongly catalyzed by acid than by base.

The effect of varying the total catalyst concentration at a 2:1 acid : base ratio was studied. The standard procedure was used in this series of experiments except that a 10% excess of benzaldehyde was employed. The data summarized in Table II show that the rate is roughly proportional to the total catalyst concentration.

TABLE II

The Effect of Varying the Total Amount of Catalyst.

Moles Acid	Moles Base	Half Reaction Time (Min.)	$k(min^{-1} \times 10^{-3})$						
			30%	40%	50%	60%	70%	80%	Average
0.0625	0.0312	117	6.07	6.02	5.97	5.99	5.75	5.51*	5.96
0.125	0.0625	71	10.27	10.13	10.22	10.13	10.18	9.75*	10.19
0.250	0.125	34	20.55*	21.15	21.76	21.60	21.51	21.63	21.53

*Not included in average.

EFFECT OF VARYING THE GROUPS SUBSTITUTED IN THE PARA POSITION OF BENZALDEHYDE

In order to determine the effect on reactivity of groups substituted in the para position of benzaldehyde, diethyl malonate was condensed with p-methoxybenzaldehyde, p-chlorobenzaldehyde, and p-nitrobenzaldehyde as well as with benzaldehyde itself. It was possible to run all four compounds at the same catalyst concentration (0.0625 mole piperidine and 0.125 mole caproic acid) and under the standard conditions. The p-chlorobenzaldehyde product has not been previously prepared. In each case first order constants were obtained indicating that the reaction mechanism was probably the same for all and that a valid comparison of reactivities could be made.

The data are summarized in Table III. In general the reaction rate constants checked well for each run. For the various benzaldehydes the constants do not differ over a large range. The most reactive aldehyde of the series was p-methoxybenzaldehyde with an average first order constant of $11.69x10^{-3}$ reciprocal minutes, and the least reactive was p-nitrobenzaldehyde with a constant of $6.78x10^{-3}$ reciprocal minutes. This is less than a two fold variation between the most and the least active.

It is clearly established that the order of decreasing reactivity on a qualitative basis is: $-OCH_3$, $-H$, $-Cl$, $-NO_2$. It is apparent that as the electron releasing ability of the group increased the rate of the reaction increased. Since

TABLE III

Condensation of Para Substituted Benzaldehydes with Malonic Ester[a]

Para Group	Half Reaction Time (Min.)	First Order Rate Constants (Min.$^{-1}$ x 10^{-3})								Yield[c] (%)
		30%	40%	50%	60%	70%	80%	Averages		
$-OCH_3$	62	11.82	11.94	11.84	11.46	11.05	10.67[b]	11.62)	11.69	86
	63	11.61	12.14	11.74	11.75	11.61	11.07[b]	11.77)		
-H	77.5	9.34	9.49	9.42	9.48	9.30	8.72[b]	9.40)	9.65	89
	75	9.82	9.92	10.02	10.07	9.95	9.61	9.90)		
-Cl	91	7.63	7.79	7.96	7.86	7.65	6.96[b]	7.72)	7.66	85
	92	7.72	7.92	7.86	7.39	7.06	6.67[b]	7.59)		
$-NO_2$	98	6.92	6.99	6.90	6.81	6.61	6.41[b]	6.64)	6.78	56
	91	6.61	6.82	6.96	6.77	6.45	6.38[b]	6.72)		

[a] Catalyst consisted of 0.0625 mole piperidine and 0.125 mole caproic acid.

[b] Omitted from average.

[c] After one distillation or crystallization; the yields of purified product were usually 5 - 10% below these values.

these effects are so small in this instance, it is believed that the aldehydes are not involved in the rate controlling step of the reaction. Their influence may be due to some secondary effect such as alteration of the reaction medium or interaction with the catalyst.

Hammett[26] has pointed out that a linear relationship is often obtained when the logarithms of the reaction rate constants for a reaction of a side chain of meta or para substituted benzene derivatives are plotted against the logarithm of the ionization constants of the correspondingly substituted benzoic acids. It was found that the data for the para $-OCH_3$, $-H$, and $-Cl$ benzaldehydes satisfied this relationship fairly well. The data for p-nitrobenzaldehyde showed considerable deviation. Perhaps this is not surprising in view of the lower yield of product isolated from this reaction. The yield of water was 92% after refluxing about 23 hours, whereas in all the other instances the theoretical amount of water was obtained in considerably less time. In any case the linear relationship has only minor value for data of this kind in which the change in rates is small.

EFFECT OF VARYING R AND R^1 IN $CH_2<^{R}_{R^1}$

The various active methylene compounds were arranged in three series for convenience in making a comparative study. The first group consisted of the four symmetrical compounds, malononitrile, acetylacetone, dibenzoylmethane and diethyl malonate. Each of these was condensed with benzaldehyde using the standard procedure described above. The results are summarized in Table IV.

TABLE IV

Condensation of Benzaldehyde with Symmetrical Active Methylene Compounds

Methylene Compound	Catalyst Conc.[a]	Half Reaction Time (Minutes)	Yield[b] (%)
$CNCH_2CN$	1	53	74[c]
$CH_3\ COCH_2COCH_3$	4	46	67
$C_6H_5COCH_2COC_6H_5$	8	112	61
$C_2H_5OOCCH_2COOC_2H_5$	64	75	69

[a] 0.000976 mole piperidine and 0.001952 mole caproic acid taken as unit catalyst concentration.

[b] Yield after one crystallization or distillation.

[c] Purified yield.

No two of these reactions could be conveniently carried out at the same catalyst concentration because there was such a wide difference in their rates. One new compound was obtained, the condensation product of dibenzoylmethane with benzaldehyde.

Of the four condensations only the one with diethyl malonate followed first order kinetics (see Table V). On the basis of exploratory calculations assuming different integral orders the malononitrile reaction appeared to be above second order, the acetylacetone condensation appeared to be between first and second order, and the dibenzoylmethane reaction also appeared to be between first and second order. It is possible that the nature of the individual steps of the reaction changes as the reactivity of the methylene compound changes over such a wide range. It may be, however, that the nature of the steps does not change but that the shift in order is due to changes in the relative rates of the various steps.

Since the orders of the reactions are not the same, comparison of reactivities must be made on a purely qualitative basis rather than on the quantitative basis of relative reaction rate constants. It is apparent from a comparison of the half-reaction times and catalyst concentrations that the order of decreasing reactivity of the -R groups is $-CN$, $-COCH_3$, $-COC_6H_5$, $-COOC_2H_5$.

In the next series studied one activating group was carbethoxy while the other was a nitrile, acetyl, or a second carbethoxy group. The results are summarized in Table V.

TABLE V

Condensation of Benzaldehyde with Active Methylene Compounds
Containing a Carbethoxy Group

Methylene Compound	Catalyst Conc.[a]	Half Reaction Time (min.)	Crude Yield[b]	First Order Rate Constants (min.$^{-1}$ x 10^{-3})							Relative Rate
				30%	40%	50%	60%	70%	80%	Average	
$CNCH_2COOC_2H_5$	2	36	72	20.55	20.40	20.80	20.63	19.62	17.55[c]	20.40	67.5
$CH_3COCH_2COOC_2H_5$	8	24.5	65	27.25	27.66	27.33	26.36	25.09	22.22[c]	26.74	21.9
$C_2H_5OOCCH_2COOC_2H_5$	64	75	89	9.82	9.92	10.02	10.07	9.95	9.66	9.90	1

[a] Unit catalyst was taken as 0.000976 mole piperidine and 0.001952 mole caproic acid.

[b] After one distillation or crystallization.

[c] Omitted from average.

The reactions of the three methylene compounds followed first order kinetics rather well; consequently there is a good basis for comparing reactivities in more than a qualitative manner. Again the catalyst concentrations had to be varied widely in order that the reactions might progress at rates which could conveniently be followed. The order of decreasing reactivity of the variable activating group is: $-CN$, $-COCH_3$, and $-COOC_2H_5$. This is in agreement with the results for the symmetrical series although that series was based only on qualitative information.

The third series investigated consisted of a group of methylene compounds in which one activating group was a phenyl group while the other was a nitro, acetyl, benzoyl, amide, carbethoxy, nitrile, or benzenesulfonyl group. The carbethoxy, nitrile and benzenesulfonyl compounds behaved alike when the condensation was attempted using 0.250 mole of piperidine and 0.500 mole of caproic acid. No product was isolated and practically a quantitative yield of the starting methylene compound was recovered although the theoretical volume of water was collected in the separator over a period of about 40 hours. A resinous residue which may have resulted from the condensation of the aldehyde and piperidine was also obtained. When a similar run was made using 0.125 mole of benzaldehyde, 0.125 mole of caproic acid, and 0.0625 mole of piperidine, and no methylene compound, 0.091 mole of water was collected in about 26 hours. A small amount of benzaldehyde was recovered and a large resinous residue was obtained which could neither be crystallized nor distilled.

The reaction of phenylacetamide was not clear cut. About 24% of pure phenylacetamide was recovered from the reaction mixture and an impure solid mixture from which no single compound could be separated. The same type of resinous residue as was obtained with each of the three previously discussed unreactive compounds was also formed. There was some indication, however, that more than this usual side reaction of benzaldehyde and piperidine occurred because the rate at which water was evolved was more rapid with phenylacetamide than with the others. With ethyl phenylacetate, phenylacetonitrile, and phenylbenzylsulfone the half-reaction time was about 10 hours, but with phenylacetamide it was only 2 hours and 25 minutes. It is possible that phenylacetamide further catalyzes the side reaction. It may be recalled that acetamide was used as a catalyst under similar conditions by Cope[11] for the condensation of ketones with cyanoesters. In any event a kinetic study is of no value under these experimental conditions for phenylacetamide.

It is interesting to note that the nitrile group which has a highly activating effect in malononitrile and ethyl cyanoacetate apparently under the conditions used here does not activate the methylene group in phenylacetonitrile strongly enough for it to condense with benzaldehyde. Phenylacetonitrile undergoes this reaction when more basic catalysts are used; it has been condensed with benzaldehyde in the presence of 20% sodium in alcohol[30].

It is not surprising that benzylphenylsulfone is not sufficiently active to condense with benzaldehyde when piperidine, a relatively mild base, is used as catalyst. The sulphone group is analogous to the carbonyl group in some respects, but it does not activate to the same extent as does the carbonyl group. Benzylphenylsulfone has been shown[31] to be considerably less active than the corresponding carbonyl compound, benzylphenyl ketone. The sulfone forms a salt with sodium ethoxide as does the analogous ketone, but it is not alkylated with methyl iodide and sodium ethoxide as is the carbonyl compound. The results of the present condensation studies bear out the differences between these two compounds. The sulfone does not condense at all under these conditions; on the other hand the ketone condenses readily.

Phenylnitromethane, phenylacetone and benzylphenyl ketone all condense with benzaldehyde in the presence of piperidine and caproic acid. Each followed the first order kinetic equation, indicating similarity in mechanism and providing an opportunity for a comparative study as discussed above for the ester series. As shown in Table VI the relative activating ability of the groups arranged in decreasing order is: $-NO_2$, $-COCH_3$, and $-COC_6H_5$.

Although the condensations of malononitrile, acetylacetone, and dibenzoylmethane appeared to be higher than first order, these compounds can be placed in a series of relative reactivities by comparing the curves for time versus

TABLE VI

Condensation of Benzaldehyde with Active Methylene Compounds

Containing a Phenyl Group

Methylene Compound	Catalyst Conc.	Half Reaction Time (Min.)	Crude Yield[b]	First Order Rate Constants (min.$^{-1}$ x 10^{-3})							Relative Rate
				30%	40%	50%	60%	70%	80%	Average	
Phenylnitromethane	69	49	68	13.09[c]	12.24	11.84	11.53	11.52	11.67	11.76	1.22
Phenylacetone	128	63	59	11.82	11.89	11.52	11.22	11.04	11.05	11.42	0.59
Phenylbenzyl Ketone	128	61	61	10.52	10.90	11.27	11.02	11.15	11.21	11.01	0.57

[a] Unit catalyst concentration 0.000976 mole piperidine and 0.001952 mole caproic acid.

[b] Yield after one distillation or crystallization.

[c] Omitted from average.

percent reaction completed. The order of decreasing reactivity including all the methylene compounds from Tables IV; V and VI is: $CH_2(CN)_2$, $CNCH_2COOC_2H_5$, $CH_3COCH_2COOC_2H_5$, $CH_2(COCH_3)_2$, $CH_2(COC_6H_5)_2$, $C_6H_5CH_2NO_2$, $CH_2(COOC_2H_5)_2$, $C_6H_5CH_2COCH_3$, and $C_6H_5CH_2COC_6H_5$. This sequence is quite definite, except that acetylacetone is practically as reactive as acetoacetic ester and phenylacetone and phenylbenzyl ketone have equal reactivities, within experimental error. The relative reactivities of phenylbenzylsulfone, ethyl phenylacetate, and phenylacetonitrile have not been established, but they are all less reactive than any of the compounds in the above series.

Quantitative comparisons among the compounds in Tables V and VI are valid since they all seem to follow first order kinetics fairly well. The order of decreasing reactivity is: $CNCH_2COOC_2H_5$(67.5), $CH_3COCH_2COOC_2H_5$(21.9), $C_6H_5CH_2CN$ (1.22), $CH_2(COOC_2H_5)_2$(1), $CH_3COCH_2C_6H_5$(0.59), and $C_6H_5COCH_2C_6H_5$(0.57). The numbers in parentheses refer to the relative reactivities on a quantitative basis if all the rates may be assumed to be proportional to the catalyst concentration and if the changes in catalyst concentration do not have any effects other than the direct catalytic ones. The proportionality was established for malonic ester (see Table II). This ester was arbitrarily assigned unit reactivity.

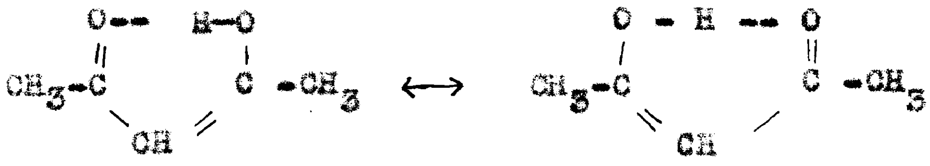
Instead of considering the entire molecule, the reactivities of the individual groups attached to the methylene carbon may be compared. Comparisons within Tables V and VI are readily made. In addition a comparison of ethyl acetoacetate and phenylacetone indicates that the relative activating effects of the carbethoxy and phenyl groups are 21.9 and 0.69 respectively.

An approximate qualitative comparison on the basis of all the data from Tables IV, V and VI gives the following order of decreasing reactivity: $-NO_2$, $-CN$, $-COCH_3$, $-COC_6H_5$, $-COOC_2H_5$ and $-C_6H_5$. The position of the $-SO_2C_6H_5$ group cannot be ascertained on the basis of evidence presented here.

The above series can only be very approximate, for it discounts any interaction between the activating groups. That such interaction may in fact be considerable is shown by a comparison of $CH_3COCH_2COCH_3$ and $C_6H_5COCH_2COC_6H_5$ with $C_6H_5CH_2COCH_3$ and $C_6H_5CH_2COC_6H_5$. With the symmetrical compounds the CH_3CO- group activates much more strongly than the C_6H_5CO- group while with the phenyl compounds the activating ability is equal. A similar conclusion results from a comparison of $CH_3COCH_2COCH_3$ and $C_2H_5COOCH_2COOC_2H_5$ with $CH_3COCH_2COOC_2H_5$. In the symmetrical compounds the CH_3CO- groups is more strongly activating than the C_2H_5COO- group but when these two groups are present in the same compound, the reactivity is about the same as $CH_3COCH_2COCH_3$. A comparison of $CH_2(CN)_2$ and $CH_2(COCH_3)_2$ or $CNCH_2COOC_2H_5$ and $CH_3COCH_2COOC_2H_5$ indicates that the $-CN$ group is more strongly activating than the $-COCH_3$ group, but a comparison of $C_6H_5CH_2CN$ and $C_6H_5CH_2COCH_3$ suggests that the reverse is true.

These examples of marked interaction clearly demonstrate the futility of attempting to assign to each group a number which quantitatively denotes its ability to activate a methylene group. The complete molecules can be quantitatively compared or the groups can be quantitatively compared so long as the second activating group in the methylene compound remains constant.

The primary influence which determines the relative abilities to activate the methylene group is doubtlessly the tendency of these unsaturated groups to attract electrons. The activity of the methylene group is greatly enhanced by the presence of more than one electron withdrawing group. A hydrogen atom may be readily removed to form an anion with such compounds as acetylacetone. In enolization a hydrogen atom which is removed by formation of the anion becomes attached to a carbonyl oxygen. The high percentage of enol form which exists for compounds of this type may be due to stabilization of the enol by the formation of chelate rings[32]. The following are the main forms which contribute to the resonance hybrid of acetylacetone:



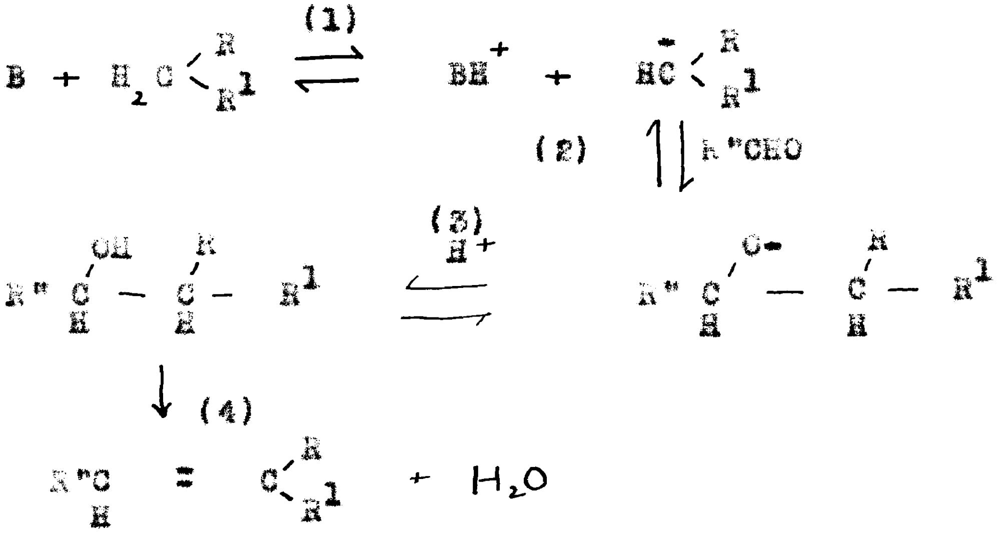
It is interesting to note that those compounds which have a high proportion of the enol form seem to be among the most reactive. Dibenzoylmethane exists 100% in the enol form, acetylacetone

76%, ethyl acetoacetate 8%, and diethylmalonate less than 0.01%[32,33]. There does not, however, appear to be any quantitative correlation between enolization and reactivity.

Although in both the ester and phenyl series there is opportunity for geometrical isomerism, there was only one instance in which a definite indication of more than one form was noted. The product derived from benzylphenyl ketone and diethyl malonate gave in one case an 88% yield of solid material from which a pure compound in 55% yield was obtained which melted at 101 - 102°, the melting point of one of the known isomeric products[34]. The remaining 33% consisted of a mixture which could not be completely purified. Two different crystalline forms could be observed when the material crystallized slowly. One was a material which melted at 97 -99°; the other form, which melted at 87 -89°, took on a slightly yellow color on standing. This change in color is characteristic of the lower melting isomer[35] which melts at 88 -89°. It is a possibility that some of the lower yields of products in the phenyl series might be due to a formation of a mixture of isomers which could not be readily separated.

MECHANISM OF THE KNOEVENAGEL REACTION

Most of the kinetic studies which have been carried out on the base catalyzed aldol type condensation seem to confirm the mechanism for this reaction as proposed by Lapworth[4] and discussed in the introduction. In brief it was proposed that the base removes a proton from the activated methylene group to form a carbanion which then joins to the carbonyl carbon and a proton adds to the carbonyl oxygen. Water is sometimes split out from the aldol product. The general scheme may be represented by the following series of equations:



Kinetic and other experimental evidence confirm this mechanism. Welch[29] investigated the kinetics of the reaction between formaldehyde and malonic ester in an alcohol solution using amine catalysts. His results showed the reaction to be second order at constant catalyst concentration; consequently it is likely that step (2) is rate controlling under these conditions. He also demonstrated, using piperidine, the specific catalytic effect of secondary amines.

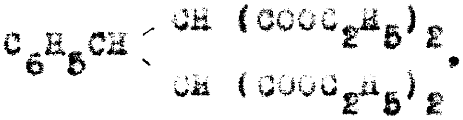
In a study of the condensation of benzaldehyde with acetophenone in alcohol solution in which sodium ethoxide was used as the catalyst[30], it was found that the speed of the reaction was proportional to the concentration of both reagents at a fixed catalyst concentration.

First order kinetics were observed by Bell[37] in the condensation of one mole of acetaldehyde with another in aqueous solution. At first he suggested that the rate determining step of this aldol condensation of acetaldehyde might be the catalyzed dehydration of the hydrate $CH_3CH(OH)_2$. Subsequent experimental data[38] showed that this could not be the case and that the attack of the base might more logically be rate determining. Investigation of the aldol condensation of isobutyraldehyde showed that the apparent order was between first and second indicating that the first two steps proceed at comparable rates.

The reactions in the present study have been carried out under quite different conditions from the ones mentioned above. Those which followed an integral order were found to be first order. These include three compounds of the ester series, diethyl malonate, ethyl acetoacetate and ethyl cyanoacetate, and three compounds of the phenyl series, phenylnitromethane, phenylacetone, and phenylbenzyl ketone. For the condensations of these compounds with benzaldehyde the evidence obtained in this study suggests that the first step, the attack by the base, is rate controlling.

In an effort to determine more clearly that the concentration of methylene compound is the controlling factor in the rate at a fixed catalyst concentration, experiments were carried out using different ratios of reactants. When a 100% excess of diethyl malonate was used with 0.125 mole of benzaldehyde, the time required for one-fourth of the ester to react was

40 minutes; with 20% excess ester the time for one-fourth of it to react was 33.5 minutes; with 0% excess ester the time was 35 minutes. The corresponding average first order constants for 100%, 20% and 0% excess ester were 7.38×10^{-3}, 9.00×10^{-3} and 9.90×10^{-3} reciprocal minutes. It is apparent that some influence is causing a serious shift in these constants. It is possible that the excess ester deactivates the catalyst causing the constants to fall or that other effects of the change in medium are responsible. The possibility that the formation of the tetra ester,



$C_6H_5CH\left\langle\begin{matrix}CH\ (COOC_2H_5)_2\\ CH\ (COOC_2H_5)_2\end{matrix}\right.$, was a serious disturbing factor was eliminated by quantitative isolation of the excess unreacted malonic ester and the isolation of a 73% yield of benzalmalonic ester.

When excess benzaldehyde was used in the same way, the kinetics results were of little value because in all cases an appreciable excess of water was evolved, indicating side reactions. For 100% excess benzaldehyde, 82% more than the theoretical amount of water was collected.

It is apparent that the evidence showing the condensation between aldehyde and methylene compound to be first order at constant catalyst concentration cannot be satisfactorily supported by studies in which excess methylene compound or aldehyde is employed. First order kinetics appear to indicate that the first step of the mechanism, attack by the base on the methylene compound, is primarily the rate determining process. It will be recalled that the results of studies on para substituted benzaldehydes* indicate that the carbonyl constituent is not involved in the rate controlling step. On the other hand studies with various active methylene compounds show that alterations in the structure of this reactant cause marked changes in the rate of the overall reaction. It was furthermore shown that it is the piperidine rather than the caproic acid which exerts the primary catalytic effect. This is consistent with the interpretation that the step in which the base attacks the methylene compound is the one which chiefly determines the rate. The possibility that the second step is also slow enough to influence the overall rate has not been entirely eliminated.

The energy of activation was calculated for the condensation of benzaldehyde with malonic ester from the data for the reaction run in benzene and in toluene. In both cases 0.125 mole of ester was used and a 10% excess of benzaldehyde with 0.0312 mole of piperidine and 0.0625 mole of caproic acid. In benzene the temperature was 84.5 - 84.3° and in toluene it was 114.6 - 114.4°. Duplicate experiments were run in each case. If it can be assumed that the solvent effects of toluene were about the same as those of benzene the energy of activation calculated from the equation,

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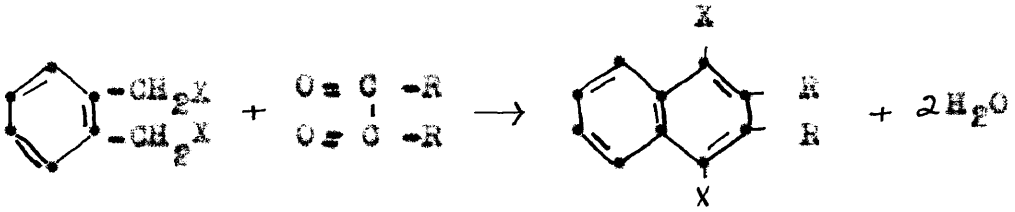
*It is interesting to note that the results of this study agree qualitatively with Hammett's[28] correlation which was discussed above but not with Mowry's[24] results on the condensations of malononitrile with p- substituted acetophenones.

$$\log \frac{k_2}{k_1} = \frac{E}{2.303R}\left[\frac{T_2-T_1}{T_2T_1}\right]$$, is 12.26 K. cal.

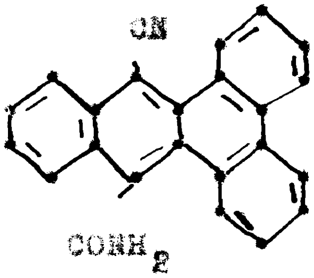
CONDENSATION OF α- DICARBONYL COMPOUNDS WITH o-PHENYLENE DIACETIC ACID

This study was directed toward the syntheses of substituted polynuclear hydrocarbons by the condensation of α- dicarbonyl compounds with aromatic compounds having two active methylene groups in the ortho positions. The general reaction is:

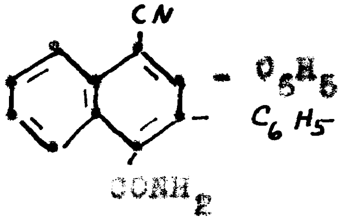


where X is an activating group such as a nitrile or a carboxyl group and R is an alkyl or aryl group. It may be seen that the reaction gives rise to a new aromatic ring. It was hoped to develop a good method for preparing polynuclear compounds substituted in the meso positions which are not readily available by other means and which might prove to be useful intermediates for the synthesis of carcinogenic hydrocarbons.

An early example of this type of condensation was reported by Hinsberg[39] who used o-phenylenediacetonitrile to supply the two necessary active methylene groups. The reaction was carried out with dicarbonyl compounds such as phenanthraquinone and benzil using sodium methoxide as the catalyst in methyl alcohol solution. After standing for eight or more days at room temperature the products were isolated; no yields were reported. The products obtained were:



I

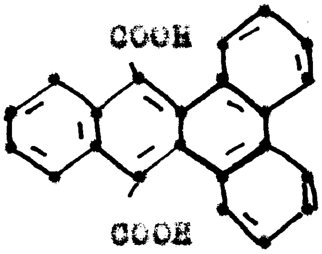


II

Hinsberg's work was repeated and extended in this study in the hope of improving the reaction so that a variety of compounds could be obtained in good yield. Compound II was isolated in only a very low yield. The method was extended to similar condensations with glyoxal and with diacetyl. When a 30% aqueous solution of glyoxal was reacted with the dinitrile using sodium methoxide in methyl alcohol, 1,4-dicyanonaphthalene was obtained in a 30% yield. With diacetyl the desired compound 2,3-dimethyl-1, 4-dicyanonaphthalene was obtained in a 15% yield using a similar procedure. It was further found that, in the case of phenanthraquinone, condensation with o-phenylenediacetonitrile occurred at about 200° in the absence of both catalyst and solvent. Only a 4% yield was obtained of the diamide instead of the amide-nitrile, compound I, which Hinsberg prepared. Preliminary attempts to raise the yields of the above compounds were not encouraging.

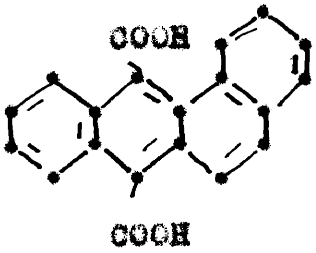
While these studies were in progress Moureu and coworkers[40] reported the same condensation using piperidine as a catalyst. They succeeded in condensing o-phenylenediacetonitrile with various dicarbonyl compounds in yields of 40- 65%. In view of their satisfactory method of synthesis, plans for the further study of condensations with the dinitrile were abandoned. It appeared, however, that the study of methylene compounds containing activating groups other than the nitrile should be continued since they would lead to valuable compounds not readily obtained from the dinitrile. Thus Moureu[41,42] found that he was unable to hydrolyze these products to the dicarboxylic acids; 10% alcoholic potassium hydroxide gave only diamides.

In order to prepare the same type of compounds containing different functional groups, it was decided to study the condensation of the dinitro and the dicarboxylic methylene compounds. Experiments with the dinitro compound did not give encouraging results, but the condensations of o-phenylenediacetic acid with various α-dicarbonyl compounds using the Perkin[43] reaction were successful. With benzil, furil, and diacetyl the condensation was unsuccessful but with ortho quinones such as phenanthraquinone, naphthaquinone, chrysenequinone, and acenaphthaquinone the expected products were formed. The compounds obtained and the yields of each were:



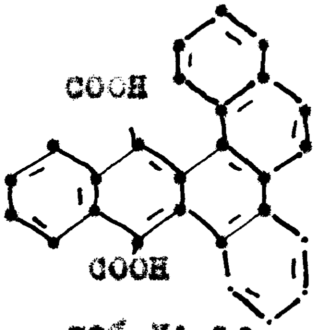
50% Yield

III



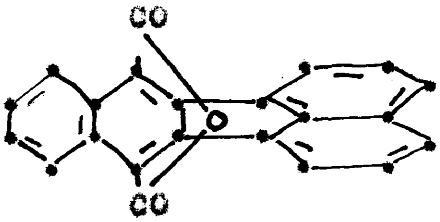
22% Yield

IV



30% Yield

V



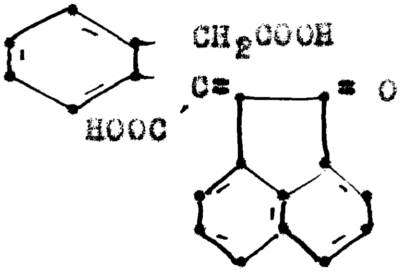
18% Yield

VI

The general procedure was to suspend a mixture of the potassium salt of o-phenylenediacetic acid and the ortho quinone in acetic anhydride. This mixture was generally stirred for about six hours in an ice bath or at some temperature up to 50° depending on the quinone which was being used. After standing overnight the reaction products which were rather insoluble solids were isolated by filtration and were purified.

The compounds obtained have not previously been reported in the literature. In all instances they were identified by analyses. The condensation product of naphthaquinone was further reacted with diazomethane to form the dimethyl ester in a small yield. In the case of the reaction of o-phenylenediacetic acid with phenanthraquinone the product was also identified by decarboxylation to 1, 2, 3, 4 dibenzanthracene.

A mixture of products was obtained from the reaction of o-phenylenediacetic acid with acenaphthaquinone. In addition to a compound formed by the reaction of both methylene groups, VI, there was also a product which according to the analyses resulted from the condensation of only one of these groups, compound VII:

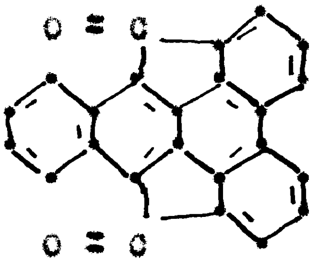


22% Yield

VII

Compound VI is the only example of the formation of an anhydride rather than the free dicarboxylic acid. It was possible to separate compounds VI and VII rather easily because the anhydride is quite insoluble in hot glacial acetic acid whereas the half-condensed compound is soluble.

Attempts were made to further cyclize III in order to prepare a compound which might be written as:



VIII

Reduction of the carbonyl groups to methylene groups would give an interesting analog of cholanthrene and of 9, 10-dimethyl-1, 2- benzanthracene, both of which are potent carcinogens. Various catalysts were used such as HF, H_2SO_4, $Z_n\ Cl_2$ in acetic acid, and P_2O_5. None of these attempts was successful. Efforts to cyclize via the acid chloride were also unsuccessful.

EXPERIMENTAL*

PRELIMINARY STUDIES

Purification of Materials. All starting materials were purified by distillation or crystallization. Physical constants for the purified materials may be found in Table VII.

Acetic Acid and Piperidine as the Catalyst. One-eighth mole of 2-ethylbutanal, the same amount of malonic ester, 0.04 mole of piperidine and 0.06 mole of acetic acid were refluxed in 500 ml. of benzene. After 23 hours the volume of water was constant; however, the reading was 0.22 ml. higher than the theoretical value, indicating that some acetic acid had distilled over with the water. This observation was confirmed by the fact that the water layer was found to be acidic. The solution was washed with 10% sodium carbonate. The benzene was distilled off at atmospheric pressure, and the product was distilled under reduced pressure, b.p.125-126°/5.5 mm. A 76% yield was obtained.

Condensation of Ketones with Malonic Ester. One-eighth mole each of diethyl ketone and malonic ester, 0.16 mole of piperidine, and 0.32 mole of caproic acid in 500 ml. benzene were refluxed for 24 hours. At the end of that time no water had collected in the liquid separator.

When the same procedure was used with one-eighth mole

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*Microanalyses were by Mrs. Mary Aldridge and Mr. Byron Baer.

TABLE VII

Physical Constants of Starting Materials

	Values Found		Values from Literature	
	Boiling Point* (°C)	n_D	Boiling Point* (°C)	n_D
Benzene	80-80.5	$n^{25.5}=1.4978$	80.1	$n^{25}=1.4981$
Toluene	110-111	$n^{25.5}=1.4936$	110.6	$n^{25}=1.4939$
o-Xylene	144.5-145.5	$n^{22}=1.5040$	144	$n^{20}=1.5050$
Caproic Acid	95-95.5/7mm	$n^{20}=1.4147$	202/761mm	$n^{19.6}=1.4145$
Piperidine	105.5-106.5	$n^{20}=1.4530$	106	$n^{20}=1.4530$
Tri-n-butylamine	96-96.5/11mm	$n^{22.5}=1.4280$	216.5	$n^{20}=1.4291$
Diethyl Ketone	102-3	$n^{22.5}=1.3920$	102.7	$n^{16.6}=1.3939$
Cyclohexanone	154-155.5	$n^{22.5}=1.4490$	155-6	$n^{20}=1.4503$
2 -Ethylbutanal	116.5-118	$n^{20}=1.4158$	117-118	$n^{20}=1.4160$
2 -Ethylhexanal	162.5-163	$n^{22.5}=1.4154$	163-4	$n^{20}=1.4160$
n-Heptaldehyde	150.5-152	$n^{25}=1.4100$	155	$n^{19.9}=1.4125$
Benzaldehyde	177.5-178.5	$n^{20}=1.5450$	179	$n^{19.5}=1.5456$
p-Methoxybenzaldehyde	80-81/1.3mm	$n^{28.5}=1.5700$	134-5/12mm	$n^{12.7}=1.5764$
p-Nitrobenzaldehyde	(105-106)		(106.5)	
p-Chlorobenzaldehyde	(46.5-47.5)		(47.8)	
Diethyl Malonate	82-3/7mm	$n^{20}=1.4136$	198.9	$n^{20}=1.4143$
Malononitrile	(30-32)		(30-32)	
Acetylacetone	136-7	$n^{24.2}=1.4485$	139	$n^{18.5}=1.4518$
Dibenzoylmethane	(78-9)		(78)	
Ethyl Cyanoacetate	80-2/2mm	$n^{22.5}=1.4165$	97/16mm	$n^{20.5}=1.4179$
Ethyl Acetoacetate	74/14mm	$n^{22.5}=1.4186$	180	$n^{20}=1.4198$
Phenylnitromethane	90-92/3mm	$n^{21.8}=1.5316$	90-92/3mm	$n^{20}=1.5323$
Phenylacetone	92/6mm	$n^{21.7}=1.5161$	104-6/13mm	$n^{20}=1.5168$
Desoxybenzoin	(58.5-59.5)		(60)	
Phenylacetamide	(156-7)		156-7	
Phenylacetonitrile	79-80/1.5mm	$n^{28.5}=1.5189$	85/3mm	$n^{25}=1.5210$
Ethyl Phenylacetate	94.5/5mm	$n^{20}=1.4985$	227	$n^{18.5}=1.4992$
Benzyl Phenylsulfone	(146-147)		(146-147)	

*Values in parentheses are melting points.

of cyclohexanone as the carbonyl compound and the same quantities of the other reagents, only 30% of the theoretical amount of water was collected after 32 hours of refluxing. The solution was not worked up.

Condensation of Aliphatic Aldehydes with Malonic Ester. When 0.0625 mole of n-heptaldehyde was refluxed with an equivalent quantity of malonic ester using 0.04 mole of piperidine and 0.08 mole of caproic acid in 500 ml. of benzene, 90% of the theoretical quantity of water was collected in 24 hours. The reaction mixture was worked up according to the standard procedure, as stated in a previous section, but no sharply boiling fraction was obtained and no pure product could be isolated.

A standard run was made with 2-ethylbutanal and malonic ester, using 0.0625 mole of piperidine and 0.250 mole of caproic acid. The temperature of the condensation was 84.1°. The half reaction time was 2 hours and 35 minutes; in 24 hours 94% of the theoretical volume of water was collected. After the standard washing and distillation the product was obtained in 76.2% yield, b.p. 86.5-88.5°/0.5-0.6 mm., $n_D^{27.5}$ = 1.4442 (lit. b.p. 146/21mm., n_D^{25} = 1.4450).

With the same quantity of 2-ethylhexanal and the identical procedure, using this time 0.125 mole of caproic acid and 0.0625 mole of piperidine, the reaction temperature was 84.5-84.7°. During 24 hours a 97% yield of water was collected. The half-reaction time was 2 hours. The product was washed as before, the benzene distilled off, and the product distilled under reduced pressure giving a crude yield of 87%. On refractionation an 80.5% yield of product was obtained, b.p. 108.5-110°/0.5-0.7 mm., $n_D^{27.5}$ = 1.4471.

Test of Various Solvents. When 0.0625 mole of piperidine and 0.125 mole of caproic acid were refluxed together for three hours in 500 ml. of benzene solution, at 82.2 ± 0.1° no water was evolved, indicating no reaction at the temperature of refluxing benzene.

The above experiment was repeated using a similar toluene solution which had a reflux temperature of 113.2 ± 0.1°. Again no reaction was observed.

A reaction did occur in o-xylene when the same quantities of piperidine and caproic acid were refluxed in this solvent at a temperature of 144.3 -144.6°. After refluxing for 26 hours, 0.05 mole of water was collected. The solvent was distilled off and the product was fractionated under reduced pressure. The first fraction, 3.2 g. boiling at 72-73.5°/2 mm., $n_D^{27.5}$= 1.4145, was caproic acid. The second fraction weighed 2.0 g. and boiled over a considerable range, 91-106°/2 mm., $n_D^{27.5}$= 1.4400. The third and main fraction, 6.8 g., boiled at 107-109°/2 mm., $n_D^{27.5}$= 1.4716. There was a residue of 2.4 g. The main fraction represented a 60% yield of N-caproyl piperidine. On a repeat run a 72% crude yield was obtained which on refractionation gave a 40% yield of a product boiling sharply at 98.2°/1.2 mm., $n_D^{27.5}$= 1.4732, (lit. b.p. 140°/12 mm.).

Anal. Calcd. for $C_{11}H_{21}ON$: C, 72.07; H, 11.55; N, 7.64. Found: C, 71.90, 71.69; H, 11.11, 11.21; N, 7.84, 7.76.

CATALYST STUDIES

<u>p-Toluenesulfonic Acid as the Catalyst.</u> A mixture of 0.062 mole of ethyl cyanoacetate, 0.093 mole of benzaldehyde and 0.008 mole of p-toluenesulfonic acid was refluxed in 250 ml. of benzene. The catalyst concentration was increased at intervals as the evolution of water slowed down until the final amount was 0.048 mole. After refluxing for 36 hours only a 42.8% yield of water was evolved. The product was not isolated.

<u>Caproic Acid as the Catalyst.</u> When 0.0625 mole of benzaldehyde and 0.0625 mole of malonic ester were refluxed with 0.0625 mole of caproic acid in 250 ml. of benzene solution for 2 hours, no water was evolved.

<u>Tri-n-butylamine as Catalyst.</u> The standard quantities of malonic ester and benzaldehyde were refluxed with 0.0625 mole of tri-n-butylamine in 500 ml. of benzene solution. No water was formed after 3-1/2 hours. When 0.125 mole caproic acid was added to the above mixture and the solution was refluxed for three hours no water was formed.

<u>Piperidine and Chloroacetic Acid as Catalyst.</u> A standard run was made with benzaldehyde and malonic ester in the presence of 0.0625 mole of piperidine and 0.125 mole of chloroacetic acid. After a 51 hour period of refluxing, with the temperature varying from 82.4° to 83.4°, 86.6% of the theoretical amount of water was collected. The half-reaction time was approximately 6 hours. Toward the end of the reflux time chloroacetic acid began to precipitate out as it became

less soluble in the reaction mixture. After cooling, 3.42 g. of the acid which had precipitated was filtered off. On titrating the water layer, 1.95 ml., with standard sodium hydroxide solution, it was found that it contained 0.033 g. of chloroacetic acid.

Standard Run with Caproic Acid and Piperidine as Catalyst. A standard run was made using 0.125 mole of benzaldehyde, 0.125 mole of malonic ester, 0.0625 mole of piperidine, and 0.125 mole of caproic acid in 500 ml. of benzene solution. At the end of a reflux period of 10-1/2 hours a 98.6% yield of water was obtained. The temperature was 83.2° ± 0.1°. After the usual standard washing and distillation an 89.3% yield of crude product was obtained which on refractionation gave a 79.4% yield of pure product, b.p. 126.5°-127.5°/0.5 mm., $n_D^{27.5}$= 1.5335 (lit. b.p. 189-190°/14mm., $n_D^{20.4}$= 1.5389). The rate data are given in Table VIII, see also Table III. For a duplicate run the average reaction rate constant was 5% lower. The temperature was 84.6-84.3° and the yield after one distillation was 88%. In this and all cases subsequently discussed the first distillation was done using a simple Claisen head. For redistillation a 6" x 1" Vigreux fractionating column was used.

TABLE VIII

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
10	0.15	80	1.22	180	1.82
20	.31	90	1.30	210	1.92
30	.48	100	1.39	240	1.99
40	.66	110	1.46	270	2.03
50	.82	120	1.52	330	2.12
60	.94	135	1.62	450	2.20
70	1.08	150	1.71	630	2.22

The Effect of Varying the Acid: Base Ratio. The standard quantities of benzaldehyde and malonic ester were reacted in the presence of 0.0625 mole of piperidine and the same amount of caproic acid. The temperature was 64.0-64.5°. Unlike the standard method, the product was not washed. The solvent was taken off at reduced pressure and the residue was distilled; a 54.5% yield of crude product was collected. The rate data are tabulated in Table IX (see also Table I). The reaction rate constant was 10% lower for a duplicate determination. The temperature was 63.2 ± 0.1° and a crude yield of 73% was obtained.

TABLE IX

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
5	0.13	80	1.30	185	1.92
10	.25	90	1.40	245	2.05
20	.42	105	1.52	305	2.10
30	.60	120	1.63	485	2.15
40	.79	135	1.71	705	2.18
50	.97	150	1.77	1320	2.25
60	1.10	165	1.83	1400	2.25
70	1.22				

The determination at a 2:1 acid:base ratio was previously described.

In another experiment the standard quantities of benzaldehyde and malonic ester were condensed in 500 ml. of benzene solution in the presence of 0.0625 mole of piperidine and 0.250 mole of caproic acid. The temperature was 84.0 ± 0.1°. The product was worked up by the standard method and a 69% yield of pure product was obtained, b.p. 146.5-148° /1.6-1.7 mm., $n_D^{27.5}$ = 1.5332. The rate data for this run are in Table X (see also Table I). The average rate constant of a duplicate experiment was 4% higher. The temperature of this reaction mixture was 84.2-84.3°. The product was obtained in 63% yield after one distillation.

TABLE X

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
10	0.13	100	1.02	245	1.70
20	.25	110	1.10	275	1.79
30	.36	125	1.19	290	1.81
40	.48	140	1.28	350	1.93
50	.59	155	1.37	455	2.05
60	.69	170	1.43	630	2.14
70	.78	185	1.49	1350	2.23
80	.88	215	1.61	1530	2.25
90	.93			1650	2.25

With the same quantities of benzaldehyde malonic ester, and piperidine as above 0.500 mole of caproic acid was used. The temperature of the refluxing benzene solution was 84.5-84.9°. The reaction was stopped after 93.3% of the theoretical amount of water was evolved. The product was not worked up. No duplicate run was made. The rate data follow in Table XI (see also Table I).

TABLE XI

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
10	0.06	115	.94	275	1.57
20	.18	130	1.02	315	1.65
30	.26	145	1.10	345	1.73
40	.36	160	1.17	375	1.79
50	.46	175	1.23	420	1.88
60	.54	200	1.30	480	1.95
70	.62	215	1.36	600	2.06
85	.75	245	1.47	735	2.10
100	.84	266	1.52		

The Effect of Varying the Total Concentration of Catalyst.

All of these determinations were made with 0.125 mole of malonic ester, a 10% excess of benzaldehyde, and an acid:base ratio of 2:1, using the standard procedure.

With one-half the amount of piperidine and caproic acid as used in the standard run the temperature was 84.2-84.5°. The product, isolated as usual, was obtained in an 89% crude yield. The rate data follow (see also Table II).

TABLE XII

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
15	0.19	105	1.05	240	1.68
30	.35	120	1.12	270	1.76
40	.46	135	1.27	300	1.82
50	.58	150	1.32	330	1.88
60	.66	165	1.42	390	1.97
70	.77	180	1.48	480	2.04
75	.82	210	1.57	600	2.22
90	.91				

For a duplicate determination the temperature of the solution was 82.6-82.5° and the average reaction rate constant was 12% higher. The data from this run were not used in the energy of activation calculations which will be referred to later because the atmospheric pressure was quite different from that of the above run and from that in toluene. The rate data are in Table XIII.

TABLE XIII

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
15	0.18	85	.99	195	1.62
25	.33	95	1.08	225	1.72
35	.47	105	1.15	265	1.83
47	.59	115	1.21	305	1.93
55	.69	130	1.30	390	2.03
65	.80	155	1.44	430	2.08
75	.90	175	1.54		

With the standard amounts of catalyst the reaction temperature was 85.7-85.3°. After washing and distilling a crude yield of 88% was obtained. Rate data are given in table XIV (see also Table II).

TABLE XIV

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
10	0.18	55	.94	135	1.66
15	.27	60	1.01	150	1.71
20	.37	70	1.11	165	1.78
25	.46	80	1.22	180	1.85
30	.54	90	1.33	210	1.93
35	.61	100	1.40	240	2.01
40	.71	110	1.48	315	2.11
45	.78	120	1.56	460	2.19
50	.86			545	2.24

When twice the catalyst concentration as in the previous experiment was used, the temperature was 85.3-85.7°. The product was not worked up. Rate data are listed in Table XV (see also Table II).

TABLE XV

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
5	0.15	40	1.26	100	2.02
10	.36	45	1.41	120	2.10
15	.53	55	1.54	150	2.22
20	.72	65	1.66	165	2.26
25	.87	70	1.73	195	2.31
30	1.00	75	1.80	255	2.35
35	1.16	85	1.90	330	2.35

PARA SUBSTITUTED BENZALDEHYDES

The para substituted benzaldehydes were condensed with malonic ester according to the standard procedure, using the standard amount of catalyst. The reaction of benzaldehyde was previously described.

p-Methoxybenzaldehyde. The temperature of the reaction mixture, a 500 ml. benzene solution, was 83.2 - 83.3°. After working up in the standard manner, a crude yield of 79.3% of product was obtained. On redistillation a 74.1% yield was obtained, b.p.167-168°/1.2 mm., $n_D^{29.5}$= 1.5572. Rate data are given in Table XVI (see also Table III). A check determination having a reaction temperature of 83.6-83.9° gave a crude yield of 85.6%. The average reaction rate constants for the two experiments checked within 1%.

TABLE XVI

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
10	0.19	50	.98	115	1.60
15	.30	55	1.05	135	1.71
20	.41	60	1.12	155	1.80
25	.53	65	1.17	165	1.84
30	.64	75	1.25	225	1.94
35	.73	85	1.35	295	2.07
40	.82	95	1.45	370	2.12
45	.91	105	1.53	495	2.17

<u>p-Chlorobenzaldehyde.</u> The reaction mixture refluxed at 83.4° for 12 hours; 97% of the theoretical amount of water was given off. The crude yield of p-chlorobenzalmalonic ester was 85%; on redistillation an 80% yield was obtained boiling at 156.5-158.5°/1.5 mm., $n_D^{27.2}$= 1.5472. So far as could be determined the product has not previously been reported in the literature; the analysis checked for the expected compound.

<u>Anal.</u> Calcd. for $C_{14}H_{15}O_4Cl$: C, 59.47; H, 5.37. Found: C, 59.60, 59.66; H, 5.76, 5.60.

The rate data are listed in Table XVII (see also Table III). The duplicate determination gave an average constant which checked within less than 2%. The temperature of the reaction was 83.4 - 83.5°; a 74% yield of crude product was obtained.

<u>TABLE XVII</u>

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
20	0.27	65	.85	145	1.50
25	.35	75	.97	165	1.59
30	.42	85	1.07	195	1.70
35	.49	95	1.16	235	1.80
40	.56	105	1.24	275	1.90
45	.64	115	1.32	335	2.00
55	.75	130	1.42	440	2.10
				720	2.18

<u>p-Nitrobenzaldehyde</u>[44]. After refluxing the reaction mixture for 23 hours, 92% of the theoretical amount of water was collected. The temperature of the reaction was 83.2-82.9°. A crude yield of 56% of the product, contaminated with an orange oil, was obtained. The pure product, a pale

yellow solid, crystallized from alcohol, m.p. 93-94° (lit. m.p. 93-94°) was obtained in 43.2% yield. The rate data are listed in Table XVIII (see also Table III). The duplicate, refluxed at 83.8 - 84.0°, gave a 91% yield of water in 22 hours; the pure product was obtained in a 40% yield. The average reaction rate constants checked within 2%.

TABLE XVIII

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
10	0.23	90	1.11	185	1.63
20	.40	100	1.19	215	1.73
30	.52	110	1.25	245	1.80
40	.64	120	1.31	275	1.86
50	.76	130	1.37	335	1.96
60	.85	145	1.45	630	2.07
70	.95	165	1.54	1380	2.07
80	1.03				

VARYING R AND R^1 IN $CH_2 <^{R}_{R^1}$

Malononitrile[45]. One-eighth mole of malononitrile was reacted with 0.125 mole of benzaldehyde using 0.000976 mole of piperidine and 0.001952 mole of caproic acid in 500 ml. of benzene solution. The reaction was refluxed for 25 hours at 84.0 - 84.3°; 91.5% of the theoretical amount of water was given off. The half reaction time was about 53 minutes. After working up the product in the standard manner, a 73.7% yield of pure benzalmalononitrile, crystallized from petroleum ether (60-80°), was obtained, m.p. 86.5-87.5° (lit.m.p.87°). The rate data are recorded in Table XIX below (see also Table IV).

TABLE XIX

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
20	0.20	55	1.21	190	1.77
25	.50	65	1.34	250	1.82
30	.68	75	1.41	370	1.90
35	.81	85	1.49	1300	2.03
40	.93	95	1.54	1645	2.06
45	1.04	115	1.59	1760	2.06
50	1.15	145	1.68		

A rate study, made with 0.00781 mole of piperidine and 0.03124 mole of caproic acid, was too fast for accurate rate data to be recorded; the half-reaction time was approximately 4 minutes. A pure yield of 60.6% of the product was obtained after crystallization as before.

Acetylacetone. One-eighth mole quantities of benzaldehyde and acetylacetone were condensed in the presence of 0.00390 mole of piperidine and 0.00781 mole of caproic acid and in 500 ml. of benzene solution according to the standard procedure. The reaction temperature was 82.0-82.5°; 90.2% of the theoretical amount of water was collected in 7-1/2 hours. The half-reaction time was about 48 minutes. A crude yield of 67% was obtained; on refractionating the yield was 58%, b.p.137°/2mm.,$n_D^{31.2}$= 1.5752 (lit.b.p.185/15mm., $n_D^{17.3}$=1.5846). Rate data are tabulated below (see also Table IV).

A rate study made with 0.001464 mole of piperidine and 0.002928 mole of caproic acid had a half-reaction time of about 2 hours. A yield of 50% of the product was obtained after one distillation.

TABLE XX

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
8	0.18	50	1.18	130	1.70
14	.36	55	1.24	160	1.79
17	.50	60	1.30	190	1.85
20	.59	70	1.39	250	1.93
23	.66	85	1.47	310	1.98
29	.79	95	1.53	355	2.01
35	.91	110	1.62	395	2.03
45	1.08				

Dibenzoylmethane. One-eighth mole of this compound was reacted with an equivalent amount of benzaldehyde in the presence of 0.00781 mole of piperidine and 0.0156 mole of caproic acid. After refluxing for 28 hours, 88% of the theoretical volume of water was given off. The temperature of the reaction was 82.6-82.9°. After working up the product, a 61% yield of a light orange solid crystallized from alcohol was obtained, m.p. 87-88°. The melting point was constant after repeated recrystallizations. So far as is known this compound was not reported before.

Anal. Calcd. for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.21, 84.56; H, 5.57, 5.64. Rate data are listed in Table XXI.

TABLE XXI

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
25	0.32	85	.95	245	1.62
30	.39	95	1.03	290	1.72
35	.46	110	1.12	400	1.82
40	.53	125	1.20	445	1.86
50	.63	145	1.30	1440	1.97
60	.73	165	1.39	1670	1.98
70	.83	200	1.51		

Ethyl Acetoacetate. The standard procedure and quantities were employed in the condensation of this ester with benzaldehyde, in the presence of 0.00781 mole of piperidine and 0.01562 mole of caproic acid. The reaction temperature was 83.3 ± 0.1°, and after an 8 hour reflux period 96.6% of the theoretical amount of water was obtained. The purified (crude yield 83%) product, representing a 73% yield, was a pale yellow liquid, b.p. 125-126°/0.9mm. This compound is reported in the literature as a solid, m.p. 60-61°. The compound obtained in this instance may either be another isomer or possibly it is a mixture of isomers. It could not be crystallized but analyses showed it to be the correct compound.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.83, 71.88; H, 7.21, 6.88.

The rate data are to be found in Table XXII (see also Table V). A check determination gave a 71% yield of pure product b.p.123°/0.8 mm. The temperature of reaction was 82.6 ± 0.1° and a 97.3% yield of water was obtained after 6 hours. This check run was made with a 4:1 acid:base ratio using 0.00781 mole of base. The average reaction rate constant was 26.28 x 10^{-3} reciprocal minutes.

TABLE XXII

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
5	.27	23	1.07	66	1.76
7	.40	25	1.13	81	1.86
9	.52	29	1.24	101	1.96
12	.66	34	1.36	156	2.07
14	.74	40	1.47	401	2.18
17	.87	47	1.56	466	2.18
20	.97	53	1.66		

__Ethyl cyanoacetate.__ For this condensation with benzaldehyde 0.001953 mole of piperidine and 0.003905 mole of caproic acid were used. The temperature during the reaction was 82.7-82.9°. At the end of six hours 92.8% of the theoretical yield of water was obtained. One crystallization of the product from alcohol gave a 72% yield of a white solid. Repurification yielded 69% of the product, m.p. 50-51° (lit. m.p. 51°). The rate data are given in Table XXIII (see also Table V).

TABLE XXIII

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
10	.36	29	.99	75	1.69
14	.52	35	1.11	90	1.78
17	.63	40	1.23	110	1.88
20	.73	45	1.33	145	1.99
23	.83	55	1.49	280	2.09
26	.93	65	1.60	370	2.09

A duplicate determination was made using 0.003901 mole of piperidine and 0.00781 mole of caproic acid. The temperature was 82.5-82.6° and after 3 hours and 20 minutes, 95.5% of the theoretical amount of water was evolved. A 72% crude yield of product was obtained. The average reaction rate constant was 34.69 x 10^{-3} reciprocal minutes.

Phenylnitromethane[46]. One-eighth mole each of phenylnitromethane and of benzaldehyde were refluxed in a 500 ml. benzene solution with 0.0625 mole of piperidine and 0.125 mole of caproic acid. After refluxing for five hours at 84.7-84.9° slightly more than the theoretical amount of water was collected. On working up the solution a crude yield of 68% was obtained and a pure yield of 53% of a yellow solid crystallized from alcohol, m.p. 74.5-75°, was isolated (lit. m.p. 75°) The rate data are listed in Table XXIV (see also Table VI). The duplicate determination was refluxed 5 hours at 82.9-83.3° and gave a pure yield of 54% of the product. The average reaction rate constant was 12.11 x 10^{-3} min.$^{-1}$

TABLE XXIV

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
5	.26	55	1.18	145	1.87
10	.50	65	1.28	165	1.95
15	.64	75	1.38	195	2.07
20	.74	85	1.48	225	2.16
25	.82	95	1.58	255	2.22
35	.96	110	1.68	280	2.26
45	1.08	125	1.77	315	2.31

Phenylacetone. This compound was reacted with benzaldehyde in the presence of 0.125 mole of piperidine and 0.250 mole of caproic acid. At the end of a 5-1/2 hours reflux period at 84.0 ± 0.1° slightly more than the theoretical amount of water was collected. Some of the product crystallized out after the routine washing and distillation of the benzene; the remainder was obtained by distillation of the mother liquor. In this way there was obtained a 59% yield of product.

On recrystallization from alcohol a white solid, m.p.53.5-54.5° (lit.m.p.53-54°), was obtained. The rate data are listed in Table XXV (see also Table VI). The check run refluxed at 83.4° and, in 7-1/2 hours, 8.4% more than the theoretical quantity of water had collected. The yield of product was 31%. The poor yield plus the fact that an excess amount of water was evolved might seem to indicate the existence of a side reaction. The average reaction rate constant was 10.99×10^{-3} min.^{-1} which agrees within about 4% with the above determination.

TABLE XXV

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
10	.18	60	1.10	155	1.82
20	.41	70	1.20	175	1.91
25	.51	80	1.30	210	2.04
30	.60	90	1.40	240	2.14
35	.70	100	1.50	270	2.20
40	.80	115	1.62	300	2.25
45	.89	135	1.72	340	2.30
50	.97				

Phenylbenzyl ketone.[47] This compound was reacted with benzaldehyde according to the standard procedure using 0.125 mole of piperidine and 0.250 mole of caproic acid. The theoretical quantity of water was given off after the benzene solution was refluxed 6 hours and 45 minutes at 84.3-84.7°. After washing as usual, distilling off the benzene, and cooling, an 81% yield of a white solid separated. On crystallization from petroleum ether (60-80°) a 55% yield of product melting at 100-100.5° was obtained. The solid remaining in the mother liquor gradually crystallized but no pure substance could be crystallized from it. Two types of crystals were formed. On mechanical separation one melted at 99-100° when further crystallized. This corresponded with the bulk of the material obtained and with the higher melting isomer (m.p.101-102°)[48] of benzaldesoxybenzoin. The other crystals which gradually turned yellow on standing melted at 87-89°, corresponding to the lower melting isobenzaldesoxybenzoin (m.p.88-89°).[35] The mixture of isomers which was not readily separated amounted to a 26% yield. The rate data are recorded in Table XXVI (see also Table VI).

TABLE XXVI

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
10	.26	50	.95	145	1.79
15	.36	60	1.10	165	1.90
20	.46	70	1.24	200	2.00
25	.55	80	1.34	260	2.09
30	.64	95	1.45	325	2.20
35	.73	110	1.57	405	2.26
40	.82	125	1.68		

The duplicate determination gave a crude yield of 88% and a pure yield of the higher melting isomer of 53%. The temperature of the reaction mixture was 84.2-83.9° during a six hour reflux period. The average reaction rate constant was 9.68×10^{-3} min.^{-1}

<u>Ethyl Phenylacetate</u>. The ester and benzaldehyde were refluxed according to the standard procedure with 0.250 mole of piperidine and 0.500 mole of caproic acid. The temperature of the reaction was 85-85.5°; the half-reaction time was 9 hours and 15 minutes. After refluxing for 39 hours, slightly more than the theoretical requirement of water was obtained.

The reaction mixture was worked up in the standard fashion. There was obtained practically a quantitative yield of a fraction, b.p. 66.5°/0.6mm., n_D^{30} = 1.4869, which corresponded with ethyl phenylacetate. No other sharply boiling fraction was obtained. Since the expected product can be distilled at 214°/26mm., the isolation of starting material did not result from decomposition. The resinous residue weighing about 10 g. and a small amount of distillate with a wide boiling range were not further characterized. The rate data are listed in Table XXVII. Similar results were obtained in a check determination. The temperature was 65-65.3° and the reaction was run for 48 hours.

TABLE XXVII

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
20	0.21	480	1.02	1270	1.66
35	.30	555	1.11	1485	1.96
65	.40	645	1.23	1605	2.07
120	.50	735	1.33	1665	2.10
170	.61	825	1.42	1875	2.21
240	.71	925	1.50	1970	2.25
315	.81	1035	1.61	2215	2.34
390	.91	1175	1.71	2315	2.35

Phenylacetamide. The amide was refluxed with benzaldehyde, 0.250 mole of piperidine and 0.500 mole of caproic acid according to the standard method. During the reflux period of 28 hours the temperature was 83.2-83.5°. The theoretical amount of water was collected. After washing, distilling, and cooling a solid precipitated which was separated from the mother liquor. A total of 24% phenylacetamide was recovered from the solid and from the mother liquor by distillation. No other pure compound could be isolated from the solid mixture. Rate data are recorded in Table XXVIII. A duplicate experiment, giving the same results, was refluxed at 84.3-84.5° for 32 hours.

TABLE XXVIII

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
10	0.21	125	1.07	635	1.78
15	.31	160	1.17	755	1.88
20	.40	230	1.27	965	1.98
30	.55	275	1.37	1115	2.09
40	.66	335	1.47	1495	2.20
55	.78	410	1.57	1620	2.24
70	.87	515	1.68	1740	2.24
90	.97				

Phenylacetonitrile. Benzaldehyde was refluxed with the nitrile in the presence of 0.250 mole of piperidine and 0.500 mole of caproic acid according to the standard method for 38-1/2 hours at 84-84.5°. The theoretical quantity of water was obtained; the half-reaction time was 10 hours and 40 minutes. After washing and distillation 66% of the pure starting nitrile was recovered and no other sharply boiling fraction. About 12 g. of resinous residue remained. The rate data were about the same as that listed in Table XXVII.

Benzylphenyl sulfone.[49] This compound was prepared by oxidation of benzylphenyl sulfide with chromic oxide in glacial acetic acid. When 0.0625 mole of the sulfone and 0.0625 mole of benzaldehyde were refluxed with 0.125 mole of piperidine and 0.250 mole of caproic acid in a total volume of 250 ml. of benzene solution for 29 hours at 82.2-82.7°, a total of 0.059 mole of water was evolved. After washing, distilling off most of the benzene, and cooling some solid was filtered off and the mother liquor was distilled. A yield of 92% of benzylphenyl sulfone was recovered. The half-reaction time was about 6 hours. The rate data are listed in Table XXIX.

TABLE XXIX

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
25	.06	225	.39	710	.72
45	.15	345	.48	1470	1.01
90	.25	465	.56	1730	1.07
155	.32	605	.65		

No Methylene Compound. One-eighth of a mole of benzaldehyde was refluxed in a 500 ml. benzene solution with 0.0625 mole of piperidine and 0.125 mole of caproic acid. After refluxing 91 hours at 82.7-82.4°, 0.11 mole of water was given off. The half-reaction time was about 28 hours. On working up the reaction mixture no sharply boiling fraction could be isolated; about 13 g. of a resinous material remained. The rate data are listed in Table XXX.

TABLE XXX

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
40	.10	1600	1.12	3835	1.62
70	.18	1915	1.22	5095	1.80
1240	.95	3235	1.46	5545	1.87
1420	1.02	3595	1.57	6475	2.01

MECHANISM

The Effect of Excess Malonic Ester. A benzene solution of 0.125 mole of benzaldehyde and 0.250 mole of malonic ester was refluxed according to the standard procedure with 0.0625 mole of piperidine and 0.125 mole of caproic acid for 4 hours and 40 minutes at 85.7-85.5°. About 3% more than the theoretical amount of water was evolved. When the reaction mixture was worked up in the standard fashion, 21 g. of malonic ester was isolated which corresponded to the excess used. A 73% yield of benzalmalonic ester was also obtained. Rate data follow in Table XXXI.

TABLE XXXI

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
10	.25	50	1.33	100	2.03
15	.40	55	1.44	110	2.10
20	.46	60	1.53	130	2.21
25	.71	65	1.63	140	2.25
30	.89	70	1.73	170	2.30
35	.99	80	1.84	240	2.32
40	1.14	90	1.93	280	2.32
45	1.23				

When 20% excess malonic ester was used for a standard run, the reflux temperature was 83.9-83.6°. The theoretical amount of water was evolved after 9 hours. After one distillation an 89% yield of benzalmalonic ester was obtained. Rate data are listed in Table XXXII.

TABLE XXXII

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
10	.16	45	.90	130	1.76
15	.27	50	.98	150	1.87
20	.40	60	1.12	170	1.99
25	.50	70	1.25	215	2.09
30	.61	80	1.32	290	2.18
35	.71	90	1.45	545	2.23
40	.80	110	1.63		

The reaction rate constants for the above two determinations are summarized in Table XXXIII. The constants for 0% excess of malonic ester are repeated for comparison.

TABLE XXXIII

Excess Malonic Ester	One-Fourth Reaction Time	Reaction Rate Constant (min.$^{-1}$ x 10^{-3})						
		30%	40%	50%	60%	70%	80%	Average
100%	40	7.33	7.46	7.63	7.39	7.11	6.69*	7.38
20%	33.5	9.08	9.26	9.28	8.93	8.46	8.12*	9.00
0%	35	9.82	9.92	10.02	10.07	9.85	9.66	9.90

*Omitted from average.

Effect of Excess Benzaldehyde. The reaction was carried out with 0.125 mole of malonic ester, 0.250 mole of benzaldehyde, 0.0625 mole of piperidine, and 0.125 mole of caproic acid. The temperature of the reaction was 84.6-85.2°. The volume of water became constant after refluxing 100 hours when 82% more than the theoretical requirement had been given off. A crude yield of 60% of benzalmalonic ester was isolated and a tarry residue of 22.6 g. was left from which no pure compound was obtained. The rate data are listed in Table XXXIV.

TABLE XXXIV

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
10	0.26	70	1.66	1345	3.21
15	.41	80	1.80	1500	3.29
20	.57	90	1.92	1755	3.42
25	.75	105	2.07	2790	3.66
30	.87	125	2.21	3440	3.78
35	.97	155	2.31	4560	3.91
45	1.21	205	2.41	5845	4.03
50	1.31	275	2.50	6430	4.09
60	1.51	505	2.67	7180	4.11

Effect of Temperature. The determinations in benzene which were run by the standard procedure using a 10% excess of benzaldehyde were described previously.

One-eighth of mole of malonic ester was refluxed with a 10% excess of benzaldehyde, 0.0312 mole of piperidine and 0.0625 mole of caproic acid. Instead of benzene, toluene was used as the inert solvent. The standard procedure with the few modifications stated above was used. The temperature of the reaction over the important 20-80% range was 114.6-114.4°. The rate data are listed in Table XXXV.

TABLE XXXV

Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)	Time (min.)	Volume (ml.)
10	.33	35	1.17	70	1.76
15	.55	40	1.29	80	1.87
20	.73	45	1.40	90	1.96
25	.90	50	1.48	110	2.08
30	1.06	60	1.63	135	2.19

A second determination was run at 114.6-114.3°. A summary of reaction rate constants is listed in Table XXXVI.

TABLE XXXVI

Determination	Reaction Rate Constants (min.$^{-1}$ x 10^{-3}).							
	30%	40%	50%	60%	70%	80%	Averages	
I	22.64	22.30	22.71	22.56	22.35	23.22	22.63	22.79
II	22.26	23.01	23.39	22.96	22.97	23.19	22.96	

CONDENSATION OF α-DICARBONYL COMPOUNDS WITH o-PHENYLENE DIACETIC ACID

Preliminary Studies. In order to check Hinsberg's results a solution of 1.0 g. of o-phenylenediacetonitrile[50], 1.5 g. of benzil and 1.2 g. of sodium methoxide in 50 ml. of methyl alcohol was allowed to stand for 10 days at room temperature. At the end of that period the solution, which was deep red in color, was diluted with water and the brownish precipitate was filtered off. After crystallization twice from 95% alcohol a white solid which corresponded to a 5% yield of compound I was obtained; the melting point was 298-300° (lit.m.p.290°).

Anal. Calcd. for $C_{24}H_{16}ON_2$: C, 82.80; H, 4.60. Found: C, 82.99; H, 4.92.

To a mixture of 0.0064 mole of o-phenylenediacetonitrile and 0.02 mole of sodium methoxide in 10 ml. of methyl alcohol, 0.03 mole of glyoxal in 30% aqueous solution was added dropwise. After standing 30 minutes at room temperature, water was added to the brown solution and the solid was filtered off. After one crystallization from alcohol the yield of slightly pink solid was 30%. On two further crystallizations from alcohol a white solid in 20% yield was obtained, m.p. 212.5-213.5°. Attempts to raise the yield by varying the time, temperature, ratio of reactants and catalyst were unsuccessful.

Anal. Calcd. for $C_{12}H_6N_2$: C, 80.91; H, 3.40. Found: C, 80.98, 81.09; H, 3.66, 3.95.

A mixture of 1.5 g. of diacetyl and 1 g. of o-phenylenediacetonitrile in 20 ml. of methyl alcohol was treated with 1.2 g. of sodium methoxide. After standing for 30 minutes at room temperature the precipitate was filtered off from the deep blue-purple liquid. On crystallizing the residue twice from ethyl alcohol a yellow solid, m.p. 265.5-266.5°, was obtained in a 15% yield.

Anal. Calcd. for $C_{14}H_{10}N_2$: C, 81.52; H, 4.89. Found: C, 81.16, 81.34; H, 4.97, 490.

A mixture of 1.0 g. of o-phenylenediacetanitrile and 1.3 g. of phenanthraquinone was finely ground together and placed in a 50 ml. flask to which was attached an air condenser fitted with a Bunsen valve. Several chunks of dry ice were also placed in the flask in order to sweep out the air. The flask was gradually heated in a metal bath to 190-200° at which temperature it was maintained for ten minutes. Some smoking and sublimation occurred during this time. After cooling, the solid mass was dissolved in benzene and extracted with aqueous sodium bisulfite solution in order to remove the original quinone; about 54% of the original amount of phenanthraquinone was recovered. On concentrating the benzene solution a solid was obtained which was filtered off and crystallized from glacial acetic acid. A 4.3% yield of a yellow crystalline solid was obtained, m.p. 284-285°.

<u>Anal.</u> Calcd. for $C_{24}H_{16}O_2N_2$: C, 80.06; H, 4.44. Found: C, 79.92; H, 4.22

An attempt was made to prepare ω,ω'-dinitro-o-xylene. A solution of 50 g. of o-xylylene dibromide in 300 ml. of ether was cooled to 5° in an ice bath and 60 g. of silver nitrite was added in small portions with stirring. After standing for a week the silver residue was filtered off and the ether solution evaporated until only an oily residue remained. This oil was dissolved in alcohol and diluted slightly with water. After standing on ice for several days a white crystalline solid was obtained in a 21.6% yield. Even after several recrystallizations it was not possible to obtain a better melting point than 73-77.5°. On standing the melting point decreased. It is possible that the compound is a mixture of isomers which could not be easily separated. Analysis checked fairly well for the expected compound.

<u>Anal.</u> Calcd. for $C_8H_8O_4N_2$: C, 48.97; H, 4.11. Found: C, 48.47; H, 4.12.

When the condensations of the above compound with glyoxal, diacetyl, and phenanthraquinone were attempted using sodium methoxide as catalyst, no products were obtained.

Condensations with o-Phenylenediacetic Acid.[51]

When 0.005 mole of dipotassium o-phenylenediacetate in 20 ml. of acetic anhydride was treated with 0.005 mole of benzil, furil, or diacetyl, no product was obtained whether the reaction stood at room temperature or was refluxed. Only tarry mixtures resulted.

When equivalent amounts (0.005 mole) of phenanthraquinone and the salt were stirred for 3 hours at 50° in 20 ml. of acetic anhydride, a 60% yield of a sandy colored solid was obtained. On recrystallizing twice from glacial acetic acid a 50% yield of a slightly yellowish solid was obtained which melted at 254-259° with decomposition.

Anal. Calcd. for $C_{24}H_{14}O_{14}$: C, 78.6%; H, 3.76. Found: C, 78. 3, 78.65; H, 4.01, 4.10.

When 0.005 mole of o-phenylenediacetic acid, 0.01 mole of potassium acetate and 20 ml. of acetic anhydride were used with 0.005 mole of phenanthraquinone under the same conditions as above, the product and yield were the same.

A mixture of 1.0 g. of naphthaquinone and 1.3 g. of dipotassium phenylenediacetate in 25 ml. of acetic anhydride was stirred in an ice bath for 4 hours and then kept on ice overnight. The solid which precipitated was filtered, washed with water and alcohol, and crystallized from glacial acetic acid. A 22% yield (0.3g.) of a light orange colored solid was obtained which melted with decomposition at 237.5-239.5°. Similar results were obtained when the alternate method of using the diacid and potassium acetate in acetic anhydride was employed under the same conditions as described before.

Anal. Calcd. for $C_{20}H_{12}O_4$: C, 75.94; H, 3.82. Found: C, 75.65, 76.03; H, 4.17, 4.08.

When 0.005 mole of the potassium salt of o-phenylenediacetic acid was mixed with 0.005 mole of chrysenequinone in 50 ml. of acetic anhydride and the mixture was stirred for four hours at 50° a crude yield of 41% of a solid was obtained. On crystallizing from hot glacial acetic acid a 33% yield of a product was obtained which melted with decomposition at 247-249°.

Anal. Calcd. for $C_{26}H_{16}O_4$: C, 80.76; H, 3.67. Found: C, 80.64, 80.73; H, 4.24, 4.20.

A mixture of 0.005 mole of o-phenylenediacetic acid, 0.005 mole of acenaphthaquinone, 0.01 mole of potassium acetate and 25 ml. of acetic anhydride was stirred at room temperature for 6 hours and allowed to stand overnight at room temperature. The solid product was filtered off, washed with water and alcohol and heated with glacial acetic acid. Some deep red material did not go into solution; this fraction was dissolved in trichloroethylene and crystallized. An 14.5% yield of a dark red fluffy solid was obtained, m.p. 305.5-306.5°. Analysis indicated it to be the anhydride of the expected material.

Anal. Calcd. for $C_{22}H_{10}O_3$: C, 81.97; H, 3.13. Found: C, 81.26; 80.93; H, 3.66, 3.71. Further recrystallisation did not improve the analysis.

A yellow solid which crystallized from the above acetic acid solution had a melting point of 276-277.5° after two recrystallizations. It represented a 22.3% yield of the half-condensed product according to the analysis.

Anal. Calcd. for $C_{22}H_{14}O_5$: C, 73.73; H, 3.94. Found: C, 73.06, 73.10; H, 3.42, 3.49.

A 0.5 g. portion of the product from the condensation of o-naphthaquinone and o-phenylenediacetic acid was suspended in 100 ml. of ether and a large excess of an ether solution of diazomethane was added and 10 ml. of methyl alcohol. The mixture was allowed to stand overnight; most of the solid went into solution at the end of that time. The ether was evaporated off and an oily solid remained. On crystallizing it twice from a small amount of alcohol, 0.1 g. of a yellow crystalline solid was obtained which melted at 189-190°. The analytical results indicated it to be the dimethyl ester crystallized with one mole of ethyl alcohol. The yield obtained was 16.6%.

Anal. Calcd. for $C_{24}H_{22}O_5$: C, 73.81; H, 5.68. Found: C, 73.19; H, 5.68.

The condensation product (0.5 g.) of phenanthraquinone and o-phenylenediacetic acid was dissolved in 10 ml. of 10% alcoholic potassium hydroxide and the alcohol was evaporated off; the residue was mixed with 1.5 g. soda line and heated in a micro sublimation apparatus at 5 mm. for 2 hours at 300-350°. A small amount of a yellow solid crystallized on the condenser. When it was recrystallized from hot glacial acid, pale yellow needles formed, m.p. 200-201°. The melting point of

1, 2, 3, 4 dibenzanthracene is 205°. The amount of product was insufficient for analysis.

<u>Attempted cyclization of Compound III.</u> When 1.0 g. of 9, 10-dicarboxylic-1, 2, 3, 4-dibenzanthracene was treated with about 20 ml. of HF and the HF was permitted to evaporate slowly the mixture turned a deep blue-green, but a 70% recovery of the starting material was obtained.

No material, other than the starting compound, could be isolated when 0.5 g. portions of the above dicarboxylic acid were treated with 20 ml. of 50%, 85%, and 98% sulfuric acid.

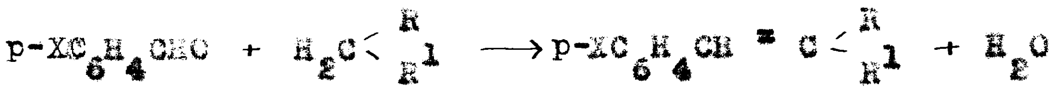
A solution of 0.65 g. of the dicarboxylic acid in 50 ml. of glacial acetic acid and 10 ml. of acetic anhydride was treated with 0.3 g. of Z_nCl_2 and refluxed for 23 hours. A deep red colored material was isolated but it could not be purified to yield any single substance other than a small amount of the starting compound.

A solution of 1.0 g. of the dicarboxylic acid and 1.5 g. of P_2O_5 in 75 ml. of dry benzene was refluxed for 2 hours. A somewhat pink solid was obtained which melted over a considerable range. It could not be purified by recrystallization.

When the diacid was refluxed with thionyl chloride, no pure acid chloride could be isolated. An impure mixture resulted which gave only tarry residues when it was treated with aluminum chloride or stannic chloride.

SUMMARY

The Knoevenagel condensation of benzaldehydes with various active methylene compounds has been studied. The general reaction is:



$$p\text{-}XC_6H_4CHO + H_2C<\begin{matrix}R\\R^1\end{matrix} \longrightarrow p\text{-}XC_6H_4CH = C<\begin{matrix}R\\R^1\end{matrix} + H_2O$$

A benzene solution of the reactants with piperidine and caproic acid as the catalyst was refluxed in an apparatus equipped with an automatic water separator. The rate at which the water collected proved to be a satisfactory measure of the rate of the reactions. Satisfactory first order constants were obtained for most of the condensations at equivalent concentrations of reactants; side reactions and other difficulties were encountered when kinetic studies were attempted at various ratios of reactants.

The piperidine rather than the caproic acid was shown to have the primary catalytic action and the rate of the reaction was proved to be proportional to the catalyst concentration for the condensation of benzaldehyde with malonic ester.

Electron-releasing groups in the para position of benzaldehyde facilitate reaction; the order of decreasing rate for various X groups was: $-OCH_3$, $-H$, $-Cl$, $-NO_2$. The effect is slight, however, for p-nitrobenzaldehyde reacted about one-half as fast as p-methoxybenzaldehyde.

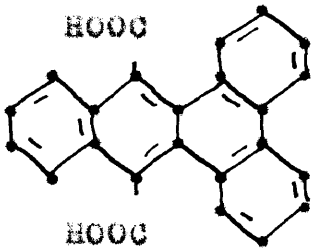
The effect of varying -R and -R^1 was, on the other hand, very large. The order of decreasing reactivity with benzaldehyde for the compounds which reacted satisfactorily was: $CH_2(CN)_2$, $CNCH_2COOC_2H_5$(67.5), $CH_3COCH_2COOC_2H_5$(21.9), $CH_2(COCH_3)_2$, $CH_2(COC_6H_5)_2$, $C_6H_5CH_2NO_2$(1.22), $CH_2(COOC_2H_5)_2$ (1), $C_6H_5CH_2COCH_3$(0.59), and $C_6H_5CH_2COC_6H_5$(0.57). The numbers in parentheses are a quantitative measure of the relative reactivities for those reactions which followed first order kinetics. The series is based on the assumption that the rate in all cases is proportional to the catalyst concentration as was proved in the case of malonic ester and that a change in the catalyst concentration had no effect other than the direct catalytic one.

The approximate order of decreasing activating ability of the various -R and -R^1 groups is: $-NO_2$, $-CN$, $-COCH_3$, $-COC_6H_5$, $-COOC_2H_5$, and $-C_6H_5$. This series can only be very approximate for the results clearly indicated that there is significant interaction between -R and -R^1 so that the order depends on the particular compounds used to determine it. When -R remains constant, however, the following series of relative reactivities of -R^1 may be noted. When -R is a carbethoxy group the series is: $-CN$ (67.5), $-COCH_3$(21.9), $-COOC_2H_5$(1). When -R is a phenyl group the series is: $-NO_2$(1.22), $-COCH_3$(0.59), COC_6H_5(0.57). When -R is an acetyl group the series is: $-COOC_2H_5$(21.9), $-C_6H_5$(0.59).

The information on the relative reactivity and the kinetics has been correlated as far as possible with the current mechanism.

Most of the products of these condensations were isolated in 70% yield or better. 2-Ethylbutanal and 2-ethylhexanal also condensed satisfactorily with malonic ester but n-heptaldehyde, cyclohexanone, and diethyl ketone did not.

In the second part of this investigation o-phenylenediacetic acid was condensed with various ∝-dicarbonyl compounds to give polycyclic diacids. Phenanthraquinone, for example, gave the following product in a 50% yield:



o-Naphthaquinone, chrysenequinone and acenaphthaquinone gave analogous products in yields of 22%, 33% and 16.5%.

For characterization the phenanthraquinone product was decarboxylated and the naphthaquinone product was converted to the dimethyl ester.

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