bonate-free alkali solutions were prepared by carefully pipetting the required amounts of clear solution from above the precipitated carbonate of a saturated sodium hydroxide solution. These were diluted with freshly boiled water and standardized against potassium acid phthalate using brom thymol blue. The approximately 0.05*N* hydrochloric acid was standardized with standard alkali.

General Kinetic Procedure.—The method was similar to that of Tommila and Hinshelwood.[12] The specific rates were determined by mixing equal volumes of alkali and ester solutions of the same concentration at the desired temperature, withdrawing aliquots at specific time intervals and quenching these in an excess of standard acid. The excess acid was back-titrated with standard base (*ca.* 0.03 *N*) using brom thymol blue.

The 70% acetone solution of alkali was prepared by diluting exactly 30.00 ml. of aqueous standard sodium hydroxide (*ca.* 0.1*N*) to 100 ml. of solution at 25° using purified acetone.

The ester solution was made by weighing on counterpoised watch glasses a quantity of ester exactly equivalent to 30.00 ml. of the standard alkali. This ester was quantitatively transferred to a 100-ml. volumetric flask with acetone; 30 ml. of water was added and the solution brought to volume at 25° with acetone.

Mixing was effected by simultaneously pouring the solutions through a powder funnel into a 250-ml. ground-glass stoppered erlenmeyer flask. An aliquot was withdrawn immediately, quenched in an ice-cold mixture of 5 ml. of standard hydrochloric acid and 10 ml. of acetone and back-titrated against standard alkali. Zero time was considered to be the contact time of this first aliquot and all time intervals were determined in a similar manner. The concentration of alkali in this first aliquot was considered to be the initial concentration (*a*). A total of 6 to 10 aliquots were withdrawn from each reaction mixture, following the first 30–50% reaction. The second-order rate constants were calculated from the customary equation for equal initial concentrations.

NOTRE DAME, INDIANA

(12) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1802 (1938).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, IOWA STATE COLLEGE]

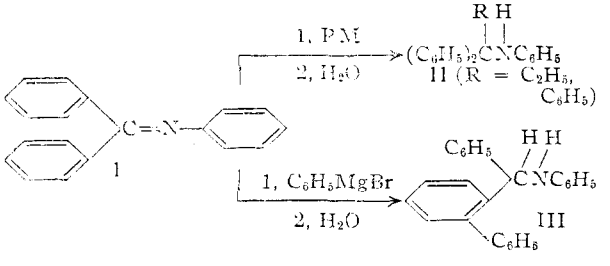
1,2-Addition of Allylmagnesium Bromide to N-Diphenylmethyleneaniline and Structurally Related Systems

BY HENRY GILMAN AND JOHN EISCH

RECEIVED NOVEMBER 24, 1956

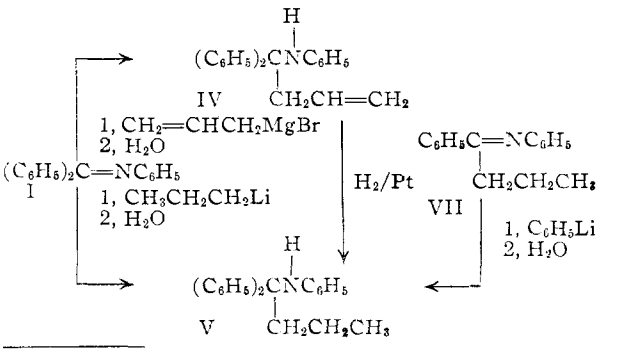
Allylmagnesium bromide readily added in a 1,2-manner to the structurally related systems, N-diphenylmethyleneaniline (I), fluorenone anil (VIII) and 6-phenylphenanthridine (IX). The structure of the product from I was demonstrated by an unambiguous synthesis. The mechanism of 1,2-addition to the azomethine linkage is discussed and an explanation is advanced for the abnormal 1,4-addition of phenylmagnesium bromide to I.

The interaction of organometallic compounds with the –C=N– linkage in N-diphenylmethyleneaniline (I) (benzophenone anil) has received considerable study due to the peculiar behavior of this system. Although the organometallic compounds of lithium,[1,2] potassium,[3] sodium,[3] calcium,[4] barium[2] and strontium[2] add to the system in a 1,2-manner (II), the ordinary Grignard reagents fail to react with this azomethine linkage in refluxing ether.[5,6] Indeed, when the reaction between phenylmagnesium bromide and N-diphenylmethyleneaniline is forced by running it in ether–toluene solution at 90–105°, the only isolable product is the result of an apparent 1,4-addition (III).[5]



Previous studies in this Laboratory have demonstrated that the allyl Grignard reagent in its interactions with aza-aromatic heterocycles exhibits an exceptionally high order of reactivity when compared with that of ordinary Grignard reagents.[7] Consequently, its behavior with N-diphenylmethyleneaniline was investigated in order to see whether it would parallel the behavior of phenyllithium or phenylmagnesium bromide toward this system.

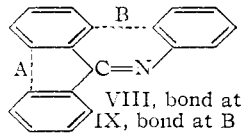
Surprisingly enough, it was found that allylmagnesium bromide reacted readily with N-diphenylmethyleneaniline in refluxing ether to give a 95% yield of product which was shown to be 1-allyl-1,1-diphenylmethylaniline (IV) in the following rigorous manner. By catalytic hydrogenation it was converted to the same substance (V) as obtained by the interaction of propyllithium and N-diphenylmethyleneaniline. Although this demonstrated that both reagents reacted with N-diphenylmethyleneaniline in the same manner, confirmation that indeed 1,2-addition had taken place was obtained by synthesizing V unambiguously.



(1) Gilman and R. H. Kirby, THIS JOURNAL, **57**, 1267 (1935).
(2) Gilman, Haubein, O'Donnell and Woods, *ibid.*, **67**, 922 (1945).
(3) Gilman and R. H. Kirby, *ibid.*, **63**, 2046 (1941).
(4) Gilman, R. H. Kirby, Lichtenwalter and Young, *Rec. trav chim.*, **55**, 79 (1936).
(5) Gilman, J. E. Kirby and Kinney, THIS JOURNAL, **51**, 2252 (1929).
(6) Short and Watt, *J. Chem. Soc.*, 2293 (1930).
(7) Gilman, Eisch and Soddy, THIS JOURNAL, **79**, 1245 (1957).

Thus butyrophenone (VI) was converted to its anil VII and the latter compound treated with phenyllithium. The 1-propyl-1,1-diphenylmethylaniline obtained upon hydrolysis was identical with that from the hydrogenation of IV.

The ease with which N-diphenylmethyleneaniline reacted with allylmagnesium bromide suggested that the azomethine linkage in related compounds also would be attacked readily. Chosen for this study were fluorenone anil (VIII) and 6-phenylphenanthridine (IX), as the former is formally derived from N-diphenylmethyleneaniline by forming bond A, while the latter results from forming bond B.

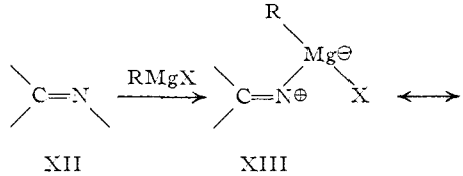


VIII, bond at A
IX, bond at B

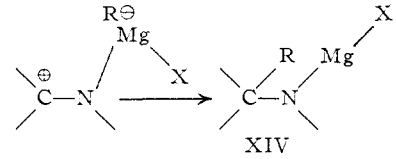
Allylmagnesium bromide added to the azomethine linkage of fluorenone anil extremely rapidly to yield α-allylfluorenylaniline (X) in 93% yield. 6-Phenylphenanthridine was attacked somewhat less readily to give 6-allyl-6-phenyl-5,6-dihydrophenanthridine (XI) in 67% yield. In the latter case it is remarkable that this endocyclic azomethine linkage reacts with such facility with this Grignard reagent. Previous studies have shown that the unsubstituted phenanthridine also has a heightened reactivity toward allylmagnesium bromide in comparison with pyridine, quinoline and isoquinoline.[7]

Based upon the previously observed behavior of N-diphenylmethyleneaniline with phenyllithium and with phenylmagnesium bromide, it was suggested that the abnormal 1,4-addition of the latter reagent might be owed to the greater steric demands of the Grignard reagent.[1,5] Subsequently, it was found that phenylcalcium iodide reacted with N-diphenylmethyleneaniline in a 1,2-manner[4] and this fact seriously weakened the case for steric hindrance. The steric bulk of the calcium and iodine atoms was not reflected in the mode of addition. In the course of studies employing N-diphenylmethyleneaniline and benzalacetophenone to index the reactivity of related organometallic compounds, it was concluded that the more reactive organometallic reagents added in a 1,2-manner, while the less reactive tended to add in a 1,4-fashion.[3] The present study shows that allylmagnesium bromide may well be classified among the more reactive organometallic reagents and that not only the metal but also the organic moiety can greatly influence the reactivity of the composite organometallic reagent. In support of this conclusion N-diphenylmethyleneaniline was allowed to react, in turn, with methylmagnesium iodide[6,8] and with propylmagnesium bromide under the conditions so successful with allylmagnesium bromide. However, almost all starting material was recovered with no sign of reaction.

In light of present knowledge it seems reasonable to view the mechanism of 1,2-addition to the azomethine linkage as proceeding through a nucleophilic attack of the organic anion of the reagent on the positive-polarized carbon atom adjacent to the nitrogen. The resonance stabilization of the allylic anion in allylmagnesium bromide seems to favor heterolysis of the magnesium–carbon bond and hence rationalizes the greater reactivity of this Grignard reagent. With certain organometallic reagents, especially those of the alkaline earth metals, it is quite probable that the reagent preliminarily complexes with the nitrogen[9] (XII → XIV).

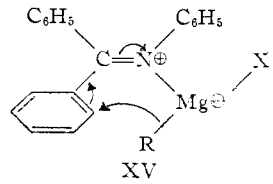


XII XIII



XIV

The abnormal 1,4-addition to N-diphenylmethyleneaniline by phenylmagnesium bromide can also be considered as a nucleophilic attack of R⊖ at the *o*-position of the benzene ring proceeding through a six-membered cyclic complex (XV). However,



XV

the stringent conditions necessary to obtain such a reaction make it quite probable that here radical processes play a part. Thus Kharasch, Goldberg and Mayo[10] have shown that aromatic Grignard reagents when heated in aromatic solvents yield products indicative of attack by aromatic radicals. It is therefore conceivable that 1,4-addition on N-diphenylmethyleneaniline may proceed by attack of phenyl radicals and that other phenylated isomers may also be formed.

Experimental

The melting points were determined on an electrically heated copper block and are corrected. Operations involved in the preparation and reactions of organometallic compounds were conducted in an atmosphere of dry oxygen-free nitrogen.

1-Allyl-1,1-diphenylmethylaniline (IV).—To 43.3 g. (0.169 mole) of N-diphenylmethyleneaniline partially dissolved in 100 ml. of dry ether was added 0.215 mole of allylmagnesium bromide[11] in 190 ml. of ether. During the 25-minute addition period the N-diphenylmethyleneaniline dissolved and spontaneous reflux set in. Toward the end, however, a white solid settled out of solution. After the mixture was stirred at the reflux temperature for 18 hours, it was hydrolyzed with 500 ml. of saturated ammonium chloride solution. The pale yellow ethereal layer, upon separation

(8) Maginnity and Cloke, THIS JOURNAL, **73**, 49 (1951), as well as Short and Watt (ref. 6) have isolated only starting material from the reaction between N-diphenylmethyleneaniline and methylmagnesium iodide.

(9) Sachs and Sachs, *Ber.*, **37**, 3088 (1904).

(10) Kharasch, Goldberg and Mayo, THIS JOURNAL, **60**, 2004 (1938).

(11) Gilman and McGlumphy, *Bull. soc. chim. France*, **43**, 1325 (1928).

and drying with anhydrous sodium sulfate, was distilled to remove the solvent. Chilling of the residual oil gave 48.1 g. (95%) of light tan solid, melting over the range 72–78°. Recrystallization from 200 ml. of 95% ethanol afforded 44.0 g. (87%) of white, close-packed crystals, m.p. 78.5–80°, and further recrystallizations did not alter the melting point.

Anal. Calcd. for $C_{22}H_{21}N$: N, 4.67. Found: N, 4.70.

The infrared spectrum in bromoform exhibited a sharp –NH band at 3.0 μ, but did not indicate the presence of any disubstituted benzene ring.

1-Propyl-1,1-diphenylmethylaniline (V). (a) From Propyllithium and N-Diphenylmethyleneaniline.—Propyllithium was prepared in 83% yield by adapting the published directions for butyllithium.[12] Over a period of 45 minutes, 0.097 mole of propyllithium in 90 ml. of ether was added to 20.0 g. (0.078 mole) of N-diphenylmethyleneaniline in 50 ml. of dry ether. The initially yellow suspension changed to a dark red solution accompanied by spontaneous reflux. The solution was refluxed for six hours and then stirred overnight without heating. The reaction mixture was hydrolyzed with water and the pale green ethereal layer was separated and dried. Removal of the ether left 21.2 g. (91%) of pale green solid, melting over the range 69–74°. Recrystallization from 100 ml. of 95% ethanol (Norit) gave 18.0 g. (77%) of white solid, m.p. 83–84.5°. The analytical sample was obtained by successive recrystallizations from ethanol, m.p. 85–85.5°. It was observed that the purer samples were very sluggish to crystallize out of solution.

Anal. Calcd. for $C_{22}H_{23}N$: N, 4.64. Found: N, 4.73.

The infrared spectrum in bromoform had a distinct band at 3.0 μ, but as with the product from allylmagnesium bromide and N-diphenylmethyleneaniline, no bands indicative of a disubstituted benzene ring.

(b) From 1-Allyl-1,1-diphenylmethylaniline (IV).—The hydrolyzed allyl Grignard adduct of N-diphenylmethyleneaniline was correlated with the hydrolyzed propyllithium adduct by reducing the former to the latter.

In the hydrogenation flask were placed 30 mg. of platinum(IV) oxide (Adams catalyst) and 50 ml. of 95% ethanol. After the catalyst was reduced, 3.0 g. (0.010 mole) of 1-allyl-1,1-diphenylmethylaniline and 50 ml. of ethyl acetate were added. The compound was hydrogenated until one molar equivalent of hydrogen had been taken up. The filtered solution upon concentration and refrigeration gave 2.5 g. (83%) of a cream-colored solid, m.p. 83–85°. This was shown to be identical with the 1-propyl-1,1-diphenylmethylaniline prepared in part a by a mixture melting point determination and comparison of infrared spectra. This verified that allylmagnesium bromide and propyllithium both added to N-diphenylmethyleneaniline in the same fashion. It remained to be confirmed that this was 1,2-addition.

(c) From Butyrophenone Anil (VII).—Phenyllithium was prepared in 99% yield according to published directions[13] by the interaction of 2.2 g. (0.33 g. atom) of lithium wire and 22.8 g. (0.145 mole) of bromobenzene in dry ether.

To 0.144 mole of phenyllithium in 100 ml. of dry ether was added a solution of 15.5 g. (0.069 mole) of butyrophenone anil in 75 ml. of dry ether over the course of 50 minutes. The mixture was stirred for four hours and then hydrolyzed. The ether layer upon separation, drying and removal of the solvent gave 22 g. of a somewhat sticky, pale yellow solid. After recrystallization from 100 ml. of 95% ethanol 12.4 g. (59%) of cream-colored solid was obtained, m.p. 80–83°. Additional recrystallizations from ethanol gave a white product, m.p. 83–84°. This solid was identical with the 1-propyl-1,1-diphenylmethylaniline obtained in parts a and b, as evidenced by mixture melting points and infrared spectra.

Butyrophenone (VI).—This compound was conveniently prepared by adaptation of procedures for the preparation of other aliphatic-aromatic ketones.[14]

To 0.60 mole of filtered propylmagnesium bromide in 600 ml. of ether was added a solution of 50.0 g. (0.485 mole) of redistilled benzonitrile in 60 ml. of dry ether during a 45-minute period. The dark yellow solution was refluxed overnight and subsequently poured into a mixture of 200 ml. of 6 *N* sulfuric acid and ice. The biphasic mixture was heated to distil off the ether and to hydrolyze the ketimine. The cooled mixture was then extracted with ether. The extracts were dried over anhydrous sodium sulfate and the ether distilled off. The residual oil was distilled under reduced pressure to yield 64.0 g. (90%) of colorless butyrophenone, b.p. 106.5–107° (13 mm.), lit.[14] b.p. 128° (27 mm.).

Butyrophenone Anil (VII).—This procedure is adapted from Reddelien's directions for acetophenone anil.[15] The necessary aniline–zinc chloride complex was prepared by adding 25 ml. of freshly distilled aniline to a solution of 25.0 g. of zinc chloride dihydrate in 40 ml. of water, 20 ml. of ethanol and 10 ml. of concentrated hydrochloric acid. The white suspension was stirred thoroughly and then filtered. The solid was washed twice with ether and upon drying the white complex weighed 30.0 g.

Freshly distilled aniline (30 ml.) and butyrophenone (30.0 g., 0.202 mole) were heated up to 100° (oil-bath) in a distillation flask. Two grams of the powdered aniline–zinc chloride complex was introduced and the bath temperature was raised slowly to 160° where it was maintained for 15 minutes. Steam began to evolve and continued to do so when the temperature was raised to 180° and held there for 30 minutes. The cooled reaction mixture was taken up in 200 ml. of chloroform and the undissolved zinc salts were filtered off. The filtrate was distilled to remove, in turn, chloroform and then the excess aniline and butyrophenone. Finally the butyrophenone anil came over as a clear yellow liquid weighing 15.8 g. (35% conversion), b.p. 183–185° (13 mm.), 128° (1.1 mm.), $n^{25}D$ 1.5926.

Anal. Calcd. for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 85.96; H, 7.83; N, 6.22.

α-Allylfluorenylaniline (X).—To a yellow solution of 25.5 g. (0.100 mole) of fluorenone anil in 100 ml. of dry ether was added an equimolar quantity of allylmagnesium bromide in 110 ml. of ether during 20 minutes. Immediate reaction was evidenced by the discharge of the yellow color and occurrence of spontaneous reflux. After the solution was stirred at room temperature for an additional two hours, it was hydrolyzed with ammonium chloride solution. The ethereal layer upon drying and removal of the solvent yielded a tan solid melting over the range 130–134°, 27.6 g. (93%). Recrystallized from ethanol (Norit), the solid formed long, glistening white needles, 25.7 g. (87%), m.p. 136.5–137.5°.

Anal. Calcd. for $C_{22}H_{19}N$: N, 4.71. Found: N, 4.71.

6-Allyl-6-phenyl-5,6-dihydrophenanthridine (XI).—To 25.5 g. (0.100 mole) of 6-phenylphenanthridine[16] suspended in 150 ml. of dry ether was added 0.125 mole of allylmagnesium bromide in 125 ml. of ether over the course of 30 minutes. Upon heating at the reflux temperature overnight the reaction mixture formed a dark green, fluorescent solution. The cooled reaction mixture was hydrolyzed in the usual fashion and from the ethereal layer was obtained 28.1 g. of crude white product, melting over the range 90–100°. This product was difficult to free from contamination with 6-phenylphenanthridine (m.p. 107°) due to the similar properties of the product and starting material. Repeated recrystallization from 95% ethanol in excess afforded 20 g. (67%) of shiny white platelets, m.p. 101–103°. The analytical sample melted at 103–104.5°. As is characteristic of 5,6-dihydrophenanthridine types,[17] this compound in ethanolic solution possessed a marked blue fluorescence.

Anal. Calcd. for $C_{22}H_{19}N$: C, 88.84; H, 6.44; N, 4.71. Found: C, 89.14; H, 6.23; N, 4.66.

Reaction of Grignard Reagents with N-Diphenylmethyleneaniline.—Neither the methyl nor the propyl Grignard reagent reacted with N-diphenylmethyleneaniline under the conditions successful with allylmagnesium bromide. Thus, when 18.0 g. (0.070 mole) of N-diphenylmethyleneaniline in 100 ml. of dry ether was heated for 18 hours with 0.10 mole of either methylmagnesium iodide or propylmagnesium bromide in ether, the usual work-up yielded

(12) Gilman, Beel, Brannen, Bullock, Dunn and Miller, THIS JOURNAL, **71**, 1499 (1949).

(13) Gilman and Morton in Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1954, Vol. VIII, p. 286.

(14) Birch, Dean, Fidler and Lowry, THIS JOURNAL, **71**, 1362 (1949).

(15) Reddelien, *Ber.*, **43**, 2476 (1910).

(16) Morgan and Walls, *J. Chem. Soc.*, 2447 (1931).

(17) Caldwell, Copp and Walls, *ibid.*, 2698 (1950).

only about 16–17 g. (88–95% recovery) of starting material.

Acknowledgments.—The authors are grateful to Dr. V. A. Fassel and Mr. R. McCord of the Institute for Atomic Research for the infrared determinations.

AMES, IOWA

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

A Kinetic Study of the Leuchs Anhydrides in Aqueous Solution. I[1]

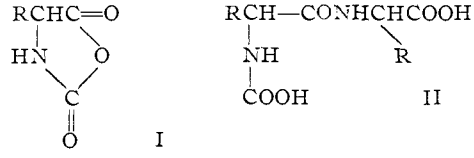
BY PAUL D. BARTLETT AND RICHARD H. JONES

RECEIVED SEPTEMBER 7, 1956

The reaction of an anhydro-N-carboxy-amino acid (Leuchs anhydride) with water is subject to general basic catalysis and is not catalyzed by acids. The reaction with the amino group of an amino acid anion is so rapid that it can compete successfully with hydrolysis. The reactions of anhydro-N-carboxyglycine, anhydro-N-carboxy-D- and L-alanine and anhydro-N-carboxy-α-aminoisobutyric acid with water and some amino acids have been followed kinetically by carbon dioxide evolution and their rate constants determined (Tables II and III). The possibility of controlled peptide synthesis in aqueous solution from the Leuchs anhydrides is discussed and experiments are reported showing the limitations of such a procedure.

Introduction

The anhydrides (I) of N-carboxy-α-amino-acids, first prepared by Leuchs,[2] have been investigated



I

II

chiefly in inert solvents where with controlled amounts of active-hydrogen compounds as initiators they lead to polypeptides[3] of moderate or high molecular weight while at very low temperatures the decarboxylation of the initial carbamic acid (II) can be repressed sufficiently by salt formation[4] to afford good yields of simple peptides. Even more attractive possibilities of control of this reaction would present themselves if it were possible to operate in aqueous solutions; with this in mind, we have studied the nature and rates of the reactions of some simple N-carboxy-anhydrides in water.

Reactions of N-Carboxy-anhydrides with Water.—The N-carboxy-anhydrides of glycine, *dl*-alanine and α-amino-isobutyric acid, on solution in water at 0°, evolve carbon dioxide at a rate convenient for measurement. The reactions were followed by observing the increase in pressure in a closed, initially evacuated system; with the first and last of these anhydrides a rate measurement by following volume increase at constant pressure agreed with the results of the pressure method. Except for a short initial period (see below) the reactions, as followed in this manner, were of the first order, yielding rate constants as shown in Table I. Reactions of anhydro-N-carboxy-α-aminoisobutyric acid in 0.1 *M* barium chloride, 0.1 *M* hydrochloric acid and 1.0 *M* sulfuric acid yielded the same average rate constant, 2.4×10^{-3} sec.$^{-1}$, as the reaction in pure water, with a mean deviation of $\pm 0.07 \times 10^{-3}$. The effect of acid catalysis upon the hydrolysis of the anhydride is therefore negligible.

TABLE I

RATE CONSTANTS FOR UNCATALYZED HYDROLYSIS AT 0°

N-Carboxy-anhydride of	No. of runs	Concentration range	k_1, sec.$^{-1}$ × 10^3	Mean deviation
Glycine	6	0.01– 0.028	4.1	0.23
dl-Alanine	3	.022– .028	6.4	.23
α-Aminoisobutyric acid	5	.019– .028	2.4	.12

Carbon dioxide is not evolved when a carboxy-anhydride reacts with two or more equivalents of sodium or barium hydroxide. An attempt was made to measure the rate of the reaction of anhydro-N-carboxyglycine with hydroxyl ion by following the conductivity of a solution of barium hydroxide to which the anhydride was added. There was a very rapid reaction which produced 74% of the expected change in conductivity within the first 40 seconds, followed by a slower process to which a second-order rate constant of 0.30 l./mole sec. could be assigned. The latter process is far too slow to be the reaction of anhydride with hydroxyl ion, as a later experiment proves. According to Stadie and O'Brien,[5] carbamates such as the Siegfried salts come rapidly to equilibrium with carbon dioxide and amino acid anion, but the carbon dioxide is much more slowly equilibrated with bicarbonate and carbonate. The calculated equilibrium concentration of carbonate ion during the preparation of a Siegfried barium salt is more than sufficient to precipitate barium carbonate; the non-appearance of such a precipitate is evidently the result of slow attainment of the carbonate equilibrium. The slow reaction observed in the conductivity experiments may well be the conversion of hydroxyl ion into carbonate.

Hydrolysis of N-Carboxy-anhydrides in Buffer Solutions.—During this work it became apparent that the amino acid formed by hydrolysis of the

(1) This work was supported by the Office of Naval Research under Contract No. N5ori-07653 with Harvard University, 1952–1953.

(2) H. Leuchs, *Ber.*, **39**, 857 (1906).

(3) For a review see E. Katchalski, "Advances in Protein Chemistry," Vol. VI, Academic Press, Inc., New York, N. Y., 1951, pp. 123–185. More recent work: D. G. H. Ballard and C. H. Bamford, "Symposium on Peptide Chemistry," Special Publication No. 2, Chemical Society, London, 1955, pp. 25–48; E. R. Blout and R. H. Karlson, THIS JOURNAL, **78**, 941 (1956); P. Doty and R. D. Lundberg, *ibid.*, **78**, 4810 (1956); E. R. Blout and M. Idelson, *ibid.*, **78**, 3857 (1956).

(4) J. Leggett Bailey, *J. Chem. Soc.*, 3461 (1950).

(5) W. C. Stadie and H. O'Brien, *J. Biol. Chem.*, **103**, 521 (1933); **112**, 723 (1935).