[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

SOME OBSERVATIONS ON THE ACETOACETIC ESTER CONDENSATION

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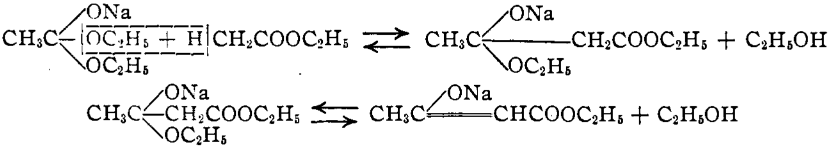
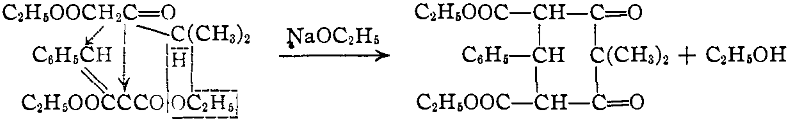
The well-known mechanism for the course of the acetoacetic ester condensation proposed by Claisen[1] was questioned by Dieckmann[2] on the basis of his work on the splitting of alkyl acetoacetic esters by alcohol and sodium ethoxide. Dieckmann preferred to represent the condensation as a reversible reaction that took place in two phases



$$CH_3C\overset{ONa}{\underset{OC_2H_5}{\boxed{OC_2H_5 + H}}}CH_2COOC_2H_5 \rightleftarrows CH_3C\overset{ONa}{\underset{OC_2H_5}{—}}CH_2COOC_2H_5 + C_2H_5OH$$

$$CH_3C\overset{ONa}{\underset{OC_2H_5}{—}}CH_2COOC_2H_5 \leftrightarrows CH_3C\overset{ONa}{=}CHCOOC_2H_5 + C_2H_5OH$$

According to this explanation it is necessary to have only one hydrogen atom on the α-carbon atom of the ester that condenses with the ortho derivative in order to bring about the first phase of the condensation. The reason for the apparent failure of an ester of the type, $R_2CHCOOC_2H_5$, to undergo the acetoacetic ester condensation is due, according to Dieckmann, to the ease with which the condensation product is split, *i. e.*, the relative completeness of the reversal of the first phase of the above reaction. In support of this mechanism Dieckmann and Kron[3] reported the condensation of ethyl *iso*butyryl acetate and benzalmalonic ester by means of sodium in absolute alcohol to 2,2-dimethyl-5-phenyl-4,6-dicarbethoxycyclohexandedione-1,3



The enolic acidity of the condensation product resulting from the simultaneous formation of two β-ketonic ester groupings prevented the reversal of the acetoacetic ester condensation.

In 1922 Scheibler and Ziegner[4] proposed a new mechanism, which resembled that of Dieckmann's to the extent that it indicated that esters of the type $R_2CHCOOC_2H_5$ should undergo the condensation. This new proposal, however, met with considerable criticism[5] and was recently

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[1] Claisen, *Ber.*, **20**, 651 (1887); *ibid.*, **21**, 1154 (1888).

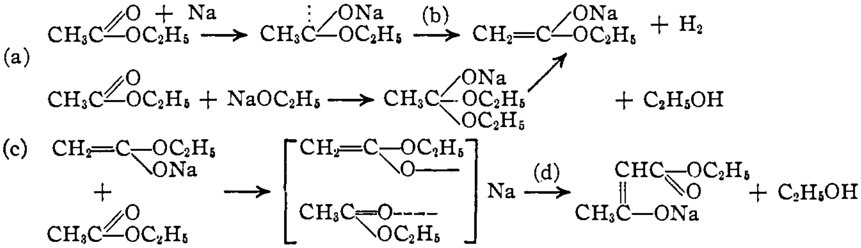
[2] Dieckmann, *ibid.*, **33**, 2678 (1900).

[3] Dieckmann and Kron, *ibid.*, **41**, 1260 (1908).

[4] Scheibler and Ziegner, *ibid.*, **55**, 789 (1922).

[5] Adickes, *ibid.*, **59**, 2522 (1926); *ibid.*, **60**, 272 (1927); Franklin and Short, *J. Chem. Soc.*, 591 (1928).

abandoned by Scheibler and Marhenkel[6] in favor of a rather complicated formulation which assumes four phases in the condensation: (a) the formation of a metal ketyl (when a metal such as sodium is used) or an addition product (when a metallic alkoxide is used) on the ester carbonyl group; (b) the change of the compound formed in (a) into an enolate; (c) reaction of the enolate with a molecule of the keto form of the ester with the formation of a molecular compound; (d) the formation of a condensation product from the molecular compound formed in (c) by splitting out alcohol. To illustrate with ethyl acetate, sodium and sodium ethoxide

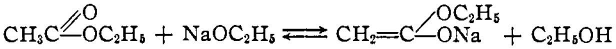


$$\text{(a)}\quad CH_3C\overset{\nearrow O}{\diagdown}OC_2H_5 + Na \longrightarrow CH_3\overset{\vdots}{C}\overset{\nearrow ONa}{\diagdown}OC_2H_5 \xrightarrow{\text{(b)}} CH_2{=}C\overset{\nearrow ONa}{\diagdown}OC_2H_5 + H_2$$

$$CH_3C\overset{\nearrow O}{\diagdown}OC_2H_5 + NaOC_2H_5 \longrightarrow CH_3C\overset{\nearrow ONa}{\underset{\searrow OC_2H_5}{\diagdown}}OC_2H_5 \nearrow + C_2H_5OH$$

$$\text{(c)}\quad \begin{matrix} CH_2{=}C{-}OC_2H_5 \\ \searrow ONa \\ + \\ CH_3C\overset{\nearrow O}{\diagdown}OC_2H_5 \end{matrix} \longrightarrow \left[\begin{matrix} CH_2{=}C{-}OC_2H_5 \\ \searrow O{-}{-}{-} \\ CH_3C{=}O{-}{-}{-}{-} \\ \searrow OC_2H_5 \end{matrix}\right] Na \xrightarrow{\text{(d)}} \begin{matrix} CHC{-}OC_2H_5 \\ \Vert\ \ \searrow O \\ CH_3C{-}ONa \end{matrix} + C_2H_5OH$$

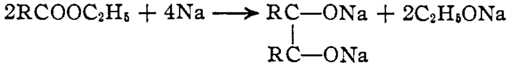
This mechanism resembles Claisen's original proposal to the extent that for complete condensation two hydrogen atoms are required on the α-carbon atom of the ester molecule that reacts with the keto form. Scheibler and Marhenkel state that when sodium ethoxide is the condensing agent, it is the alcohol split out when the enolate is formed (b) that prevents the continuation of the reaction; in other words, the ester enolate is a necessary intermediate and the reversible phase of the acetoacetic ester condensation is



$$CH_3C\overset{\nearrow O}{\diagdown}OC_2H_5 + NaOC_2H_5 \rightleftharpoons CH_2{=}C\overset{\nearrow OC_2H_5}{\diagdown}ONa + C_2H_5OH$$

They state further that an ester of the type $R_2CHCOOC_2H_5$ will proceed in the above transformations through phase (c) but cannot go through phase (d) for obvious structural reasons. This conclusion is based on their observation that such an ester forms with sodium ethoxide a ketene acetal.

In the application of the acetoacetic ester condensation to ethyl acetate and its higher homologs, the choice between sodium and sodium ethoxide as condensing agents is an important consideration. It has been shown[7] that such esters in ether solution react with sodium at 0° to form sodium derivatives of acyloins



$$2RCOOC_2H_5 + 4Na \longrightarrow \begin{matrix} RC{-}ONa \\ | \\ RC{-}ONa \end{matrix} + 2C_2H_5ONa$$

This reaction is quite distinct from the acetoacetic ester condensation and in no way involves the hydrogens of the α-carbon atom of the ester

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[6] Scheibler and Marhenkel, *Ann.*, **458**, 1 (1927).

[7] Bouveault and co-workers, *Bull. soc. chim.*, **35**, 629 (1906), and preceding papers,

because it will proceed when R is tertiary butyl. Work now in progress in this Laboratory and which will be the subject of a future communication indicates that this competing reaction takes place at higher temperatures than 0° and that the acyloin type may be the major if not the sole product of the reaction between esters of this type and sodium.

In order to avoid this complication sodium ethoxide was used as a condensing agent in the work reported here. It seemed that the difficulty of the reversal of the condensation (which Dieckmann[2] has shown to be more serious with alkyl acetoacetic esters than with the unsubstituted ester) could be overcome by the removal of the alcohol by distillation as it was formed in the reaction. This principle has been applied[8] to the large scale production of acetoacetic ester from ethyl acetate using sodium, potassium or magnesium as condensing agents.

In the procedure that was used in the present work the ester was allowed to react with sodium ethoxide, the reaction mixture periodically distilled and the distillate replaced with pure ester. The amount of alcohol formed in the reaction was determined from the refractive indices of the distillates and when it was indicated that no more alcohol was being formed, the β-keto-ester was isolated from the reaction mixture.

Ethyl acetate, ethyl propionate, ethyl butyrate and ethyl *iso*butyrate were treated in this manner. Since a large excess of ester was necessarily taken, the yield calculations were based on the amount of sodium ethoxide used, according to the equation

$$2RCH_2COOC_2H_5 + NaOC_2H_5 = RCH_2C(ONa)CRCOOC_2H_5 + 2C_2H_5OH$$

The yields of β-keto-esters and of alcohol obtained from these various esters, using 0.5 mole (34 g.) of sodium ethoxide as the condensing agent are summarized in Table I.

TABLE I

YIELDS OF β-KETO-ESTERS

Ester used	Condensation product	Keto-ester isolated Mole	Keto-ester isolated % of theoretical	Alcohol in distillate Mole	Alcohol in distillate % of theoretical
Ethyl acetate	Ethyl acetoacetate	0.340	68	0.83	83
Ethyl propionate	Ethyl α-propionylpropionate	.405	81	0.97	97
Ethyl butyrate	Ethyl α-butyrylbutyrate	.380	76	1.03	103
Ethyl *iso*butyrate	....		0	0.03[a]	6[a]

[a] In this case the theoretical yield of alcohol would be 0.5 mole instead of 1 mole as is the case with the other esters under consideration.

While under ideal conditions the percentage yield of alcohol should be the same as that of the β-keto-ester in each case, the discrepancy between the two that is shown in the above table is not particularly great when manipulative losses during the isolation of the keto-ester, effect of traces of water on the yield of alcohol ($1H_2O$ produces $2C_2H_5OH$), possible im-

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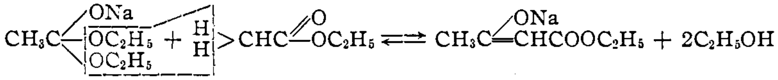
[8] U. S. Patent 1,472,324; reissue 16,591.

purities in the sodium ethoxide, and the method of analysis for alcohol in the distillates are considered. The results show that the reversal of the condensation can be prevented by such a procedure, since Higley[9] has found that the equilibrium point in the acetoacetic ester condensation represents about 36% of the keto-ester and the work of Dieckmann[2] indicates that a still smaller percentage of keto-ester would be present at the equilibrium point of alkyl-substituted acetoacetic esters.

The results obtained with ethyl *iso*butyrate are of some interest in connection with the mechanisms that have been proposed for the condensation. It is seen that no keto-ester and an insignificant amount of alcohol are formed in the reaction of this ester with sodium ethoxide. If Dieckmann's proposal were correct, it is difficult to see why this ester under the conditions of the experiment should not condense to form the sodium ethoxide addition compound of ethyl *iso*butyryl-*iso*butyrate, $(CH_3)_2C(ONa)(OC_2H_5)C(CH_3)_2COOC_2H_5$, with the simultaneous appearance of alcohol in the distillate, for this keto-ester is known[10] to be sufficiently stable to isolate. Both Claisen's original proposal and Scheibler's later suggestion as to the mechanism of the reaction are in accord with the fact that none of the β-keto-ester is formed from ethyl *iso*butyrate, but Scheibler's postulate that an intermediate enolate is an essential step in the course of the reaction is not in agreement with the fact that no alcohol is found in the distillate.

It seems on the basis of these results that the original mechanism for the acetoacetic ester condensation proposed by Claisen, supplemented by the reversible feature



$$CH_3C\begin{cases}ONa\\ OC_2H_5\\ OC_2H_5\end{cases} + \begin{matrix}H\\H\end{matrix}\!>CHC\begin{matrix}\!\!/\!\!/O\\ \!\!\diagdown OC_2H_5\end{matrix} \rightleftharpoons CH_3C\overset{ONa}{=}CHCOOC_2H_5 + 2C_2H_5OH$$

is the most acceptable of those that have been considered. It may be suggested that the results presented here do not prove conclusively the correctness of the Claisen mechanism, but rather that they support it to the extent that they do not show it to be incorrect. The behavior of ethyl *iso*butyrate does show, however, that the mechanisms proposed by Dieckmann and by Scheibler and Marhenkel for the reaction of sodium ethoxide and esters of the type of ethyl acetate are questionable.

Since Scheibler and Marhenkel postulate the same enolate (b) and molecular compound (c) as necessary precursors for both the acetoacetic ester condensation and ketene acetal formation it appears that their mechanism for the formation of the latter type is also in error. The ketene acetal from ethyl *iso*butyrate has been prepared[11] by the action

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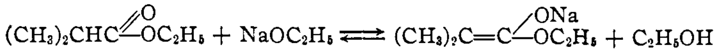
[9] Higley, *Am. Chem. J.*, **37**, 299 (1907).

[10] Salkind, *Chem. Centr.*, II, 315 (1906).

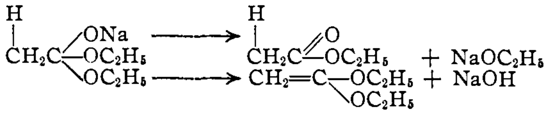
[11] Scheibler and Friese, *Ann.*, **445**, 149 (1925).

of sodium ethoxide on this ester, but it has been pointed out above that these two reactants do not enter into the reversible reaction



$$(CH_3)_2CHC\overset{\displaystyle /\!\!/O}{\diagdown}OC_2H_5 + NaOC_2H_5 \rightleftharpoons (CH_3)_2C{=}C\overset{\displaystyle /ONa}{\diagdown}OC_2H_5 + C_2H_5OH$$

which is essential to the Scheibler and Marhenkel mechanism. For this reason it seems that a different explanation for the formation of ketene acetals is needed. In this connection it may be suggested that it would not be unreasonable to assume that Claisen's ester–sodium ethoxide addition product might undergo decomposition in two ways, (a) into the original ester and sodium ethoxide and (b) into a ketene acetal and sodium hydroxide, *e. g.*



Experimental

Materials Used.—Each of the esters, ethyl acetate, ethyl propionate, ethyl butyrate and ethyl *iso*butyrate, that was used was purified in the following manner. The ester was shaken in a separatory funnel with an equal volume of 2% potassium carbonate solution and then with an equal volume of water. The ester layer was separated and allowed to stand for three days over anhydrous potassium carbonate, after which it was filtered and distilled. The distillate was treated with 2% of its weight of phosphorus pentoxide and after standing for twenty-four hours it was distilled from the phosphorus pentoxide. The distillate was then fractionally distilled. The boiling points and refractive indices of the esters used in the experiments described below were:

Ethyl ester	Acetate	Propionate	Butyrate	*Iso*butyrate
B. p. (735 mm.), °C.	76.4–76.5	97.5–98.4	119–121	108.5–109.5
n_D^{25}	1.36899	1.38053	1.38883	1.38404

The ethyl acetate so purified showed no apparent reaction with a bright piece of sodium after six hours. The ethyl propionate showed a slight reaction after about one hour. The ethyl butyrate and ethyl *iso*butyrate reacted completely with sodium (acyloin formation) within a few minutes. In no case, however, was there any evidence of evolution of hydrogen. Although it has been pointed out[12] that the distillation of ethyl acetate from phosphorus pentoxide caused a slight amount of decomposition, as indicated by a change in density of the ester, it was felt that the decomposition induced by this treatment was not sufficient to have any marked effect on the results of this work.

The sodium ethoxide that was used was prepared by dissolving freshly cut sodium in absolute alcohol (distilled from sodium) and, while the final hydrogen was being evolved from the reaction, removing the excess alcohol by distillation. The resultant sodium ethoxide was then heated in an oil-bath to 150° at 20 mm. for four hours.

Determination of Alcohol in the Ester Distillates.—Mixtures of varying percentages of the different esters and absolute alcohol were made up, their refractive indices taken, and these values plotted against the percentage composition. The points thus determined did not fall on the line joining the refractive index of the pure ester and that of pure alcohol (n_D^{25} 1.35774) but formed a smooth curve, quite close to this line, of the

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[12] Wade and Merriman, *J. Chem. Soc.*, 101, 2429 (1912).

type recently reported by Adkins and Broderick[13] for mixtures of different aldehydes and alcohols. Within the range used (80–100% ester) for the analyses of the distillates the greatest difference between the refractive indices as given by the curve and the straight line amounted to only 0.0004. In spite of this small difference the curves obtained from mixtures of ester and alcohol of known composition and their corresponding refractive indices were used for the analyses. The refractive indices were determined with a Pulfrich refractometer at 25° and with an accuracy, it is believed, of 0.0001.

Reaction of the Esters with Sodium Ethoxide.—The standard procedure that was used for all of the esters with the exception of ethyl *iso*butyrate was: 280 g. of the ester and 34 g. (0.5 mole) of sodium ethoxide were placed in a 1-liter three-necked flask fitted with a reflux condenser, a mercury seal stirrer and a condenser for downward distillation. The receiver to this latter condenser was arranged to fit tightly or loosely depending on whether it was desired to send the vapors of the boiling reaction mixture into the reflux condenser or through the other condenser for distillation. All connections in the apparatus were ground-glass joints in order to prevent any contamination from stoppers. The top of the reflux condenser carried a calcium chloride tube. The contents of the flask was refluxed for four hours, with stirring, by heating in an oil-bath. After this time the excess ester was distilled off and collected in two portions (1 and 2, Table II). Then 200 g. of pure ester was added to the reaction flask and the mixture allowed to reflux for three hours. After this time the excess ester was again distilled off and collected in two portions (3 and 4, Table II). Finally 100 g. of pure ester was added to the flask and after allowing it to reflux for three hours it was distilled off and collected in one portion (5, Table II).

In the case of ethyl *iso*butyrate a similar procedure was followed except that after the four-hour period of refluxing of 0.5 mole of sodium ethoxide and 280 g. of the ester, the distillation was carried on slowly over a period of three hours. The distillate was

TABLE II

SUMMARY OF EXPERIMENTAL DATA

	Portion	Weight, g.	n^{25}_{D}	C_2H_5OH, %	C_2H_5OH, g.	
Ethyl acetate	1	104.0	1.36699	17	17.7	Total, 38.5 g. (0.83 mole)
	2	75.0	1.36726	15	11.2	
	3	79.0	1.36835	6	7.6	
	4	102.0	1.36881	2	2	
	5	153.0	1.36909	0	0	
Ethyl propionate	1	108.0	1.37649	17	18.3	Total, 44.9 g. (0.97 mole)
	2	85.5	1.37676	16	13.6	
	3	114.5	1.37846	9	10.2	
	4	71.5	1.37967	4	2.8	
	5	103.5	1.38045	0	0	
Ethyl butyrate	1	171.5	1.38291	18	30.8	Total, 47.3 g. (1.03 mole)
	2	54.0	1.38567	10	5.4	
	3	74.5	1.38663	7	5.2	
	4	98.5	1.38709	6	5.9	
	5	71.0	1.38892	0	0	
Ethyl *iso*butyrate	1	52.3	1.38326	3	1.5	Total, 1.5 g. (0.03 mole)
	2	64.3	1.38405	0	0	
	3	30.0	1.38405	0	0	
	4	51.2	1.38405	0	0	

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[13] Adkins and Broderick, THIS JOURNAL, **50**, 499 (1928).

collected in four portions. Due to the fact that practically no alcohol appeared in the distillate and that the boiling point of the latter was identical with that of the pure ester, no fresh portions of the ester were added to the reaction flask.

A summary of the weights, refractive indices and alcohol content of the distillate portions for the different esters used is shown in Table II.

The condensation product was isolated from the residue in the reaction flask by the addition, with constant cooling and stirring, of a solution of 35 g. of glacial acetic acid in 70 cc. of water. When complete solution of the salt had taken place, the ester layer was separated and the aqueous portion extracted with two 50-cc. portions of ether. The combined ester layer and ether extract was then fractionated. In this manner there were obtained 44 g. of ethyl acetoacetate (68% of calcd.), b. p. 78–80° (16 mm.); 64 g. of ethyl α-propionylpropionate (81% of calcd.), b. p. 88–90° (12 mm.); 70 g. of ethyl α-butyrylbutyrate (76% of calcd.), b. p. 102–105° (12 mm.). All yield calculations were based on the amount of sodium ethoxide used. The two latter compounds were definitely characterized by hydrolysis to diethyl ketone and di-*n*-propyl ketone, the semicarbazones of which melted at 139–140° and 133–134°, respectively.[14] In the case of ethyl *iso*butyrate this ester was the highest boiling product that was isolated from the reaction mixture.

Ethyl α-propionylpropionate has been prepared in rather poor yields by the action of sodium on ethyl propionate.[15] Although ethyl α-butyrylbutyrate has previously been prepared,[16] it has not heretofore been prepared by a Claisen condensation of ethyl butyrate.

Summary

1. A study of the action of sodium ethoxide on ethyl acetate and certain of its higher homologs has been made and the amounts of both reaction products, β-keto-ester and alcohol, that were formed have been determined.

2. Certain of the mechanisms that have been proposed for the course of the acetoacetic ester condensation are discussed in the light of the results which have been obtained.

Madison, Wisconsin

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[14] *Cf.* Haehn, *Ber.*, **39**, 1703 (1906).

[15] Israel, *Ann.*, **231**, 198 (1886); Hantzsch and Wohlbruck, *Ber.*, **20**, 1320 (1887).

[16] Beilstein, "Handbuch der organischen Chemie," 1921, Vol. III, p. 706.