## [CONTRIBUTION NO. 731 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

# CONDENSATIONS EFFECTED BY THE ALKALI AMIDES. IV. THE REACTIONS OF ESTERS WITH LITHIUM AMIDE AND CERTAIN SUBSTITUTED LITHIUM AMIDES<sup>1</sup>

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When a basic reagent reacts with an ester, the ester may be attacked at at least two different positions (1), the carbonyl carbon and the  $\alpha$ -hydrogen as indicated by the following scheme. It has been shown earlier (2, 3) that when B<sup>-</sup> is amide ion (from sodium amide), both (a), the amide of the starting ester, and (b), the ester anion, which is the reactive intermediate in the preparation of  $\beta$ -ketoesters, are formed. However, when the larger but weaker base, sodium triphenylmethide, is used in condensations apparently only  $\alpha$ -hydrogen attack occurs (4).



 $M = Na \text{ or } K, B = OC_2H_{\overline{5}}, NH_{\overline{2}} \text{ or } (C_6H_5)_3C^- \text{ etc.}$ 

The present investigation was undertaken to study the course of the reactions between a number of esters and several lithio-amides of varying sizes and basic strengths. The condensing agents used in this study were lithium amide, lithium diethylamide, lithium diisopropylamide, and lithium N-methyl-N-phenylamide.

The yields of the  $\beta$ -ketoesters obtained in the present investigation (Table I) using lithium amide as the condensing agent were considerably lower that those reported previously using sodium amide to effect the same condensations. As part of our investigation, we self-condensed ethyl phenylacetate by means of both sodium amide and lithium amide. We obtained a 68% yield of  $\beta$ -ketoester using

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<sup>&</sup>lt;sup>1</sup> For paper III in this series see J. Am. Chem. Soc., 71, 1120 (1949).

sodium amide, while that reported earlier (3) was 82%. However, when lithium amide was used as the base, a considerably lower yield (47%) of  $\beta$ -ketoester was obtained. In order to show that the greater yield of self-condensation product obtained with sodium amide as compared with lithium amide when the reactions were carried out in the relatively polar medium, diethyl ether, was probably not due to solvation effects alone, ethyl phenylacetate was self-condensed by these

ESTER	PRODUCTS ISOLATED	REAC- TION TIME,	в.р <i>.</i> , °С.	<u>м</u> м.	vield, %
	-				
n-Propyl acetate	n-Propyl acetoacetate	2	80-81	10 (3)	30
Isopropyl acetate	Isopropyl acetoacetate	3	75-79	16ª	34
tert-Butyl acetate	tert-Butyl acetoacetate	12	71–75	12(19)	28
Ethyl phenylacetate	Ethyl $\alpha$ , $\gamma$ -diphenyl- acetoacetate	2;36	77.5-79 <sup>b</sup> (m. p.)		47;48
	Phenylacetamide		152-152.5 (m. p.) (20)		0.7;
tert-Butyl-propionate	<i>tert</i> -Butyl α-propionyl- propionate	3	87-89	15°	20
Ethyl <i>n</i> -butyrate	Ethyl α-n-butyrl-n- butyrate	2	87-95	10 <sup>d</sup>	trace
	n-Butyramide		113-114 (m.p.) (21)		5.2

## TABLE I

## REACTIONS OF ESTERS WITH LITHIUM AMIDE

<sup>a</sup> Copper salt, m.p. 174-174.5° (18).

<sup>b</sup> Converted to 1,4-diphenyl-3-benzylpyrazalone-5, m.p. 231-232° (19).

<sup>c</sup> Anal.: Calc'd for C<sub>10</sub>H<sub>18</sub>O<sub>8</sub>: C, 64.51; H, 9.68. Found: C, 64.10; H, 9.66.

<sup>d</sup> Gave a positive enol test with alcoholic ferric chloride solution.

TABLE II

SELF-CONDENSATION OF ETHYL PHENYLACETATE IN PETROLEUM ETHER (B.P. 30-36°)

BASE	REACTION TIME, HOURS	YIELD OF ETHYL $\alpha$ , $\gamma$ -Diphenyl- acetoacetate, $\%$
LiNH <sub>2</sub>	2	13.4
$LiNH_2$	6	19.2
$NaNH_2$	2	35.4
$NaNH_2$	6	50.3

two bases in low-boiling petroleum ether (b.p.  $30-36^{\circ}$ ). Although the yields of  $\beta$ -ketoester were lower in petroleum ether than in diethyl ether, it may be seen (Table II) that sodium amide still gives the higher yield.

In attempting to explain the differences in action between lithium and sodium amides, it appears that the anion of the bases  $(i.e., NH_2)$  is probably not independent of the cation with which it is associated when the alkali amides effect condensations. If this were not the case, then there should be no difference in the effectiveness of lithium amide and sodium amide in the reactions studied, since the action of the amide ion should be the same regardless of its source.

Morton (5) has suggested that in spite of the ionic character of organoalkali compounds, the probability that they dissociate to any appreciable extent in organic solvents is rather remote. They probably exist and react as ion pairs rather than as the free anion and cation. The cation is in close proximity to the anion and probably has a very definite influence on it. The data obtained in the present work indicate that the concept of ion pairs is applicable to reactions effected by the alkali amides in organic solvents.

When an ester reacts with a base, it has been suggested (4) that the stronger and larger the base is, the more readily is the  $\alpha$ -hydrogen of the ester attacked, to give the ester anion, the active intermediate in condensations. Pauling (6) has pointed out that the alkali metals decrease in electronegativity with increasing atomic weight. If, therefore, in the ion pairs Li<sup>+</sup>NH<sup>-</sup><sub>2</sub> and Na<sup>+</sup>NH<sup>-</sup><sub>2</sub>, sodium is less electronegative than lithium, then the amide portion of the sodium amide is more electronegative than that of lithium amide. Therefore, sodium amide is probably a stronger base than lithium amide and hence the former should react with the  $\alpha$ -hydrogen of an ester to a greater extent than does the latter. In this connection, it has been shown recently (7) that in the conversion of o-aroyloxyacetarones by the alkali metals into the corresponding o-hydroxydiaroylmethanes (these reactions may be regarded as intramolecular Claisen condensations), the yields of the  $\beta$ -diketones produced increase with the increasing basicity of the metal used. Thus, lithium is less effective than sodium which is less effective than potassium for these transformations. Also, these workers have shown that these conversions do not take place with lithium carbonate while with caesium and rubidium carbonates the transformations are rapid. Also, it is of interest to note that ethyllithium, ethylsodium, and ethylpotassium metalate benzofuran with increasing ease (8).

It then appeared of interest to show what effect variations in the size and basic strength of the condensing agents would have on the course of the condensations studied. Three lithic bases were used, namely the lithium derivatives of N-methylaniline, diethylamine, and diisopropylamine. On the basis of steric and electrical effects one would predict that the extent to which these reagents attack the  $\alpha$ -hydrogen of an ester should increase in the order in which these bases are listed, *i.e.*, lithium N-methyl-N-phenylamide should give the most carbonyl carbon attack while lithium diisopropylamide should react mostly at the  $\alpha$ -hydrogen of the ester.

These predictions have been confirmed in the present investigation (Table III). It may be seen that lithium diethylamide, prepared by the method of Ziegler and Ohlinger (9), is a satisfactory reagent for the self-condensation of *tert*-butyl acetate and ethyl phenylacetate. In all the other condensations effected by this base, the  $\beta$ -ketoester was contaminated with the N, N-diethylamide of the starting ester. These latter compounds were apparently formed by the attack of the base at the carbonyl carbon of the ester. The contaminated  $\beta$ -ketoesters were subjected to a ketonic cleavage (10) and the yields of the  $\beta$ -ketoester calculated on the basis of the ketone isolated.

	AMIDES
	LITHIUM
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	REACTIONS

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ESTER	BASE <sup>4</sup>	REACTION TIME, HOURS	PRODUCTS ISOLATED	B.P., °C.	WW.	VIELD, $c_0^{\prime \prime}$
tert-Butyl acetate	LDEA	8	tert-Butyl acetoacetate	72–73	10 (19)	58.5
Ethyl phenylacetate	LDEA	2.5	Ethyl $\alpha, \gamma$ -diphenylacetoacetate	78-79.5 (m.p. <sup>b</sup> )		95.5
Ethyl propionate	LDEA	1.5	Diethyl ketone	97-103	760°, d	20
·	LDIA	0.5	Ethyl α-propionylpropionate	88-90	12 (23)°	21.3
<u>,</u>	LMPA	0.25; 1.5	Ethyl α-propionylpropionate N-methyl-N-phenylpropionamide	80-124 57-57.5 (m.p.) (24) <sup>a</sup>	11′	trace; trace 44.4; 57
Ethyl <i>n</i> -butyrate	LDEA	1.5	Di-n-propyl ketone	141-147	7604. i	20
Ethyl isobutyrate	LDEA	3.5; 15	Diisopropyl ketone N, N-Diethylisobutyramide	121-126 192-194 76-77	760 <sup>i</sup> 760 (26) 14	16; 3.5 —; 5.6
	LDIA	0.25; 3	Ethyl α-isobutyrylisobutyrate	87-90	14 (27)	47.1;49.3
Ethyl isovalerate	LDEA	ñ	Diisobutyl ketone N, N-Diethylisovaleramide	170-174 93-95	760 <sup>k</sup> 14 <sup>i</sup>	46.6 6.6
Ethyl pelargonate	LDEA	1.5	Di-n-octyl ketone	50-50.5 (m.p.) (29)		44.1

lithium N-methyl-N-phenylamide. <sup>b</sup> See note (b) of Table I. <sup>c</sup> 2,4-Dinitrophenylhydrazone, m.p. 155–155.5<sup>o</sup> (22). <sup>d</sup> There was also isolated 9.7 g. of a clear, yellow, nitrogen-free oil, b.p. 90-160° at 10 mm. which gave a positive enol test with ferric chloride solution. This may have been formed by a dehydroacetic acid type of condensation. \* There was also obtained 10.6 g. of the oil described in note (d). ' Gave a red enol test with ferric chloride solution. A sample was hydrolyzed to methylaniline, which was converted to its benzenesulfonamide, m.p. 78-79° [(17) p. 194]. <sup>A</sup> 2, 4-Dinitrophenylhydrazone, m.p. 74.5-75° (22). <sup>i</sup> There was also obtained 11.1 g. of a clear, yellow, nitrogen-free oil, • The abbreviations in this column have the following meanings: LDEA, lithium diethylamide; LDIA, lithium diisopropylamide; LMPA, b.p. 75-142° at 4 mm. which gave a positive enol test with ferric chloride. i 2,4-Dinitrophenylhydrazone, m.p. 87-88° (25). \* Semicarbazone, m.p. 121-121.5° (28). <sup>1</sup> Anal. Cale'd for C<sub>9</sub>H<sub>19</sub>NO: C, 68.79; H, 12.10; N, 8.92. Found: C, 68.67; H, 12.22; N, 9.18.

165

## CONDENSATIONS EFFECTED BY THE ALKALI AMIDES. IV

It may be seen (Table III) that while the reaction between ethyl isobutyrate and lithium diethylamide gives a mixture of ethyl  $\alpha$ -isobutyrylisobutyrate (isolated as diisopropyl ketone) and N,N-diethylisobutyramide, the reaction between the more complex base, lithium diisopropylamide, and ethyl isobutyrate results apparently only in attack on the  $\alpha$ -hydrogen of the ester with the production of a 49% yield of pure  $\beta$ -ketoester. It is also of interest to note that the reaction between lithium diisopropylamide and ethyl isobutyrate is a rapid one. Increasing the reaction time from fifteen minutes to three hours resulted in no substantial increase in  $\beta$ -ketoester formation. Finally, the relatively weak base, lithium N-methyl-N-phenylamide, has been shown to react mainly at the carbonyl carbon of ethyl propionate to give a 57% yield of N-methyl-N-phenyl propionamide.

The results reported here agree essentially with those published recently for similar condensations with the analogous magnesium bases (11, 12).

### EXPERIMENTAL

### REACTIONS OF ESTERS WITH LITHIUM AMIDE

(a) Preparation of the ethereal suspension of lithium amide. The apparatus used in this preparation is the same as that described previously for the preparation of sodium amide (13). To the reaction flask, 300 ml. of anhydrous liquid ammonia and a few crystals of hydrated iron (III) nitrate are added, and the solution stirred rapidly for ten minutes. The rate of stirring is then reduced and 0.5 mole (3.5 g.) of small pieces of lithium is added. When the lithium has been converted to lithium amide (as indicated by the disappearance of the blue color in the solution and the formation of a blue-gray sludge in the reaction flask), 250 ml. of absolute ether is added. The reaction mixture is placed on a steam-bath and the liquid ammonia evaporated. When the ether begins to reflux, indicating that no liquid ammonia is left in the flask, the reaction mixture is allowed to come to room temperature. Sufficient absolute ether is then added to the flask so that it contains about 500 ml. of liquid. In this reaction the conversion of lithium to lithium amide is assumed to be quantitative.

(b) General procedure for the condensations. To one equivalent of lithium amide, prepared as described above, is added 1.1 equivalents of the ester dissolved in an equal volume of anhydrous ether. After the addition of the ester is complete and spontaneous refluxing of the ether stops, the reaction mixture is stirred and refluxed on a steam-bath for the time indicated in Table I. After cooling to room temperature, the contents of the flask are stirred into crushed ice and about 100 ml. of conc'd hydrochloric acid. The chilled mixture phases are separated, the aqueous phase is extracted with several 100-ml. portions of ether, and the combined ethereal phases are dried over Drierite and the solvent distilled. Distillation is continued at atmospheric pressure to remove any unreacted ester. The residue is then distilled *in vacuo* if the product is a liquid or crystallized if the product is a solid.

#### REACTIONS OF ESTERS WITH DISUBSTITUTED LITHIUM AMIDES

(a) Preparation of phenyllithium. The procedure followed is essentially that of Gilman, et al. (14) except that lithium sand instead of pieces of the metal was allowed to react with the bromobenzene, using diethyl ether as a solvent. A 5-ml. portion of the reagent was standardized with 0.1 N hydrochloric acid after being hydrolyzed with water (15). A Gilman test (16) for the Grignard reagent was also performed on a 1-ml. sample.

(b) Preparation of disubstituted lithium amides. To 500 ml. of a 1 molar solution of phenyllithium contained in a 1000-ml. round-bottomed flask equipped with a mercury

sealed stirrer, a reflux condenser, and an addition funnel was added 0.5 mole of the appropriate secondary amine listed in Table III, at such a rate as to keep the ether gently refluxing. The solution was stirred for five minutes after the addition of the amine was completed and a 1-ml. sample was withdrawn and a Gilman test (16) made. If the test was negative, the solution of the lithium disubstituted amide was ready for use. The conversion of the amine to the corresponding lithium derivative was assumed to be quantitative.

(c) General procedure for the condensations and isolation of products. To a solution of 0.5 mole of the disubstituted lithium amide, prepared as described above, is added 0.55 mole of the appropriate ester, dissolved in an equal volume of absolute ether, just rapidly enough to keep the ether in the reaction flask gently refluxing. After the addition of the ester is complete, the reaction mixture is refluxed for the appropriate length of time (Table III). The reaction mixture is hydrolyzed as described above for the condensations effected by lithium amide. After the solvent is removed, the residue is fractionated *in vacuo* if the  $\beta$ -ketoester is a liquid or crystallized if it is a solid. Samples of both the  $\beta$ -ketoester and of any higher-boiling material are fused with metallic sodium and a qualitative test for nitrogen (17) performed.

In those cases where the  $\beta$ -ketoester is contaminated with nitrogenous material, the  $\beta$ -ketoester fraction is subjected to a ketonic cleavage according to the procedure of Hudson and Hauser (10) and the yield of  $\beta$ -ketoester calculated on the basis of the ketone isolated. The ketone is isolated by distillation at atmospheric pressure. In those cases where there is a significant residue after the removal of the ketone, the distillation is continued at reduced pressure and the N, N-disubstituted amide of the starting ester isolated.

### SUMMARY

Lithium diethylamide has been found to be a satisfactory reagent for the selfcondensation of *tert*-butyl and ethyl phenylacetate. When the ethyl esters of propionic, *n*-butyric, isobutyric, isovaleric, and pelargonic acids were treated with this base, the  $\beta$ -ketoesters produced were found to be contaminated with the diethylamide of the starting esters.

Lithium diisopropylamide is a satisfactory reagent for the self-condensation of ethyl isobutyrate, while lithium N-methyl-N-phenylamide reacts with ethyl propionate to give N-methyl-N-phenylpropionamide.

It has been noted that when the same esters are treated with sodium amide and lithium amide, the former base gives higher yields of  $\beta$ -ketoester. It is suggested that the large differences in yields may be explained on the basis that the alkali amides function as ion pairs in organic solvents.

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