drochloric acid saturated with 2,4-dinitrophenylhydrazine was added 0.1 ml. of the pyran IV. The mixture was heated to its boiling point for a few minutes. From the cooled solution was obtained the 2,4-dinitrophenylhydrazone of IIa (see above), m.p. and mixed m.p. 102–103°.

RAHWAY, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

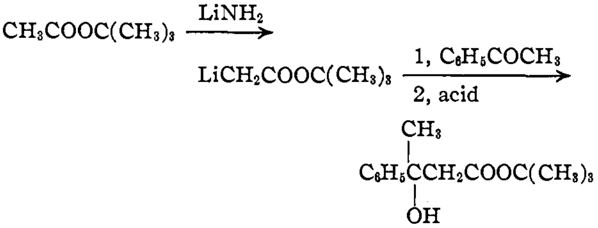
Synthesis of N,N-Dialkyl-β-hydroxyamides from N,N-Dialkylamides and Ketones Using Lithium Reagents[1]

BY W. H. PUTERBAUGH[2] AND CHARLES R. HAUSER

RECEIVED JANUARY 19, 1953

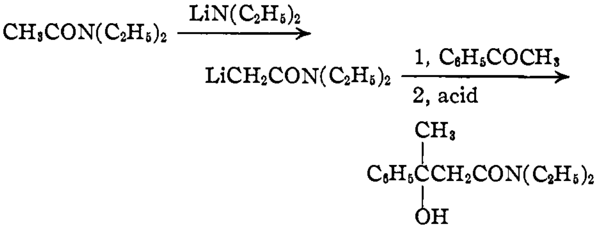
The aldol condensation method described previously for preparing β-hydroxy esters from esters and ketones or aldehydes by means of lithium amide has been adapted to the synthesis of N,N-dialkyl-β-hydroxyamides from N,N-dialkylamides and ketones by employing the appropriate lithium dialkylamide. This new method appears to be as satisfactory as the extension of the Reformatsky reaction described by other workers. Certain of the β-hydroxy amides were dehydrated to form the corresponding α,β-unsaturated amides.

Recently, we[3] described a new method for the synthesis of β-hydroxy esters that involved an aldol condensation between esters and ketones or aldehydes. The reaction, which was effected by lithium amide, may be illustrated with *t*-butyl acetate and acetophenone.



$$CH_3COOC(CH_3)_3 \xrightarrow{LiNH_2} LiCH_2COOC(CH_3)_3 \xrightarrow[2,\ acid]{1,\ C_6H_5COCH_3} C_6H_5\overset{\overset{CH_3}{|}}{\underset{\underset{OH}{|}}{C}}CH_2COOC(CH_3)_3$$

The present paper describes the analogous aldol condensation of certain N,N-dialkylamides with ketones by means of the corresponding lithium dialkylamide (prepared from lithium phenyl and dialkylamine) to form N,N-dialkyl-β-hydroxyamides. The method may be illustrated with N,N-diethylacetamide and acetophenone.

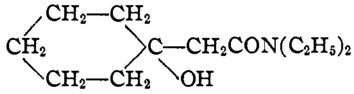


$$CH_3CON(C_2H_5)_2 \xrightarrow{LiN(C_2H_5)_2} LiCH_2CON(C_2H_5)_2 \xrightarrow[2,\ acid]{1,\ C_6H_5COCH_3} C_6H_5\overset{\overset{CH_3}{|}}{\underset{\underset{OH}{|}}{C}}CH_2CON(C_2H_5)_2$$

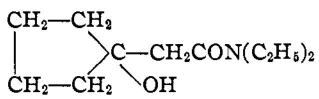
I

An α-hydrogen of the N,N-diethylacetamide was first metalated, and the resulting lithio derivative then condensed with the ketone. In contrast to esters which may self-condense unless the intermediate lithio ester is soon treated with the ketone,[3] N,N-diethylacetamide showed no such tendency for self-condensation.[4]

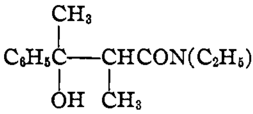
N,N-Diethylacetamide was also condensed with cyclohexanone and cyclopentanone to form β-hydroxyamides II and III, respectively. Similarly, N,N-diethylpropionamide and N,N-di-*n*-butylacetamide were condensed with acetophenone to give β-hydroxyamides IV and V, respectively. The yields were reasonably good (Table I).



II

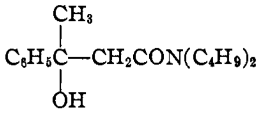


III



$$C_6H_5\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}—\underset{\underset{CH_3}{|}}{C}HCON(C_2H_5)_2$$

IV



$$C_6H_5\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}—CH_2CON(C_4H_9)_2$$

V

However, N,N-diethylacetamide and N,N-diethylpropionamide failed to condense satisfactorily with *p*-nitroacetophenone even on application of the inverse addition technique, which was previously applied successfully in corresponding condensations with esters.[3]

In most of these reactions, considerable amounts of the original ketones were recovered. This has been taken into account in the calculations of the yields of condensation products given in parentheses in Table I. The recovery of ketone may indicate either that the reaction time was not sufficient for complete condensation or that part of the ketone underwent, with the reactive intermediate, "enolization" involving an α-hydrogen of the ketone. Since the reaction of *p*-nitroacetophenone with the intermediate was permitted to proceed longer than usual and yet the ketone was largely recovered, enolization appears to have predominated. Such enolizations have been observed previously with lithio *t*-butyl isobutyrate and acetophenone,[3] and in certain Reformatsky reactions.[5]

The reaction of N,N-diethylacetamide with acetophenone was also effected by means of lithium

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(1) Paper XLIX on Condensations.

(2) Carbide and Carbon Chemicals Company Fellow, 1950–1952.

(3) C. R. Hauser and W. H. Puterbaugh, THIS JOURNAL, 75, 1068 (1953).

(4) Whereas isopropyl acetate gave a 54% yield of self-condensation product on treatment with lithium amide for 15 minutes in liquid ammonia followed by 40 minutes in ether at −70°, N,N-diethylacetamide gave none of its self-condensation product on treatment with lithium diethylamide for 40 minutes in ether at room temperature.

(5) See M. S. Newman, THIS JOURNAL, 64, 2131 (1942).

Table I

N,N-Dialkyl-β-hydroxyamides from N,N-Dialkylamides and Ketones

Amide, N,N-Diethyl	Ketone	Product, N,N-Diethyl-β-hydroxy	B.p. °C.	B.p. Mm.	Yield,[a] %		Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Acetamide	Acetophenone	β-Phenylbutyramide (I)	149–151	2	58	(84)	71.45	71.63	9.00	8.78	5.95	5.96
Acetamide	Cyclohexanone	Cyclohexylacetamide (II)[b]	124–127	1	47	(55)	67.56	67.94	10.87	10.99	6.57	6.59
Acetamide	Cyclopentanone	Cyclopentylacetamide (III)[b]	123–125	3	29	(36)	66.29	65.92	10.62	10.42	7.03	6.56
Propionamide	Acetophenone	α-Methyl-β-phenylbutyramide (IV)	142–144	1.5	69	(86)	72.25	72.11	9.30	9.28	5.62	5.58
N,N-Di-*n*-butylacetamide	Acetophenone	N,N-Di-*n*-butyl-β-hydroxy β-phenylbutyramide (V)	163–166	1	59	(76)					4.81	4.62

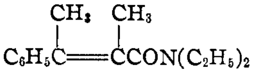
[a] The yield in parentheses is based upon the amount of ketone employed minus that recovered. [b] These compounds are generally named 1-hydroxy rather than β-hydroxy.

amide[6] and diethylaminomagnesium bromide[7] under essentially the same conditions employed with lithium diethylamide, but mixtures of products were obtained from which the β-hydroxyamide (I) was isolated in yields of only 23 and 12%, respectively. The lithium amide may have reacted partly with the carbonyl group of N,N-diethylacetamide to form acetamide.

β-Hydroxyamides I and IV were dehydrated by means of refluxing formic acid to form α,β-unsaturated amides VI and VII, respectively.

$$C_6H_5C(CH_3){=}CHCON(C_2H_5)_2$$

VI



$$C_6H_5C(CH_3){=}C(CH_3)CON(C_2H_5)_2$$

VII

Two of the β-hydroxyamides described above, II and III, have been prepared previously[8] by an extension of the Reformatsky reaction involving the action of zinc on mixtures of α-bromo-N,N-diethylacetamide and the appropriate ketone. The yields reported were 60% for II, and 14% for III. The first of these yields is somewhat higher, but the second considerably lower than those obtained by our method (see Table I). The other three β-hydroxyamides obtained by us, which were isolated in good yields (58–69%), were not made by the Reformatsky reaction. Since N,N-dialkylamides are more readily available than their α-bromo derivatives, our method appears more convenient than the modified Reformatsky reaction. Moreover, the latter method has been observed to produce lower yields when an alkyl substituent is present on the α-carbon of the α-bromo amide, whereas our method has given an 11% better yield with the propionamide than with the acetamide.

Experimental[9]

The compounds used in this study were obtained from commercial sources, except as designated below, and purified in the usual manner.

N,N-Diethylpropionamide was prepared by a modification of the method of Montagne.[10] To an ice-cold stirred solution of 73 g. (1.0 mole) of diethylamine in 100 ml. of dry benzene was added dropwise (4 hours), 46.3 g. (0.5 mole) of propionyl chloride in 100 ml. of dry benzene. After stirring 2.5 hours at room temperature and standing 6.5 hours longer, the mixture was cooled and shaken with ice-water. The benzene layer was washed with 2 *N* hydrochloric acid followed by brine, and, after combining with a benzene extract of the aqueous layer, dried over potassium carbonate. The solvent was removed and the residue distilled yielding 48.8 g. (76%) of product, b.p. 79.5–80.5° (13 mm.). Constant boiling amide was thus obtained without the centrifugation and treatment with warm potassium carbonate solution employed by Montagne.

Lithium phenyl solutions (1 *N*) were prepared and standardized according to the method described by Jones and Gilman.[11]

N,N-Dialkyl-β-hydroxyamides from N,N-Dialkylamides and Ketones.—In a 500-ml. three-necked round-bottomed flask (flame-dried and purged with nitrogen), equipped with a Friedrichs condenser, ground glass-sealed stirrer and separatory funnel (the system being protected with Drierite drying tubes) was placed 200 ml. (0.2 mole) of a 1 *N* ether solution of lithium phenyl. To the stirred liquid was added dropwise during 15–25 minutes a solution of 16.1 g. (0.22 mole) of diethylamine in an equal volume of ether. After stirring for an additional 15–30 minutes to ensure formation of the lithium diethylamide, a solution of 0.2 mole of N,N-diethylacetamide (or N,N-diethylpropionamide) in an equal volume of ether was added dropwise during 20–30 minutes. To the resulting lithio N,N-diethylacetamide (or lithio N,N-diethylpropionamide) was added dropwise during 20 minutes, 0.2 mole of the ketone in an equal volume of ether. After stirring and refluxing for 2 hours, the reaction mixture was cooled in an ice-bath and decomposed with 100 ml. of ice-cold 3 *N* hydrochloric acid. The ether layer was washed with 2 *N* hydrochloric acid, saturated sodium bicarbonate solution and water, and, after combining with ether extracts of the aqueous and acidic layers, dried over Drierite. The solvent was removed and the residue distilled *in vacuo*, the β-hydroxyamide and original ketone being isolated.

In a similar manner, N,N-di-*n*-butylacetamide was converted to its lithio derivative by means of lithium di-*n*-butylamine (prepared from lithium phenyl and di-*n*-butylamine), and the lithium derivative condensed with acetophenone.

The results are summarized in Table I.

Dehydration of N,N-Diethyl-β-hydroxyamides.—In a 200-ml. flask equipped with a reflux condenser was placed 20.0 g. (0.085 mole) of N,N-diethyl-β-hydroxy-β-phenylbutyramide and 75 ml. of 88% formic acid. The reaction mixture was refluxed for 3 hours, then poured into 150 ml. of ice-water and extracted with two 100-ml. and one 50-ml. portions of benzene. The benzene layer was washed twice with 50 ml. of saturated sodium carbonate solution and once with 50 ml. of water, and, after combining with a benzene extract of the aqueous layers, dried over Drierite. The solvent was removed and the residue distilled *in vacuo* to yield 14.8 g. (81%) of N,N-diethyl-β-methylcinnamamide, b.p. 142.5–145° (2 mm.) and at 135° (1 mm.) on redistillation.

Anal. Calcd. for $C_{14}H_{19}ON$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.37; H, 8.84; N, 6.45.

Similarly from 20.0 g. (0.0803 mole) of N,N-diethyl-β-

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[6] The N,N-diethylacetamide was added to the lithium amide in liquid ammonia, the ammonia replaced by ether, and the acetophenone added. The mixture was refluxed two hours and then worked up as usual.

[7] This reagent was prepared in ether from ethylmagnesium bromide and diethylamine (C. R. Hauser and H. G. Walker, This Journal, **69**, 295 (1947)) and refluxed with the N,N-diethylacetamide for two hours.

[8] N. L. Drake, P. Eaker and W. Shenk, *ibid.*, **70**, 677 (1948).

[9] Analyses by Clark Microanalytical Laboratories, Urbana, Ill. Melting points and boiling points are uncorrected.

[10] M. Montagne, *Ann. chim.*, [10] **13**, 48 (1930).

[11] R. G. Jones and H. Gilman, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 353.

hydroxy-α-methyl-β-phenylbutyramide and 75 ml. of 88% formic acid there was obtained 14.8 g. (80%) of N,N-diethyl-α,β-dimethylcinnamamide, b.p. 123–126° (1 mm.) and at 117–118° (0.75 mm.) on redistillation.

Anal. Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.06. Found: C, 77.40; H, 9.08; N, 6.02.

DURHAM, N. C.

[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE]

The Hydrolysis of Substituted Ethyl *p*-Biphenylcarboxylates

BY ERNST BERLINER AND LIANG HUANG LIU[1]

RECEIVED DECEMBER 18, 1952

The rates of hydrolysis of substituted ethyl *p*-biphenylcarboxylates have been determined at 25 and 40° and compared with those of substituted ethyl benzoates. The substituent effects are qualitatively the same in both systems, but the transmission of the effects is only about one-fourth as large in the biphenyl esters as in ethyl benzoates.

As a result of a study of the dissociation constants of various substituted *p*-biphenylcarboxylic acids,[2] it was concluded that substituent effects can be transmitted through the biphenyl system. Substituents in the ring not carrying the carboxyl group influence the dissociation constants qualitatively in the same way in which the same substituents influence the dissociation constants of benzoic acids. Quantitatively the transmission is appreciably less in the biphenyl than in the benzene system, *i.e.*, rho[3] is only about one-third as large for the dissociation of biphenylcarboxylic acids as for benzoic acids. Because dissociation constants are concerned with permanent polarities only, it seemed worthwhile to study the behavior of the biphenyl system in a chemical reaction, where polarizability effects can also be observed. In order to make the comparison between the benzene and the biphenyl structure expressible in terms of the reaction constant, ρ, the rates of the alkaline hydrolysis were determined for the esters of those substituted biphenylcarboxylic acids whose dissociation constants had previously been measured.

In Table I are listed second-order rate constants at 25 and 40° for the alkaline hydrolysis of these esters, as well as energies of activation and log *PZ* factors. The reactions were conducted with equal concentrations of ester and hydroxide ion in 88.7% by weight aqueous ethanol. The conditions were similar to those employed by Evans, Gordon and Watson,[4] and by Kindler,[5] except that the alcohol concentration was somewhat larger, because of the low solubility of some of the esters.

TABLE I

RATES OF HYDROLYSIS OF SUBSTITUTED ETHYL *p*-BIPHENYLCARBOXYLATES IN 88.7% ETHANOL

Substituent	$k_2^{25} \times 10^4$, l.m.$^{-1}$ sec.$^{-1}$	$k_2^{40} \times 10^3$, l.m.$^{-1}$ sec.$^{-1}$	*E*, kcal.	log *PZ*, l.m.$^{-1}$ sec.$^{-1}$
4'-OCH_3	3.55 ± 0.03	1.56 ± 0.005	18.3 ± 0.2	9.96
4'-CH_3	4.37 ± .05	1.90 ± .02	18.2 ± .3	9.98
4'-H	5.50 ± .06	2.32 ± .02	17.8 ± .2	9.79
4'-Cl	7.52 ± .05	3.13 ± .02	17.6 ± .2	9.78
4'-Br	7.60 ± .05	3.18 ± .01	17.7 ± .2	9.85
3'-Br	9.32 ± .1	3.88 ± .03	17.6 ± .2	9.87
3'-NO_2	....	5.95 ± .03	....	...
4'-NO_2	15.8 ± .15	6.58 ± .05	17.6 ± .2	10.10

The substituents have the same qualitative effect on the biphenyl esters that they have on ethyl benzoate hydrolysis. The rate-determining step is a nucleophilic attack, and the favorable effect of electron-attracting groups is relayed through the two benzene rings. The 4'-methoxy compound is the slowest and the 4'-nitro compound the fastest, even though the over-all spread between these two extreme compounds is considerably less than in the corresponding ethyl benzoates. The spread in activation energies between the fastest and the slowest compounds is only 0.7 kcal., compared to 4.15 kcal. in benzoate hydrolysis,[6] but the log *PZ* factors are of similar magnitude, indicating no unusual differences in a steric sense between the two systems. Although the differences in activation energies are small, the general pattern of rate differences being determined by differences in activation energies, with the log *PZ* factors remaining constant, is discernible.

When the logarithms of the rate constants are plotted against Hammett's σ-values, the usual linear relationship is obtained (Fig. 1).[3] The least square line has a slope (ρ) of $+0.623$ with a median deviation of 0.0089. At 40°, ρ is $+0.594$ and r is 0.0066. The most comparable literature data for the alkaline hydrolysis of substituted ethyl benzoates at 25° are those reported for reaction in 85% by weight ethanol.[4,6] For that reaction ρ is calculated to be $+2.567$ ($n = 14$, $r = 0.043$). Assuming that the small difference in solvent composition will not alter ρ appreciably, in ester hydrolysis the biphenyl system transmits only about one-fourth as much of the effect of substituents as can be relayed through the benzene system, compared to the value of one-third found in the case of the dissociation constants.

It might have been expected that the relative ρ-values for dissociation constants and ester hydrolysis would be more nearly alike. However, in Table II are collected data for similar systems, in which ρ-values for dissociation constants are compared with those of ester hydrolysis. The reaction constant for the hydrolysis of ethyl phenylpropionates was calculated from the data of Kindler,[7]

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[1] Helen Schaeffer Huff Memorial Post-doctorate Fellow, 1949–1950.

[2] E. Berliner and E. A. Blommers, THIS JOURNAL, **73**, 2479 (1951).

[3] L. P. Hammett, "Physical Organic Chemistry," McGraw–Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII.

[4] D. P. Evans, J. J. Gordon and H. B. Watson, *J. Chem. Soc.*, 1430 (1937).

[5] K. Kindler, *Ann.*, **450**, 1 (1926).

[6] C. K. Ingold and W. S. Nathan, *J. Chem. Soc.*, **222** (1936).

[7] K. Kindler, *Ann.*, **452**, 90 (1927). ρ is $+0.488$, n is 4 and r is 0.025.