urea concentration was increased, either by direct addition of urea or by evaporation of the solution.

TABLE II

ENZYMATIC HYDROLYSIS

Expt.	Buffer	Concn. of added urea soln., %	Ammonia nitrogen direct, mg.	Ammonia nitrogen after acidification, mg.
1	1 Vol. 3%	1	0.22	0.22
2	NaOAc +	3	.29	.29
3	1 Vol. N	5	.28	.27
4	HOAc	10	.28	.29
5	3 Vol. 3%	1	.23	.25
6	NaOAc +	3	.30	.34
7	1 Vol. N	5	.29	.38
8	HOAc	10	.28	.40
9		1	.17	.17
10		3	.16	.20
11	3% NaOAc	5	.13	.20
12		10	.11	.16

In the enzymatic hydrolysis, the amount of ammonia obtained on nesslerization after acidification is greater than that obtained on direct nesslerization only in the more alkaline solutions (Table II). Since neither cyanate nor carbamate can be detected in the decomposition of urea by urease in acetate buffer,[5] and since the increased ammonia production is shown only in the more concentrated urea solutions (a fact which would not be expected if cyanate or carbamate were the cause of the increase), the increase in ammonia on acidification might be postulated as due to the presence of the ammonia–urea compound in the alkaline solution.

It should be noted that inhibition of urease activity occurs only under those conditions which give rise to increased ammonia production on acidification, and these conditions are those which would be expected to favor the formation of the ammonia–urea compound, *i.e.*, higher urea concentrations and higher alkalinity. It might be postulated, then, that the ammonia–urea compound is the real inhibitor of urease activity. Howell and Sumner's[1] results are in agreement with this postulate.

Summary

In an alkaline solution containing higher concentrations of urea, a portion of the ammonia present can be detected by Nessler reagent only if the solution is first acidified. This effect can be postulated as due to the presence of the compound $NH_3 \cdot CO(NH_2)_2$ in the alkaline solution.

The hydrolysis of urea by urease in acetate buffer solution is not inhibited by higher urea concentrations if the *p*H is sufficiently low; under these conditions no increase in ammonia is obtained if the solution is acidified before nesslerization. If the hydrolysis is carried out in more basic solutions, inhibition of urease activity with increasing urea concentrations is observed, and increased ammonia production on acidification before nesslerization is found at the higher urea concentrations.

The results can be explained if it is assumed that the compound $NH_3 \cdot CO(NH_2)_2$ is present at higher urea concentrations and that it acts as an inhibitor of urease activity.

PHILADELPHIA 40, PA. RECEIVED SEPTEMBER 18, 1946

(5) J. B. Sumner, D. B. Hand and R. G. Holloway, *J. Biol. Chem.*, **91**, 333 (1931).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Condensation of Certain Esters by Means of Diethylaminomagnesium Bromide[1,2]

BY CHARLES R. HAUSER AND HOWARD G. WALKER, JR.

Diethylaminomagnesium bromide may react with carboxylic esters either at the α-hydrogen to effect their condensations or at the carbonyl carbon to produce the corresponding N,N-diethylamides. These two courses of reaction with alkyl acetates may be represented as

$$2CH_3CO_2R \xrightarrow{(C_2H_5)_2NMgBr} CH_3COCH_2CO_2R + ROH$$

$$CH_3CO_2R + (C_2H_5)_2NMgBr \longrightarrow CH_3CON(C_2H_5)_2 + Mg(OR)Br$$

We have self-condensed various esters by means of the magnesium reagent the results for which are summarized in Table I. The resulting β-keto esters were obtained free from the amide, as determined by qualitative tests for nitrogen,[3] with the exception of that from ethyl *n*-butyrate. The β-keto ester from this ester was evidently contaminated with the amide, which was not removed by simple fractionation; on ketonic cleavage in the presence of acid[4] the crude product yielded mainly di-*n*-propyl ketone and a substance assumed to be the amide. Attempts to self-condense ethyl *i*-butyrate or ethyl *i*-valerate were unsuccessful; the products appeared to consist mainly of the corresponding amide, since they failed to decarboxylate appreciably and gave strong tests for nitrogen.

(1) Paper XXXVIII on "Condensations"; paper XXXVII, THIS JOURNAL, **69**, 119 (1947).

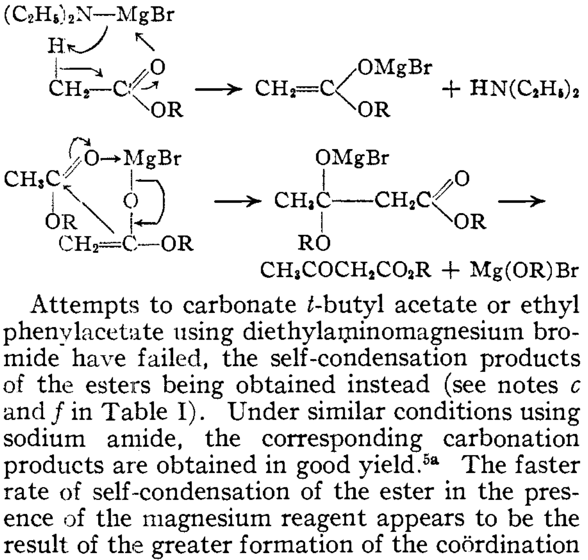
(2) This work was supported in part by a grant from the Duke University Research Council.

(3) Moreover, no diethylamine could be detected when the product from the self-condensation of ethyl propionate was boiled with concentrated sodium hydroxide solution.

(4) Hudson and Hauser, THIS JOURNAL, **63**, 3163 (1941).

Although the yields of certain of the condensation products have been less than 50%, it appears that diethylaminomagnesium bromide reacts mainly with the α-hydrogens of ethyl phenylacetate, the alkyl acetates, ethyl propionate, *t*-butyl *n*-butyrate and even ethyl *n*-butyrate, but largely with the carbonyl carbons of ethyl isobutyrate and ethyl isovalerate. These observations, in general, parallel those reported recently for sodium amide,[5] except that the magnesium reagent effects relatively more of the α-hydrogen reaction and relatively less of the carbonyl carbon reaction with ethyl propionate and probably also with ethyl *n*-butyrate.

The mechanism for the condensations with diethylaminomagnesium bromide is considered to involve the usual three steps,[6] conversion of part of the ester to its magnesium derivative (enolate), condensation of the enolate with unchanged ester, and the conversion of the resulting β-keto ester to its magnesium enolate. However, these steps appear to take place through the primary formation of coördination complexes and the operation of an ephemeral ring type of mechanism.[7] The first two steps may be represented as[8]



Attempts to carbonate *t*-butyl acetate or ethyl phenylacetate using diethylaminomagnesium bromide have failed, the self-condensation products of the esters being obtained instead (see notes *c* and *f* in Table I). Under similar conditions using sodium amide, the corresponding carbonation products are obtained in good yield.[5a] The faster rate of self-condensation of the ester in the presence of the magnesium reagent appears to be the result of the greater formation of the coördination complex between the magnesium enolate and the ester as represented above in the second step; this allows the α-carbon of the enolate to approach readily the carbonyl carbon of the ester with which it condenses. The sodium enolate may form the analogous coördination complex but to a smaller extent. Of course the greater ether solubilities of the magnesium derivatives may also be an important factor.

Diethylaminomagnesium bromide should be a useful laboratory reagent for the self-condensations of several of the esters, especially ethyl propionate[9] and *t*-butyl *n*-butyrate.[10] The magnesium reagent is also capable of effecting certain mixed ester condensations. Thus, *i*-propyl acetate has been acylated with phenyl benzoate to form *i*-propyl benzoylacetate. However, this β-keto ester was contaminated with N,N-diethylbenzamide, which probably resulted from reaction of the reagent with phenyl benzoate. The β-keto ester was identified by ketonic cleavage to acetophenone.

In contrast to diethylaminomagnesium bromide, the potentially weaker basic reagent, methylanilinomagnesium bromide, reacts with ethyl propionate to form the corresponding amide. Bodroux[11] found that anilinomagnesium bromide reacts in a similar manner. This influence of the potential basic strength of the magnesium reagents on the two courses of reaction is paralleled with basic anions; for example, the amide ion[5] reacts with the α-hydrogen of ethyl phenylacetate whereas the weaker basic anion, hydroxyl ion, reacts with the carbonyl carbon (alkaline hydrolysis).

Experimental

Self-condensations of Esters.—In a 500-ml., three-necked flask equipped with a mercury-sealed stirrer (Hershberg), dropping funnel and reflux condenser (having drying tube), was placed 100 ml. (0.20 mole) of a two molar ether solution of ethylmagnesium bromide,[12] and the flask immersed in an ice-bath. To the stirred solution was added 0.20 mole (14.6 g., 20.6 ml.) of dry diethylamine in 20 ml. of dry ether,[13] and the mixture stirred for about fifteen minutes longer to complete the formation of diethylaminomagnesium bromide.[14] The ester (0.20 mole) in 50 ml. of dry ether was then added as

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[5] (a) Hauser, Levine and Kibler, THIS JOURNAL, **68**, 26 (1946); (b) Shivers, Dillon and Hauser, *ibid.*, **69**, 119 (1947).

[6] See Hauser and Hudson, "Organic Reactions," Roger Adams, editor-in-chief, John Wiley and Sons, Inc., New York, N. Y., 1942, Chap. IX.

[7] See Johnson, "Organic Chemistry," Vol. II, 2nd ed., Henry Gilman, editor-in-chief, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 1880–1881.

[8] Although only one equivalent of diethylaminomagnesium bromide to two of the ester enters into reaction in the first two steps, a second equivalent of the magnesium reagent is neutralized in the third step. Hence, as in condensations with sodium amide (ref. 5), or sodium triphenylmethide (ref. 6), the magnesium reagent should be capable of condensing only an equivalent of an ester. Actually, only a 28% yield has been obtained from ethyl propionate and one-half of an equivalent of the magnesium reagent.

[9] Ethyl propionate has been condensed in slightly higher yield with sodium ethoxide under forced conditions. [Roberts and McElvain, THIS JOURNAL, **59**, 2007 (1931)] but we believe the reaction is effected more conveniently with the magnesium reagent.

[10] It is doubtful whether the good yield obtained from *t*-butyl *n*-butyrate could be duplicated conveniently using sodium amide or sodium *t*-butoxide, since, at least with sodium amide, esters of this type apppear to undergo self-condensation very slowly (see ref. 5a).

[11] Bodroux, *Compt. rend.*, **138**, 1427 (1904).

[12] This solution may be prepared conveniently by siphoning under nitrogen pressure a more concentrated solution of ethylmagnesium bromide prepared in the usual manner, to a graduated glass stoppered bottle (stopper well greased), titrating this solution, and diluting it with sufficient ether to bring the concentration to exactly 2 *M*.

[13] Since the reaction may not start immediately and yet may suddenly become vigorous, it was found expedient to add first only a small amount of the diethylamine solution. After the reaction had started the remainder of the solution was added as rapidly as possible.

[14] A test for the presence of the Grignard reagent in a sample of the reaction mixture at the end of this time using Michler's ketone was negative. Ziegler and Ohlinger [*Ann.*, **495**, 84 (1932)] prepared this reagent in a similar manner.

TABLE I

SELF CONDENSATIONS OF ESTERS BY $(C_2H_5)_2NMgBr$

Ester	β-Keto ester	B. p. °C. uncor.	Mm.	Yield, %
Ethyl phenylacetate	Ethyl α,γ-diphenylacetoacetate[a]	75–76	M. p.[b]	62[c]
t-Butyl acetate	*t*-Butyl acetoacetate[a]	76–78	15[d]	55[e,f]
n-Amyl acetate	*n*-Amyl acetoacetate[a]	138–140	50[g]	35[h]
Benzyl acetate	Benzyl acetoacetate[a]	155–157	15[i]	36[h]
Ethyl propionate	Ethyl α-*n*-propionylpropionate[a]	91–92.5	19[j]	76
Ethyl *n*-butyrate	Ethyl α-*n*-butyryl-*n*-butyrate[m]	94–102	12[k]	..
t-Butyl *n*-butyrate	*t*-Butyl α-*n*-butyryl-*n*-butyrate[a]	102.5–105	10[l]	53[e]

[a] Product gave a negative test for nitrogen. [b] After further recrystallization the m. p. was 77–78° in agreement with that reported by Shivers, Hudson and Hauser, THIS JOURNAL, **65**, 2051 (1943). [c] In an experiment in which excess Dry Ice was added to the reaction mixture immediately after adding the ester, the β-keto ester was obtained in 56% yield; none of the carbonation product, ethyl α-phenyl hydrogen malonate was found. [d] See ref. in note *b*. [e] Reaction time was two hours. [f] On attempted carbonation (as described in note [c]), the β-keto ester was obtained in 38% yield. Titration of a sample of reaction product indicated that the carbonation product, *t*-butyl hydrogen malonate, was not formed in more than 5% yield. [g] J. C. Shivers, Ph.D. Thesis, Duke University. [h] A considerable amount of the ester was recovered. [i] *Anal.* Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.73; H, 6.07 (analysis by T. S. Ma, Chicago, Ill.). [j] Reported b. p., 92–93° at 20 mm. [Dieckmann and Kron, *Ber.*, **41**, 1269 (1908)]. Our product, on ketonic cleavage (ref. 4), gave a good yield of diethyl ketone which was identified by its 2,4-dinitrophenylhydrazone, m. p. 155–156° [Huntress and Mulliken, John Wiley and Sons, Inc., New York, N. Y., 1941]. [k] Reported b. p., 102–105° at 12 mm. (ref. 9). On ketonic cleavage (ref. 4) our product gave a 41% yield (based on the original ester) of di-*n*-propyl ketone (b. p., 142–146°) and a 9% yield of a substance presumed to be N,N-diethyl-*n*-butyramide boiling at 89° at 12 mm. [reported b. p., 92° at 12 mm., v. Braun and Heymans, *Ber.*, **62**, 411 (1929)]. [l] *Anal.* Calcd. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.03; H, 10.42 (analyses by Arlington Laboratories, Fairfax, Va.). [m] Product gave a positive test for nitrogen.

rapidly as feasible. Even though the flask was immersed in an ice-bath, the reaction tended to become very vigorous if the ester was added too rapidly. The ice-bath was replaced by a steam-cone and the mixture refluxed for thirty minutes except where otherwise indicated in Table I. The mixture was poured onto 150 g. of ice and 12.5 ml. of concentrated sulfuric acid and the flask rinsed with some of the solution. After acidification, the ether phase was separated and the aqueous phase extracted twice more with ether. The combined ether solution was washed with water and then with saturated sodium bicarbonate solution, dried with sodium sulfate followed by drierite, and the solvent distilled. The residue was distilled *in vacuo* or recrystallized. The products were tested qualitatively for nitrogen by the sodium fusion method,[15] and certain of them were subjected to ketonic cleavage in the presence of acid.[4] The amide apparently failed to hydrolyze appreciably under the conditions employed for this cleavage.

Mixed Ester Condensation.—A mixture of 0.20 mole of *i*-propyl acetate and 0.20 mole of phenyl benzoate was added to 0.40 mole of diethylaminomagnesium bromide reagent. After stirring for thirty minutes, the reaction mixture was worked up as described for the self-condensation of esters. The product (21.1 g.), boiling at 155–158° at 15 mm., evidently consisted of approximately three-quarters of isopropyl benzoylacetate (reported b. p. 158–158.5° at 15 mm.)[5b] which produced on ketonic cleavage a 75% yield of acetophenone (b. p. 93.5–95.5° at 20 mm.).[5b] The other one-quarter of the product consisted of a nitrogen containing substance (b. p. 150–151° at 15 mm.), presumably N,N-diethylbenzamide, which was recovered after the ketonic cleavage.

Anal. Calcd. for $C_{11}H_{15}ON$: N, 7.91. Found: N, 7.69.

Reaction of Methylanilinomagnesium Bromide and Ethyl Propionate.—When methylaniline was substituted for diethylamine and the self-condensation of ethyl propionate attempted using the procedure described above for the self-condensation of esters, the only product isolated was propionyl methylaniline, melting at 55–56°[16] (yield, 57%). The ethereal solution containing all the crude reaction products failed to give an enol test indicating self-condensation of the ester did not take place.

Summary

1. Diethylaminomagnesium bromide effects the self-condensation of certain esters to form the corresponding β-keto esters. The reaction is remarkably rapid. A cyclic mechanism is suggested.

2. Although ethyl propionate is self-condensed by diethylaminomagnesium bromide, it reacts with methylanilinomagnesium bromide to form the corresponding amide.

3. Diethylaminomagnesium bromide effects the mixed ester condensation between phenyl benzoate and isopropyl acetate.

4. These results are compared with those with sodium amide and certain other bases.

DURHAM, NORTH CAROLINA

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(15) Shriner and Fuson, "Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 114, procedure C.

(16) Norton and Allen [*Ber.*, **18**, 1998 (1885)] report the m. p. 58.5°.