by reduction with sodium and alcohol and then destroyed the ether grouping by treatment with phosphorus pentachloride and water. The phenol was obtained as a solid melting at 39°. The same compound is formed smoothly by reduction of 1-chloroaceto-3,4-dihydroxybenzene[1] with zinc-amalgam and hydrochloric acid. Dzerzgowski[2] has already shown that the chloroketone is reduced to the corresponding ketone, $(HO_2).C_6H_3.COCH_3$, only when treated with zinc and hydrochloric acid.

Twelve grams of the chloroketone and 100 grams of amalgamated zinc were suspended in 200 cc. of hydrochloric acid (2 parts water and 1 part concentrated hydrochloric acid) and the mixture digested on a sand bath for about 22 hours. We obtained a light yellow oil, which was extracted with ether, dried over calcium chloride and finally purified by distillation under diminished pressure. It practically all boiled at 172–175° at 35 mm. and, on cooling, immediately solidified. The phenol gave no test for chlorine, turned brown on standing in the air and melted at 39°. The yield was good.

NEW HAVEN, CONN.

[CONTRIBUTIONS FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

THE CATALYTIC ACTION OF ESTERS IN THE CLAISEN CONDENSATION.

BY TREAT B. JOHNSON AND ARTHUR J. HILL.

Received June 21, 1913.

The writers communicated to the Eighth International Congress of Applied Chemistry,[3] in September, 1912, an interesting observation that esters have a marked effect on the course of the Claisen condensation. It was shown that the yield of the β-ketone ester was, in some cases, increased by incorporation of another ester, and we published the results of several experiments with ethylphenoxyacetate, which indicated that this was probably due to catalytic action. Since the publication of this original paper we have continued the investigation of this subject and are now able to discuss, in this paper, new data, which still further confirm our original conclusions. We shall also discuss here the role, which the catalyzer possibly plays in these reactions.

Ethyl phenoxyacetate (I) and ethyl naphthoxyacetate (β) (II) both undergo a Claisen condensation in dry ether, and in the presence of metallic sodium, forming the sodium salts of the corresponding β-ketone esters[4] (III), and (IV). The yields obtained, however, are very poor in both

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[1] Dzerzgowski, *J. Russ. Chem. Soc.*, 25, 154.

[2] *Loc. cit.*

[3] *Original Communications*, 6, 147.

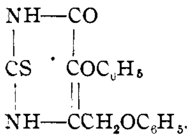
[4] Johnson and Hill, *Am. Chem. J.*, 48, 296.

$$C_6H_5OCH_2COOC_2H_5. \qquad\qquad C_{10}H_7OCH_2COOC_2H_5.$$

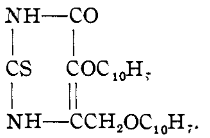
$$\downarrow \text{I.} \qquad\qquad \text{II.} \downarrow$$

$$\underset{\text{III.}}{C_6H_5OCH_2C(ONa):C(OC_6H_5)COOC_2H_5.} \qquad \underset{\text{IV.}}{C_{10}H_7OCH_2C(ONa):C(OC_{10}H_7)COOC_2H_5.}$$

cases, but that of the phenoxy compound (III) is the better of the two. In both condensations these salts are not the only products formed, and furthermore, only part of the esters take part in the reactions even when more than the required amount of sodium is used. The formation of the β-ketone esters was established by digesting their crude sodium salts with thiourea in alcohol and in the presence of sodium ethylate, when they interacted with the thiourea, forming the corresponding thiopyrimidines, *viz.*, 2-thio-4-phenoxymethyl-5-phenoxy-6-oxypyrimidine (V), and 2-thio-4-naphthoxymethyl-5-naphthoxy-6-oxypyrimidine (VI), respectively.[1] These pyrimidines are very insoluble substances and proved, by experience, to be of practical utility for measuring indirectly the amounts of β-ketone esters formed in the different condensations.



V.



VI.

If these two esters (I) and (II) are mixed with ethylacetate and then subjected to the action of metallic sodium some interesting results are obtained. In fact, the effect produced will depend upon the proportional amount of ethyl acetate used. In the first place, the same β-ketone esters (III) and (IV) are formed and the corresponding ethyl acetoacetate derivatives (VII) and (VIII) are not produced, as might be expected,

$$\underset{\text{VII.}}{C_6H_5OCH_2COCH_2COOC_2H_5} \qquad\qquad \underset{\text{VII.}}{C_{10}H_7OCH_2COCH_2COOC_2H_5}$$

no matter how much ethyl acetate is introduced. Secondly, the presence of the acetate apparently increases the velocity of the condensation-reaction and was productive of a much smoother reaction. Thirdly, the yields of the β-ketone esters (III) and (IV) were greatly increased and the formation of secondary products retarded. This last effect was far more pronounced in the case of ethyl naphthoxyacetate. The best conception of this effect of the ethyl acetate on the yields of β-ketone esters (III) and (IV) may be gained from inspection of Tables I, II, III and IV, and also of the curves plotted below in Charts I, II, and III.

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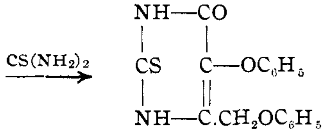
[1] Johnson and Hill, *Loc. cit.*

Experiments with Ethyl Phenoxyacetate.

$$2C_6H_5OCH_2COOC_2H_5 \xrightarrow{Na} C_6H_5OCH_2COCH(OC_6H_5)COOC_2H_5$$



V.

TABLE I.

Experiment.	Moles of catalyzer, $CH_3COOC_2H_5$.	Weight of $C_6H_5OCH_2COOC_2H_5$ used. Grams.	Total yield of pyrimidine V. Grams.	Per cent. of theoretical.	Percentage increase.
1........	0.000	25	5.00	44	...
2........	0.125	25	7.00	62	40
3........	0.250	25	7.00	62	40
4........	0.250	25	6.50	57.5	30
5........	0.375	25	8.00	69	60
6........	0.500	25	9.00	79.6	80
7........	0.625	25	10.5	92.9	110
8........	0.625	25	10.2	90.2	104
9........	0.750	25	9.0	79.6	80
10........	0.875	25	9.0	79.6	80
11........	1.000	25	10.0	88.5	100
12........	1.000	25	9.0	79.6	80
13........	1.500	25	7.0	62.0	40

These condensations recorded in Table I were all conducted under similar conditions and in the presence of one atomic proportion of sodium (3.2 grams).

TABLE II.

Experiment.	Moles of catalyzer. $CH_3COOC_2H_5$.	Weight of $C_6H_5OCH_2COOC_2H_5$ used. Grams.	Total yield of pyrimidine V. Grams.	Per cent. of theoretical.	Percentage increase.
1.........	0.000	25	4.50	39.8	..
2.........	0.000	25	4.80	42.4	..
3.........	0.000	25	4.80	42.4	..
4.........	0.000	25	4.40	38.9	..
5.........	0.500	25	8.00	70.8	78
6.........	0.500	25	7.00	62.3	55
7.........	1.000	25	7.50	66.3	66
8.........	2.000	25	5.30	46.8	18

The condensations recorded in Table II were all conducted under conditions practically identical with those employed in the first set of experiments (Table I) except that 0.5 atomic proportion of sodium was used (1.6 grams). A graphical representation of the influence of the ethylacetate is given in Chart I. On curve A are plotted the yields obtained in the first ten condensations recorded in Table I, and on curve B are plotted the corresponding yields obtained in Experiments 2, 3, 5, 7 and 8 of Table II.

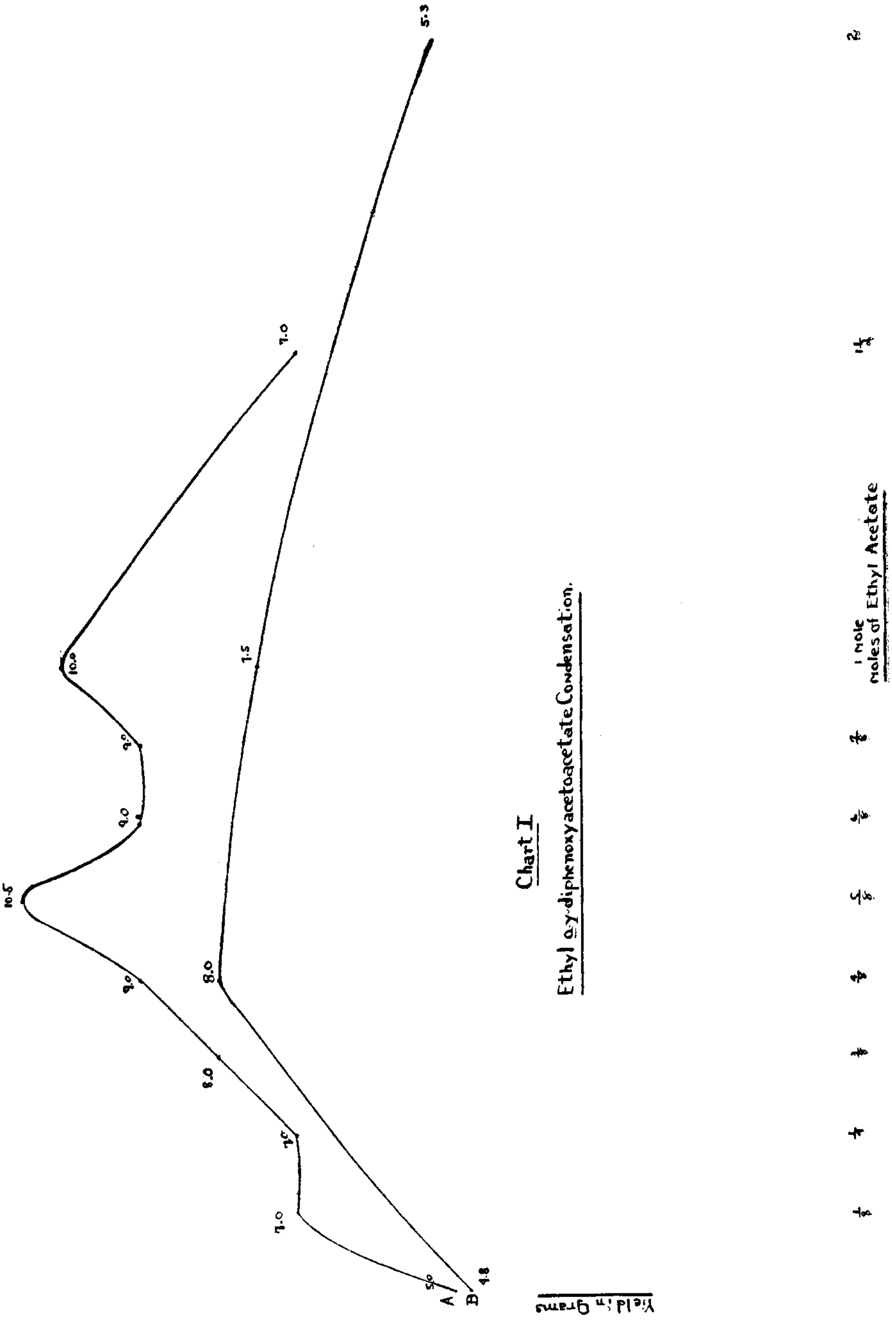
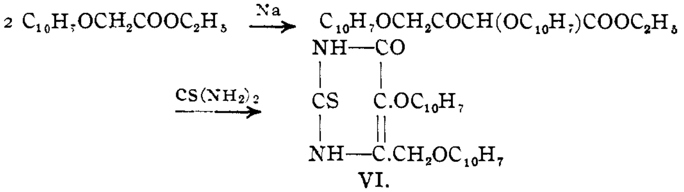


Chart I

Ethyl αγ-diphenoxyacetoacetate Condensation.

In both of these curves the same order of phenomenon is shown, namely an abrupt rise in the curves when ethyl acetate is incorporated with ethylphenoxyacetate. These attain their maximum point on addition of four-eighths and five-eighths of a molecular proportion, respectively of the catalyzer. This maximum effect is then maintained until more than one atomic proportion of the catalyzer is used, when the curves begin to fall, and continue to do so, as the amount of catalyzer used is increased. The curves are considerably depressed with one and five-tenths moles of the catalyzer. The physical aspects of the reactions were striking indeed, particularly when two experiments, with and without catalytic influence, were conducted simultaneously side by side. By incorporating the acetate, the speed of the reaction was greatly increased and the sodium salt of the β-ketone ester (III) deposited in a more granular condition. A decided oiliness of the salt, that was evidenced when the condensation was conducted without the influence of the acetate, had practically disappeared at the point of maximum efficiency. In brief, then, whether we employ one or one-half atomic proportions of sodium the effect of the acetate is the same. Sodium alone cannot be the active agent producing these interesting results. Perhaps the most impressive summary of the results of our experiments with ethyl phenoxyacetate may be expressed in the facts, that in no experiment did the percentage increase of the yield of β-ketone ester fall below 30%, and that in one case the maximum increase of 110% was actually attained.

Experiments with Ethyl Naphthoxyacetate.



$$2\ C_{10}H_7OCH_2COOC_2H_5 \xrightarrow{Na} C_{10}H_7OCH_2COCH(OC_{10}H_7)COOC_2H_5 \xrightarrow{CS(NH_2)_2}$$

VI.

TABLE III.

Experiment.	Moles of catalyzer, $CH_3COOC_2H_5$.	Weight of $C_{10}H_7OCH_2COOC_2H_5$ used. Grams.	Total yield of pyrimidine VI. Grams.	Per cent. of theoretical.	Percentage increase.
1	0.000	15	2.7	39.1	...
2	0.000	15	2.7	39.1	...
3	0.250	15	3.7	53.6	37
4	0.500	15	4.5	65.2	66.66
5	0.500	15	5.3	76.8	96.3
6	1.000	15	3.8	55	40.7
7	1.000	15	2.8	40	...
8	1.000	15	4.8	69.5	77.77

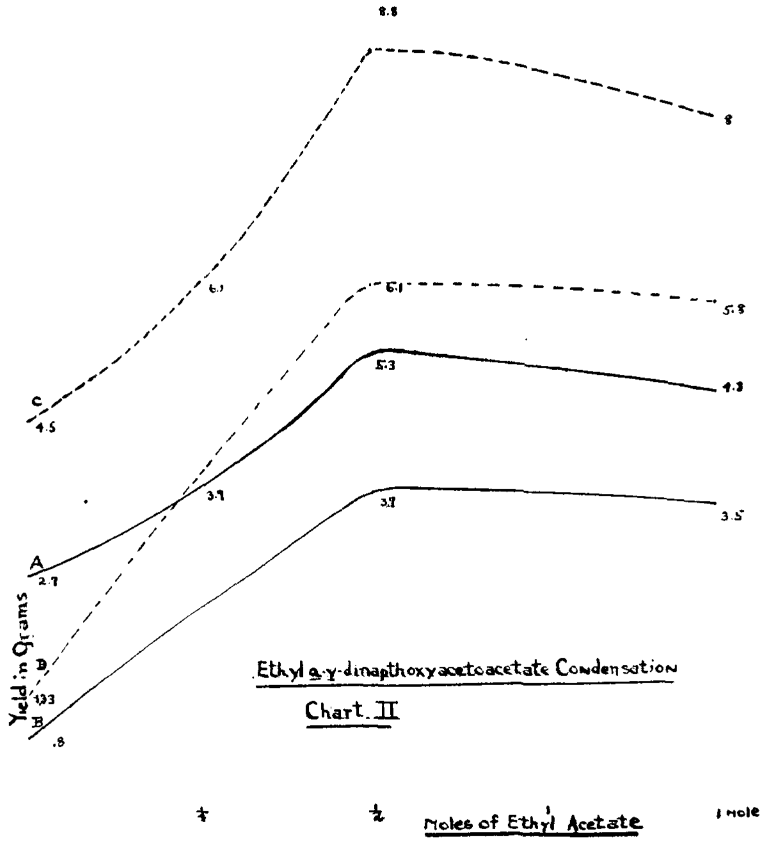
In these condensations recorded in Table III one atomic proportion of sodium was used (1.5 grams).

TABLE IV.

Experiment.	Moles of catalyzer. $CH_3COOC_2H_5$.	Weight of $C_{10}H_7OCH_2COOC_2H_5$ used. Grams.	Total yield of pyrimidine VI. Grams.	Per cent. of theoretical.	Percentage increase.
1	0.000	15	0.6	8.0	...
2	0.000	15	0.8	11.5	...
3	0.000	15	0.3	4.3	...
4	0.500	15	3.7	55	362
5	1.000	15	1.7	24.6	112
6	1.000	15	3.5	50	337

In these condensations recorded in Table IV, 0.5 atomic proportion of sodium was used (0.75 gram).

A graphical representation of the influence of ethylacetate on the ethyl β-naphthoxyacetate condensation is given in Chart II. On Curve A are plotted the yields of pyrimidine (VI), which are recorded in Table III, and on Curve B are plotted the yields obtained in the second set of experiments (Table IV).



Ethyl α-γ-dinapthoxyacetoacetate Condensation

Chart. II

The same order of phenomenon is shown in Curves A and B of this chart as was shown in the corresponding curves in Chart I. In fact, the curves are more uniform, in this case, and the effect of the catalyzer more pronounced. A striking feature of all the experiments with the naphthoxy compound was the fact that the condensations were more sluggish than in the case of the ethyl phenoxyacetate. Furthermore, the yield of the sodium salt of the β-ketone ester, $C_{10}H_7OCH_2CO.CH(OC_{10}H_7)COOC_2H_5$, was small and always contaminated with amorphous secondary products. On the other hand, when ethyl acetate was added the effect was marvelous as is manifested by the abrupt rise in the curves. Instead of depositing in an amorphous condition and being oily, the sodium salt of the ketone ester (IV) was now nearly colorless and assumed a fine, granular condition. Furthermore, the reaction velocity was increased. It is an interesting fact also that, in this series, the best results were obtained by using one atomic proportion of sodium for the condensation. In fact, by using only one-half an atomic proportion, and no catalyzer, we were able to obtain only about 0.8 gram of the pyrimidine (VI). In one experiment the yield was actually as low as 0.3 gram. The combined effect of the extra one-half atomic proportion of sodium and that of the catalyzer was remarkable and actually increased the yield of pyrimidine, in one case, 562% (Curve A in Chart III).

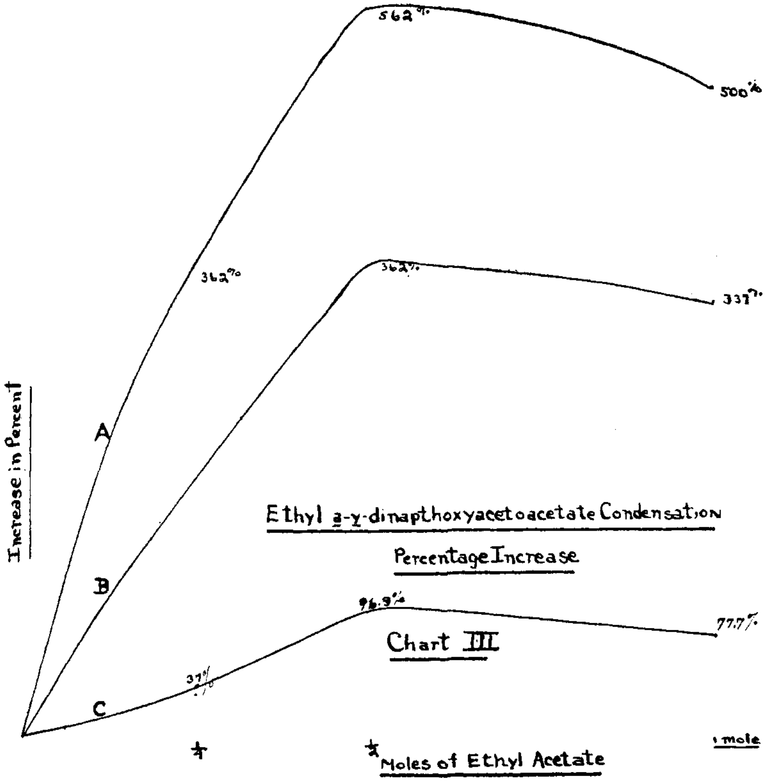
The Curves C and D show the effect of the catalyzer when 25 grams of the naphthoxy ester were used for each experiment. Curves C and A depict the results when one atomic proportion of sodium was used for the condensation, and D and B those when one-half an atomic proportion of sodium was used.

In the percentage-chart (Chart III) curves C and B represent the effect of the catalyzer when one-half and one atomic proportions of sodium are used. Curve A shows the combined effect of the catalyzer and one atomic proportion of sodium when the calculations are based on a yield of 0.8 gram of pyrimidine, which was obtained with no catalyzer and one-half atomic proportion of sodium.

The results of this investigation on the influence of ethyl acetate may be summarized as follows: In no case has the incorporation of ethyl acetate with ethyl phenoxyacetate and ethyl naphthoxyacetate failed to produce an increase in the amount of the corresponding β-ketone esters III and IV formed. In other words, no point on any of the curves in Charts I and II falls to the point of inception of the curve on the ordinate. Whether one or one-half atomic proportions of sodium are used, the effect of the ethylacetate is the same, namely, to increase the yield of sodium salt. This influence is favorable until the concentration of the acetate reaches a certain maximum, when a further addition is detrimental and the yield of sodium salt diminishes.

The results obtained, therefore, lead to the conclusion—*that ethyl acetate actually plays the role of a catalyst in these two Claisen condensations.*

So far as the writers are aware, it has not hitherto been observed that esters may have an accelerating effect on reactions leading to the formation of β-ketone esters. That the solvent used may influence the condensation has, however, been observed by Tingle and Gorsline.[1] They have shown, for example, that certain reactions, involving β-ketone ester formation, take place with equal ease in ether and ligroin solutions while, on the other hand, others require hours in ligroin but take place readily when the materials are dissolved in ether. They found also that the incorporation of ether with the ligroin solution also accelerated the reaction and concluded that there is an apparent parallelism between the Claisen and Grignard reactions so far as the solvent is concerned. They write as follows: "We can accelerate or retard a given condensation by adding or withholding ether from the solution." These investigators also found that the tertiary bases—pyridine and quinoline—also acted



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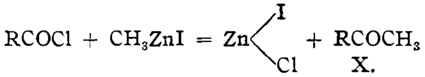
[1] *Am. Chem. J.*, 37, 483 (1907).

as accelerators and in this influence on the Claisen condensation were about equal in efficiency.

That ethyl acetate can influence certain chemical reactions has already been observed by other investigators. In fact, it has been shown that the effect can be either one of acceleration or retardation. One of the most interesting observations is that of Claisen and Ehrhardt,[1] in their work on the synthesis of acetylacetone and its homologues by condensation of ethylacetate with ketones in the presence of sodium or sodium ethylate. They found, for example, that if ethylacetate was used as a diluent, instead of ether, the yields of the 1,3-diketones were greatly improved. The following extract from their paper is very significant in connection with our observations: "Eine wesentlich bessere Ausbeute kann, wie sich bei Wiederaufnahme dieser Versuche zeigte, erzielt werden, wenn man statt des Aethers als Verdünnungsmittel überschüssigen Essigäther anwendet, und die Einwirkung, statt unter Abkühlen, in der Wärme vornimmt. Nach folgendem Verfahren haben wir uns in einigen Tagen mehrere Hundert Gramm des Diketons bereiten können."

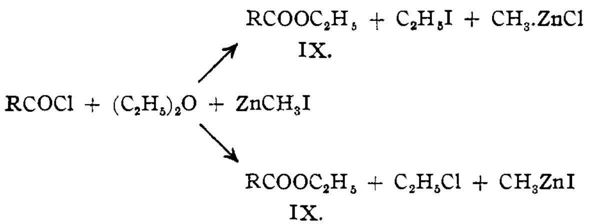
Recently E. Blaise,[2] in a paper entitled: Les Dérivés Organo-Metalliques Mixtes du Zinc et leur Emploi dans la Synthése Organique," has demonstrated the superiority of ethyl acetate over ether as a solvent for the study of the action of acid chlorides on organo-zinc compounds of the type Zn.CH_3I, etc. In other words, it acts here as a catalyzer. The use of ether was found to be attended with complicating results, in that esters (IX) as well as ketones (X) (the normal products of the reaction) were formed.

Normal Reaction in Ethyl Acetate:



$$RCOCl + CH_3ZnI = Zn\begin{matrix}I\\Cl\end{matrix} + \underset{X.}{RCOCH_3}$$

Abnormal Reactions in Ether:



$$RCOCl + (C_2H_5)_2O + ZnCH_3I \nearrow \underset{IX.}{RCOOC_2H_5} + C_2H_5I + CH_3.ZnCl$$

$$RCOCl + (C_2H_5)_2O + ZnCH_3I \searrow \underset{IX.}{RCOOC_2H_5} + C_2H_5Cl + CH_3ZnI$$

The two observations just reviewed[3] illustrate the accelerating influence of ethylacetate on chemical reactions. That its effect may be of

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[1] *Ber.*, 22, 1010.

[2] *Bull. soc. chim.*, [4] 9, I, 26 (1911).

[3] Other examples might be given.

an opposit character (retardation) has been shown by Bischoff.[1] Tissier and Grignard,[2] for example, observed that ethylene bromide interacts immediately with powdered magnesium, in anhydrous ether, giving ethylene and magnesium bromide according to the following equation:

$$BrCH_2.CH_2Br + Mg = CH_2 : CH_2 + MgBr_2.$$

Bischoff reinvestigated this reaction and made the observation that it could be retarded and even inhibited by dissolving certain organic reagents in the ether. Among those compounds which were found to retard the reaction were *ethylacetate*, phenetole and anisole. He writes as follows: "Aehnlich verhielt sich Essigsäureäthylester (0.88 gram), wobei die Reaction sehr träge verlief und zwar umso träger, je reiner der Ester war." The introduction of acetone, acetophenone, benzophenone, diethyloxalate, diethyl malonate and diethylsuccinate completely checked (verhindert) the reaction.

The catalytic action of ethyl acetate in these β-ketone ester condensations is very obscure, and from the data at hand any idea which is presented is purely a matter of speculation. It is permissible, however, to present a scheme of equations, which are in accord with our work and also convey a reasonable conception of the possible, intermediate phases of the reaction. Whether our scheme is an accurate expression of the changes will be decided by further work and critical discussion.

Very pertinent to this question of reaction-mechanism are the interesting speculations of Claisen[3] on the mechanism of the rearrangement of acetophenone-*o*-benzoate (XI) into dibenzoylmethane (XII); a trans-

$$\underset{\text{XI.}}{C_6H_5C(O.COC_6H_5) : CH_2} \longrightarrow \underset{\text{XII.}}{CH_2(COC_6H_5)_2.}$$

formation which is brought about by the action of sodium in benzene solution. Claisen made the interesting observation that the velocity of this change was greatly accelerated by adding a small quantity of acetophenone (XVII) to the benzene. It was plainly a case of catalytic action and Claisen offered the following, unique interpretation of the role of the ketone: The small amount of acetophenone first reacts with the sodium giving the corresponding salt (XIII). This then combines with the carbonyl group of the acetophenone-*o*-benzoate (XI) forming the addition-product (XIV). The latter then undergoes a molecular transformation into the isomer (XV), which finally breaks down with regeneration of acetophenone (XVII) and formation of the sodium salt of dibenzoylmethane (XVI). These various changes may be represented by the following formulas:

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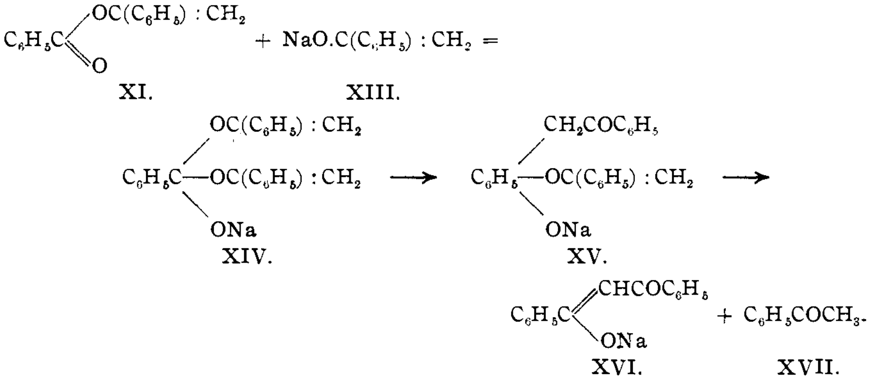
[1] *Ber.*, **38**, 2078.

[2] *Compt. rend.*, **132**, 836.

[3] *Ber.*, **36**, 3677.



$$C_6H_5C\begin{cases}OC(C_6H_5):CH_2\\O\end{cases} + NaO.C(C_6H_5):CH_2 =$$

XI. XIII.

$$C_6H_5C\begin{cases}OC(C_6H_5):CH_2\\OC(C_6H_5):CH_2\\ONa\end{cases} \longrightarrow C_6H_5\begin{cases}CH_2COC_6H_5\\OC(C_6H_5):CH_2\\ONa\end{cases} \longrightarrow$$

XIV. XV.

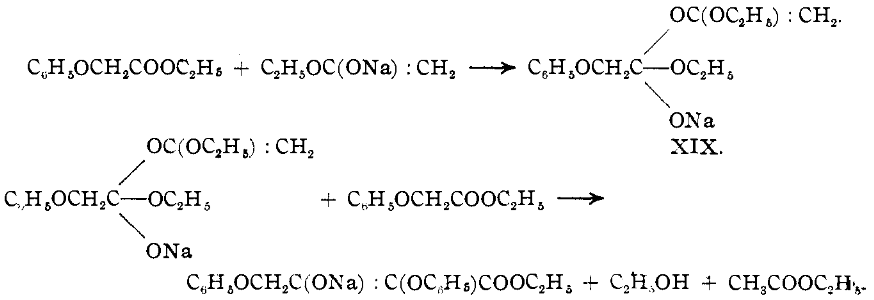
$$C_6H_5C\begin{cases}CHCOC_6H_5\\ONa\end{cases} + C_6H_5COCH_3.$$

XVI. XVII.

The catalyzer employed by Claisen (acetophenone), and the ethyl acetate used in our work, have in common an unsaturated carbonyl group. Consequently it seems to the writer a reasonable assumption that these two substances probably undergo analogous changes when brought in contact with sodium, namely, that they are transformed momentarily into the corresponding sodium salts (XIII) and (XVIII). Both of these salts would possess, theoretically, the basic properties of alcoholates and therefore be capable of forming addition products with esters. Assuming that ethylacetate does undergo such a change with sodium, then the active agent in our reactions would be the sodium derivative[1] (XVIII). This salt, which contains positive energy, interacts with the ethylphenoxyacetate forming the addition product (XIX) corresponding to that (XIV) assumed to be formed by Claisen.[2] This addition product then reacts with another molecule of the ethyl phenoxyacetate; ethyl acetate and alcohol are detached and the sodium salt of the β-ketone ester (XX) is formed. The complete synthesis, therefore, of the β-ketone ester, in the presence of ethylacetate, may be expressed by the following equations:

$$CH_3COOC_2H_5 + Na = H + C_2H_5OC(ONa):CH_2.$$

XVIII.



$$C_6H_5OCH_2COOC_2H_5 + C_2H_5OC(ONa):CH_2 \longrightarrow C_6H_5OCH_2C\begin{cases}OC(OC_2H_5):CH_2.\\OC_2H_5\\ONa\end{cases}$$

XIX.

$$C_6H_5OCH_2C\begin{cases}OC(OC_2H_5):CH_2\\OC_2H_5\\ONa\end{cases} + C_6H_5OCH_2COOC_2H_5 \longrightarrow$$

$$C_6H_5OCH_2C(ONa):C(OC_6H_5)COOC_2H_5 + C_2H_5OH + CH_3COOC_2H_5.$$

XX.

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[1] Michael, *Ber.*, 38, 1922.

[2] *Loc. cit.*

This new interpretation of the mechanism of these reactions embodies the essential features of both Michael's and Claisen's explanations of the mechanism of the Claisen condensation.

Experimental Part.

It is unnecessary to discuss here in detail the various condensations conducted in this investigation. The quantitative relationships are expressed in Tables I, II, III and IV. They were all conducted under practically the same conditions except that in one series, in the case of ethylnaphthoxyacetate, 15 grams of the ester were used in each experiment. In all the other condensations 25 grams of the respective esters were taken. We used ethylacetate that had been carefully purified by distillation and thoroughly dried over anhydrous calcium chloride. The ethyl phenoxyacetate was purchased from Kahlbaum and carefully examined before use. The ethylnaphthoxyacetate was prepared by esterification of naphthoxyacetic acid. The ether that was employed in our work was repeatedly washed with water to remove all alcohol and then dried for several hours over calcium chloride. It was finally digested with sodium and then allowed to stand over sodium. In all our operations every precaution was taken to exclude moisture.

The following proportions were generally used in all our experiments: For every 25 grams of ester about 200 cc. of dry ether were used. The required amount of sodium (finely cut) was then introduced and finally the exact proportion of ethylacetate. The reactions were generally considered complete when all the sodium had disappeared. This sometimes happened within a few hours and was dependent on the temperature of the laboratory and the amount of catalyzer introduced. In some cases, when the catalyzer was used, the reactions were especially vigorous and it was necessary to cool the solutions in order to prevent the ether from boiling. Before condensation of the salts with thiourea, to obtain the pyrimidines, the mixtures were always allowed to stand for several hours (15-20) after the disappearance of the sodium. This was to insure complete formation of the condensation-products. A complete description of the pyrimidines V and VI and their derivatives has already been published in a previous paper by the writers.[1]

The yields of the pyrimidines in per cent. are based on the assumption, that only one-half of the sodium salt of the β-ketone esters (*cis*-modifications) condense with thiourea to form pyrimidines.

NEW HAVEN, CONN.

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[1] *Loc. cit.*