[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Acetoacetic Ester Condensation. XI. The Extent of the Condensation of Certain Monosubstituted Acetic Esters[1]

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From his studies of the cleavage of various β-keto esters, Dieckmann[3] concluded that those keto esters carrying substituents on the methylene carbon atom were more susceptible to cleavage than the unsubstituted acetoacetic ester, and consequently less completely formed from the corresponding substituted acetic ester. The outstanding illustration of this behavior was ethyl isobutyrylisobutyrate. The failure of this ester to form from ethyl isobutyrate and sodium ethoxide was due, according to Dieckmann, to the fact that it was rapidly and completely cleaved, in the presence of sodium ethoxide, by the alcohol resulting from its formation. It would, therefore, be expected that monosubstituted acetic esters would form the corresponding β-keto esters to a less extent than acetoacetic ester is formed from ethyl acetate.

In earlier papers[4] it was shown that the higher homologs of ethyl acetate gave yields of the corresponding keto esters amounting to 74–84% of the theoretical when the reversible reaction

$$2RCH_2COOC_2H_5 + NaOC_2H_5 \rightleftharpoons RCH_2C(ONa)CRCOOC_2H_5 + 2C_2H_5OH$$

was driven to the right by removal of the alcohol as it was formed. The present paper reports the determination of the extent to which the above reaction proceeds with certain of the monosubstituted acetic esters when the alcohol produced in the condensation is not removed from the reaction mixture.

The results of these determinations are summarized in the table below. The ratio of ester to sodium ethoxide which was used was sufficient to form an apparently homogeneous reaction mixture[5] in each case except with ethyl isovalerate and ethyl trimethylacetate. The reaction time shown in the table is the time that was found to give the maximum yield of the keto ester. Longer or shorter periods of time resulted in decidedly lower yields of the keto ester;[5] for example, ethyl butyrate gave a yield of 32% of the theoretical amount of ethyl α-butyrylbutyrate in eight hours, 36% in sixteen hours, and 34% in forty-one hours. The yield of keto ester is based on the amount of sodium ethoxide used in the reaction. The percentage yields reported in the last column of the table represent the limits of the values obtained from at least two determinations.

THE EXTENT OF THE CONDENSATION OF THE ESTERS, $RCH_2COOC_2H_5$ TO $RCH_2COCHRCOOC_2H_5$ BY SODIUM ETHOXIDE

R is	Moles of $NaOC_2H_5$ used	Moles of ester used	Reaction time, hr.	Reaction temp., °C.[a]	Yield of keto ester, %[b]
H	0.4	2.4	8	78	75–76
CH_3	.4	2.4	16	95	46–47
CH_3CH_2	.4	2.4	32	95	40–42
$CH_3CH_2CH_2$	.2	1.2	32	95	34–35
$(CH_3)_2CH$	.2	1.2	48	95	0
$(CH_3)_3C$	.2	1.2	68	95	0
C_6H_5	.2	0.42	6[c]	95	53–55[c]

[a] Approximate. [b] Based on sodium ethoxide. [c] Shorter reaction periods gave lower yields; 12 hrs. gave a 39% yield with a small amount of an oily, non-crystalline by-product; still longer reaction periods, *viz.*, 24, 35 and 44 hrs., gave so much of the viscous oily product that the α,γ-diphenylacetoacetic ester did not crystallize. Volhard [*Ann.*, **296**, 1 (1897)] reports a 66% yield of this keto ester using a ratio of 1 mole of ester to 1 mole of sodium ethoxide. His yield was based on the ester which was not recovered. The yield in the above table, calculated on the ester not recovered, amounts to 78% of the theoretical. Scheibler and Mahboub [*Ber.*, **60**, 564 (1927)] report a 92% yield of this ester from the action of metallic potassium (1 atom) on ethyl phenylacetate (1.15 mole).

From the data presented in the above table it is seen that the substitution of a hydrogen atom of ethyl acetate by a normal alkyl group increases the time necessary to obtain the maximum yield and, at the same time, decreases the extent of the condensation. The latter observation is in ac-

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[2] Most of the experimental work of this paper was completed by David C. Roberts prior to his death in November, 1936.

[3] Dieckmann, *Ber.*, **33**, 2670 (1900).

[4] (a) McElvain, THIS JOURNAL, **51**, 3124 (1929); (b) Briese and McElvain, *ibid.*, **55**, 1697 (1933).

[5] It is doubtful if true equilibria were reached under the conditions which prevailed in this or Dieckmann's[3] work. While the reaction mixture appeared to be homogeneous, the solution of sodium ethoxide and sodium enolate in the ester was probably colloidal, since, on cooling, the reaction mixture generally set to a gel. Also the fact that yields of the β-ketoesters were lowered by the longer reaction periods indicates that other reactions involving the condensation product had reached noticeable proportions. This was particularly true in the case of ethyl phenylacetate with which longer reaction periods gave increasing amounts of a non-crystalline product (*cf.* footnote *c* of table below).

cord with the conclusions of Dieckmann.[3,6] The effects of the isopropyl and *t*-butyl groups are striking. Not only do the esters containing these groups fail to give any keto ester under the experimental conditions shown above, but when the reaction was carried out in such a manner as to allow for removal of the alcohol formed in the condensation[4] no trace of keto ester could be found. It must be concluded, therefore, that sodium ethoxide does not cause these esters to condense even though they contain two hydrogens on the α-carbon atom. It is interesting to note that the phenyl group allows a greater amount of condensation than do any of the alkyl groups. The yields of acetoacetic ester from ethyl acetate obtained in the present work are higher than any previously reported from this Laboratory. When the condensation of this ester was carried out in such a manner as to allow the alcohol formed in the reaction to distil out, the yield of acetoacetic ester rose to 80% of the theoretical.

Experimental

Materials Used.—Ethyl acetate, ethyl propionate, ethyl butyrate, ethyl valerate and ethyl isovalerate were purified by the procedure described in an earlier paper.[4a] Ethyl *t*-butylacetate was prepared by the procedure of Homeyer, Whitmore, and Wallingford.[7] This ester boiled at 143–144°. Ethyl phenylacetate was prepared by the alcoholysis of benzyl cyanide.[8] The product so obtained was treated with Raney nickel and hydrogen for six hours at 130° and 2000 lb. (136 atm.) pressure to remove any unchanged benzyl cyanide. The resulting ester boiled at 100–101° (9 mm.). Sodium ethoxide was prepared from absolute alcohol and powdered sodium under absolute ether.[9]

Condensation of the Esters with Sodium Ethoxide.—The general procedure followed for the aliphatic esters was that previously described for the condensation of the various alkyl acetates.[10] The keto esters obtained have already been described.[4] The attempts to condense ethyl isovalerate and ethyl *t*-butylacetate by removal of any alcohol formed in the reaction followed the procedure described by Briese and McElvain.[4b]

For the condensation of ethyl phenylacetate the following procedure gave the maximum yield: to the sodium ethoxide prepared from 4.6 g. (0.2 atom) of sodium was added 70 g. (0.42 mole) of ethyl phenylacetate. This reaction mixture, which was contained in a 500-cc. flask carrying a sealed stirrer and reflux condenser, was heated with stirring in a steam-bath to approximately 95° for six hours. The solid material in the reaction mixture completely disappeared after a few minutes of heating. When this period of heating was finished the contents of the flask were cooled to 20° and treated with a solution of 15 cc. of glacial acetic acid in 100 cc. of water. At this point considerable of the solid α,γ-diphenylacetoacetic ester separated from solution. Sufficient ether (150 cc.) was added to return this precipitate to solution and the lower aqueous layer was withdrawn. After this aqueous layer was extracted with another 50-cc. portion of ether the combined ether extracts were treated with a saturated solution of sodium bicarbonate, until all free acid was neutralized. The ether extract was dried over drierite and then distilled. After the removal of the ether the residue was allowed to crystallize. To the resulting crystalline mass was added 20 cc. of alcohol and the mixture cooled to 0°. The precipitated α,γ-diphenylacetoacetic ester was filtered off by suction and dried on a porous plate; 28 g. of material was thus obtained. The filtrate was then distilled from an oil-bath. After the removal of the alcohol 24 g. of uncondensed ethyl phenylacetate was recovered by distillation under 5 mm. pressure. The residue in the distilling flask was dissolved in 10 cc. of hot alcohol and allowed to crystallize by cooling to 0°. An additional 3 g. of the keto ester separated at this point. Total yield, 31 g., 55% of the theoretical based on the sodium ethoxide used, or 78% of the theoretical based on the ethyl phenylacetate not recovered. The product melted at 75–77°.[11]

Summary

A study of the extent of the acetoacetic ester condensation of certain substituted acetic esters by sodium ethoxide is reported. It was found that the substitution of a normal alkyl group for one of the methyl hydrogen atoms of ethyl acetate progressively lowered the extent of the condensation as size of the alkyl group increased.

Secondary and tertiary substituents, such as are present in ethyl isovalerate and ethyl *t*-butylacetate, completely prevented the condensation, even under conditions that would allow the reaction to proceed to completion.

Ethyl phenylacetate condensed to a less extent than did ethyl acetate but to a considerably greater extent than did any of the alkyl substituted acetic esters.

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(6) Even though this agreement exists it is questionable whether Dieckmann was justified in relating susceptibility to cleavage (a reaction rate) to the extent of reaction at equilibrium. These are undoubtedly distinct and unrelated values for any given set of reactants.

(7) Homeyer, Whitmore and Wallingford, THIS JOURNAL, **55**, 4209 (1933).

(8) "Organic Syntheses," Coll. Vol. I, p. 265.

(9) Houben-Weyl Vol. II, 1922, p. 578.

(10) Fisher and McElvain, THIS JOURNAL, **56**, 1768 (1934).

(11) *Cf.* Conant and Blatt, *ibid.*, **51**, 1232 (1929).