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

The Acetoacetic Ester Condensation. VII. The Condensation of Various Alkyl Acetates

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The reversibility of the acetoacetic ester condensation was first suggested by Dieckmann[1] as a result of his study of the splitting of various substituted acetoacetic esters by alcohol and sodium ethoxide. Later Higley[2] reported that the equilibrium point in the acetoacetic ester condensation represents about 36% of the keto ester. More recently Kutz and Adkins[3] reported that both synthesis and alcoholysis showed 44-50% acetoacetic ester to be present at equilibrium in a homogeneous reaction mixture of the components. Confirmation of the synthesis results of this latter work has been reported.[4]

For some time it has seemed that information on the rate and extent of formation of the various acetoacetates from the corresponding acetates, according to the reaction

$$2CH_3COOR + NaOR \rightleftharpoons CH_3C(ONa){=}CHCOOR + 2ROH$$

was needed. Besides the possibility of shedding further light on the mechanism of the reaction, such information might lead (1) to some definite conclusions in regard to the effect of the structure of R on the rate and extent of the condensation, (2) to the discovery of an acetate which would undergo the condensation very slowly or not at all with the corresponding NaOR. Such an acetate would be useful in the study of the course of the reaction of metallic sodium with esters.[5]

The present paper reports the results of a study of the condensation of nine different acetates with the corresponding alkoxides. For the results of these different condensations to be strictly comparable, it was realized that the three conditions (a) similar ratios of reactants, (b) constant temperature of condensation, and (c) the homogeneity of the reaction mixture, should be maintained in each experiment. However, certain factors made it impossible to adhere to such a set of reaction conditions. Preliminary experiments with ethyl and *n*-propyl acetates indicated that a ratio of six moles of the ester to one of the alkoxide and a reaction temperature of 77° produced a reaction mixture that was homogeneous throughout the course of the reaction. When these conditions were applied to some of the other alkyl acetates, it was found that the homogeneity of the reaction mixture could not be maintained. It was decided, therefore, to raise the temperature of the condensation in these cases in order to keep the reaction homogeneous, for it seemed that the settling out of an insoluble reaction product of a reversible reaction would have much more effect on the concentrations at equilibrium than a not too great increase in the reaction temperature. By such increases in the reaction temperature it was possible to maintain homogeneity of the reaction mixture in all cases except those in which isopropyl and isobutyl acetates were used. In the case of methyl acetate it was necessary, on account of its lower boiling point, to carry out the condensation at 57°.

The yields of the alkyl acetoacetates obtained at different time intervals from the condensation of the various alkyl acetates, together with the temperature at which each condensation was carried out, are summarized in Table I. The yields are based on the amount of sodium alkoxide (0.2 mole) used.

The most striking feature of the results presented in Table I is the high yields of the various alkyl acetoacetates. Comparison with previous work is possible only in the case of ethyl acetoacetate, the equilibrium point in the synthesis of which has been reported as 36–50% of the keto ester.[2,3,4] The present work shows that this keto ester is present to the extent of 66% at equilibrium. An experiment in which the equilibrium was approached from the reverse direction, *i. e.*, by the alcoholysis of ethyl acetoacetate under the same conditions that were used for the synthesis, gave a 71% recovery of the keto ester. The only apparent explanation for the high yields of condensation products that were obtained in the present work is the quality of the alkoxides used for the condensations. Since the yield calculations are based on this reactant it is essential that it be absolutely pure. Alkoxides made from

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

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

[3] Kutz and Adkins, THIS JOURNAL, **52**, 4392 (1930).

[4] Snell and McElvain, *ibid.*, **53**, 2310 (1931).

[5] Ref. 4, p. 2315.

TABLE I

THE RATE AND EXTENT OF THE CONDENSATION OF VARIOUS ALKYL ACETATES BY THE SODIUM ALKOXIDES

CH_3COOR used, R is	Yield of alkyl acetoacetate, %, in			
	2	8	16	32 hr.
	at temperature of condensation, (°C).			
Methyl	39 (57)	56 (57)	58 (57)	61 (57)
Ethyl	51 (77)	61 (77)	65 (77)	66 (77)
n-Propyl	58 (77)	63 (77)	73 (77)	70 (87)
n-Butyl	51 (77)	71 (115)	68 (115)	....
Isobutyl	50 (77)[a]	71 (115)[b]	....	....
Isopropyl	39 (77)[a]	75 (87)[a]	75 (87)[a]	....
s-Butyl	40 (77)	80 (87)	80 (108)	....
t-Butyl	20 (77)	29 (77)	36 (77)	52 (77)[c]
Phenyl	0 (77)	....	0 (77)	....

[a] In these runs solid material separated to such an extent that the reaction mixture was thick and pasty at the end of the run. [b] This run was made at 115° for four hours and then allowed to stand for twelve hours at room temperature before it was worked up. The separation of solid material was so great that it did not seem worth while to make any further runs with this ester. [c] 52% also after sixty-four hours at 77°.

sodium and excess alcohol were found to give low sodium analyses, indicating the presence of the alcohol, and other samples made from the theoretical quantities of alcohol in xylene showed considerable decomposition (as evidenced by a darkening in color) and loss of efficiency as condensing agents on standing. All alkoxides used in the present work were made from the reaction of the theoretical amount of the alcohol with sodium and used at once in the condensation.

The effect of the structure of the alkyl group on the rate of the reaction may be seen from the two-hour column of Table I. With the exception of methyl acetate, the primary acetates appear to be the most reactive, the secondary acetates somewhat less, while the only tertiary acetate studied is definitely the least reactive of the alkyl acetates. The lower rate and extent of condensation in case of methyl acetate may be due to the use of a lower reaction temperature or to some inherent property of the methyl group.

The extent of the condensation at equilibrium does not appear to be as much affected by the structure of the alkyl group as is the rate of reaction during the first two hours. The secondary acetates give noticeably higher yields of keto ester than any of the other alkyl acetates. In the case of isopropyl acetate this increase in yield might possibly be ascribed to the fact that homogeneity of the solution could not be maintained and an insoluble condensation product precipitated from the reaction mixture. With secondary butyl acetate the homogeneity of the reaction was maintained by increasing the reaction temperature. This temperature increase might appear to have been responsible for the high yield of secondary butyl acetoacetate, but it should be noted that no increase in yield of the condensation product was obtained from secondary butyl acetate when the reaction was run for sixteen hours at 108° instead of eight hours at 87°. Also, similar yields of *n*-propyl acetoacetate were obtained with *n*-propyl acetate in the sixteen-hour run at 77° and the thirty-two-hour run at 87°. It would seem, therefore, that the temperature at which the reaction is carried out has little or no effect on the extent to which the condensation takes place.

The high yields of the condensation products obtained in this work add further support to the contention previously made[4] that sodium ethoxide rather than sodium metal is the active condensing agent in the acetoacetic ester condensation, since it now appears that the alkoxides give decidedly higher yields of keto ester than have ever been obtained from the action of metallic sodium on ethyl acetate.

The behavior of phenyl acetate is not without significance. The failure of sodium phenoxide to condense this ester emphasizes the fact that the acetoacetic ester condensation fundamentally involves the formation of the salt of the enolic form of the condensation product. One of the functions of the condensing agent is to form this salt. Condensing agents such as the sodium salts of alcohols or ammonia (sodamide) are readily decomposed by the weakly acidic enol, but if the salt of the more acidic phenol is not decomposed by the enolic form of the β-keto ester no condensation can occur.[6]

Experimental

Preparation and Purification of Esters.—Commercial ethyl acetate (Mallinckrodt absolute) was further purified as described below. Methyl, *n*-propyl and *n*-butyl acetates were prepared by refluxing 8–10 hours each of the alcohols with a 5–10% excess of the theoretical quantity of glacial acetic acid which contained a volume of concentrated sulfuric acid corresponding to about 5% of the volume of the alcohol used. The reaction mixture was washed once with an equal volume of water and then with an equal volume of a sodium carbonate solution to which solid sodium carbonate was added until the aqueous layer reacted alkaline to litmus. The ester was then washed with an equal volume of a saturated calcium chloride solution. The separated ester layer was allowed to stand for three days over solid calcium chloride, the solid then re-

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[6] *Cf.* mechanism for the condensation proposed by Cox, Kroeker and McElvain, THIS JOURNAL, **56**, 1176 (1934).

moved by filtration and the ester distilled. This procedure was repeated using anhydrous potassium carbonate instead of solid calcium chloride. The ester obtained from this latter treatment was allowed to stand for twenty-four hours with 2% of its weight of phosphorus pentoxide. After directly distilling from the phosphorus pentoxide the ester was finally fractionated through a 30-cm. Widmer column.

Isopropyl, isobutyl, *s*-butyl and *t*-butyl acetates were prepared from the alcohols and acetic anhydride according to the procedure of Norris and Rigby.[7] In the case of isobutyl alcohol it was necessary to add the alcohol to the anhydride in small portions, with vigorous shaking and to allow the mixture to stand several hours before refluxing in order to avoid a too violent reaction. Isobutyl acetate was purified as described above. In the purification of the secondary and tertiary alkyl acetates the final treatment with phosphorus pentoxide was omitted.

Phenyl acetate was prepared from phenol and acetyl chloride[8] and after washing with alkali, fractionally distilled.

The acetates that were used had the following boiling points: methyl, 56.5° (752 mm.); ethyl, 76.3° (752); *n*-propyl, 100.8° (743); isopropyl, 87–88° (742); *n*-butyl, 124–124.4° (743); isobutyl, 115.3–115.6° (735); *s*-butyl, 110–110.3° (743); *t*-butyl, 96.8–97.3° (746); phenyl, 193.5–194.5° (744).

Sodium Alkoxides and Sodium Phenoxide.—Sodium methoxide, sodium ethoxide and sodium phenoxide were made by the reaction of the theoretical quantity of alcohol with powdered sodium in xylene.[9] The higher alkoxides could not be made satisfactorily by this method. The following procedure was developed and used for the preparation of not more than 0.5 mole amounts of sodium *n*-propoxide, isopropoxide, *n*-butoxide and isobutoxide.

A hot Soxhlet extractor was mounted in one neck of a 2-necked round-bottomed flask. The top of the extractor supported an efficient reflux condenser which carried a calcium chloride tube. In the siphon cup of the extractor was placed 0.5 atom (or less) of freshly cut sodium which was then covered with xylene. A plug of glass wool or a Gooch crucible placed at the bottom of the siphon cup served as a filter to retain small pieces of sodium. Approximately 500 cc. of xylene and 0.5 mole (or less) of the alcohol was poured into the flask through the second neck. This neck was then closed by a gas inlet and a stream of dry nitrogen passed through the flask, extractor, and condenser. The flask was heated in an oil-bath sufficiently to maintain refluxing of the alcohol–xylene mixture. After several hours of refluxing the drippings from the condenser had dissolved practically all of the sodium in the siphon cup. Clogging of the siphon tubes could be prevented by the addition of small quantities of xylene from the top of the condenser as the necessity arose.

When the reaction was complete the extractor and reflux condenser were removed from the flask and replaced with a condenser set for distillation. With nitrogen gas passing through the flask most of the xylene was distilled off. The last portion of the xylene was removed under diminished pressure. The sodium alkoxides so prepared were used at once in the condensations.

It was not possible to prepare sodium *s*-butoxide or sodium *t*-butoxide by the above procedure. The former, which is the most sensitive of the alkoxides that were prepared, appeared to decompose during the distillation of the xylene. Exposed to the air this alkoxide immediately chars and often ignites spontaneously. *t*-Butyl alcohol reacts so slowly with sodium and the alkoxide is so insoluble in the xylene–alcohol mixture that the above procedure is not practicable. The following method was used for these particular alkoxides.

In a 1-liter 3-necked flask 0.5 atom of sodium was powdered under xylene. After cooling the xylene was decanted off and the metal washed several times by decantation with dry ether. The sodium was then covered with 500 cc. of dioxane, which previously had been refluxed with and distilled from sodium, and 0.5 mole of the alcohol added. The flask was then fitted with a mercury seal stirrer, a reflux condenser and an inlet for nitrogen. A thermometer was arranged in one of the necks of the flask so that it dipped below the surface of the dioxane. With a steady stream of nitrogen passing through, the flask was heated, with stirring, in an oil-bath so that the temperature of the dioxane solution was maintained at 90°. After twenty-four hours, when most of the sodium had disappeared, the dioxane was heated to boiling, whereupon any unreacted sodium congealed into a few spheres that floated on the surface of the liquid. On cooling, these spheres of sodium were readily removed. The alkoxide that had not dissolved in the dioxane settled to the bottom of the flask and was entirely free from unreacted sodium. Most of the dioxane was removed from the alkoxide by distillation and the last traces drawn off under diminished pressure.

The purity of each of the alkoxides, with the exception of sodium *s*-butoxide, was checked by sodium analyses of samples selected at random from the different preparations. Because of its sensitiveness to air, sodium *s*-butoxide was not analyzed, but used directly, after its isolation, in the condensations.

General Procedure for the Condensation of the Esters.—In a 500-cc. 3-necked flask, fitted with a stirrer, reflux condenser and a thermometer placed to dip below the surface of the reaction mixture, was placed 0.2 mole of the sodium alkoxide and 1.2 moles of the corresponding alkyl acetate. The contents of the flask were heated, with stirring, to the temperature and for the time indicated in Table I. At the end of the reaction time the flask was surrounded by ice and the reaction mixture cooled to 10°. The reflux condenser was then replaced by a dropping funnel and 36 g. of 33.3% aqueous acetic acid added dropwise to the mixture at such a rate that the temperature remained below 15°. When complete solution of the solid material had occurred, the ester layer was separated and the aqueous layer extracted with four 50-cc. portions of ether. The combined ester layer and ether extracts, after drying over anhydrous sodium sulfate, was fractionally distilled. The alkyl acetoacetate was collected and weighed. The yields of these esters are shown in Table I, and the physical properties and analyses of those not previously described are listed in Table II. In the determination of the per-

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[7] Norris and Rigby, THIS JOURNAL, 54, 2097 (1932).

[8] Hoeflake, *Rec. trav. chim.*, 36, 30 (1916).

[9] Houben-Weyl, 1922, Vol. II, p. 578.

centage yields these esters were collected over a 2–5° range of boiling point. The boiling points shown in Table II represent carefully fractionated material taken for analyses.

TABLE II

ALKYL ACETOACETATES

CH_3COCH_2COOR R is	B. p., °C. (11 mm.)	d_4^{25}	n_D^{25}	M_D	
				Calcd.	Found
n-Propyl	78	0.9959	1.4205	36.38	36.63
Isopropyl[a]	69	.9835	1.4153	36.38	36.64
n-Butyl	90	.9761	1.4245	41.08	41.28
Isobutyl[b]	84.5	.9697	1.4219	41.08	41.42
s-Butyl	79.1	.9701	1.4208	41.08	41.38
t-Butyl	71.5	.9698	1.4178	41.08	41.02

Formula	Analyses, %			
	Carbon		Hydrogen	
	Calcd.	Found	Calcd.	Found
$C_7H_{12}O_3$	58.33	58.15	8.33	8.41
$C_7H_{12}O_3$	58.33	58.44	8.33	8.46
$C_8H_{14}O_3$	60.74	60.50	8.86	8.91
$C_8H_{14}O_3$	60.74	60.89	8.86	8.87
$C_8H_{14}O_3$	60.74	60.74	8.86	8.69
$C_8H_{14}O_3$	60.74	60.42	8.86	8.81

[a] Reported by Moureu and Delange, *Bull. soc. chim.*, [3] **27**, 384 (1902), as boiling at 75–76° (15 mm.); no other physical constants are given. [b] Reported by Emmerling and Oppenheim, *Ber.*, **9**, 1097 (1876), as boiling at 202–206°; d^{25} 0.932.

In the case of phenyl acetate the residue remaining after the distillation of the ether was extracted with three 50-cc. portions of 5% potassium hydroxide, washed with water and distilled. From a run of 245 g. of phenyl acetate and 34.8 g. of sodium phenoxide 227 g. (93%) of the phenyl acetate was recovered. Acidification and ether extraction of the alkaline extract yielded 29 g. (103% based on sodium phenoxide used) of phenol.

Alcoholysis of Ethyl Acetoacetate.—In a one-liter, 3-necked flask bearing a thermometer, mercury seal stirrer and reflux condenser, were placed 68 g. (1 mole) of sodium ethoxide, 352 g. (4 moles) of ethyl acetate and 46 g. (1 mole) of ethyl alcohol and finally 130 g. (1 mole) of ethyl acetoacetate, added in small portions through the reflux condenser. The mixture, then homogeneous, was heated at 77° for thirty-two hours. The reaction product was acidified and extracted with ether according to procedure described above. The combined ester portion and ether extracts was washed once with one-half the volume of saturated sodium bicarbonate solution. The ether solution, after being dried over anhydrous sodium sulfate, was fractionally distilled. By determining the saponification equivalent of the liquid which distilled below the boiling point of ethyl acetoacetate, its ethyl acetate content was estimated to be 346 g. By distillation of the remainder there was obtained 72.2 g. of ethyl acetoacetate, and 13.5 g. of dehydracetic acid, m. p. 108–109° after one recrystallization from alcohol. The combined yield of ethyl acetoacetate and dehydracetic acid corresponds to 71% recovery of the original ethyl acetoacetate put into the reaction.

Summary

A study of the rate and extent of the acetoacetic ester condensation of various alkyl acetates by the corresponding sodium alkoxides has been made.

Methods for the preparation of the sodium alkoxides in a high state of purity are described.

The properties of a number of new alkyl acetoacetates are listed.

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Some Substituted Tetrahydroisoquinoline Hydrochlorides

BY JOHANNES S. BUCK

The physiological action of certain tetrahydroisoquinolines should prove to be of great interest on account of their relationship to such well-known compounds as tetrahydropapaverine, hydrohydrastinine, etc. The tetrahydroisoquinolines are also closely related to β-phenyethylamines, in that they may be regarded as containing the side chain $—CH_2CH_2N$ and to the benzylamines, in that they contain the group $—CH_2N$. Their relationship to the benzyl-β-phenylethylamines previously described[1] is evident, the two terminal benzene rings of the benzyl-β-phenylethylamines being represented by one shared ring in the tetrahydroisoquinolines.

The writer has prepared a series of methoxy-, dimethoxy-, hydroxy- and dihydroxytetrahydroisoquinolines and the corresponding N-methyl compounds, all as the hydrochlorides. Certain of the compounds also contain the pharmacologically important so-called catechol group, two hydroxy groups ortho to one another. The physiological effects are under investigation and will be described in another place.

After some trials, a method of preparation similar to that used by Decker[2] for nor-hydrohydrastinine was selected. The requisite β-phenylethylamine or β-phenylethylmethylamine

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(1) Buck, THIS JOURNAL, **53**, 2192 (1931).

(2) Decker, German Patent 257,138; Decker and Becker, *Ann.* **395**, 342 (1913).