Anal. Calcd. for $C_{10}H_{11}NO_3$: N, 7.25. Found: N, 7.31.

Reactions with ethylene carbonate. A stirred mixture of 17.6 g. (0.2 mole) of ethylene carbonate and 8.25 g. (0.05 mole) of ethyl *p*-aminobenzoate was heated for 6 hr. at temperatures ranging from 95° to 190° as shown in Table I. After being cooled to room temperature the solidified melt was extracted with three 50-ml. portions of warm benzene. The combined extracts were allowed to cool to room temperature and after 24 hr., the crystallized products were filtered, washed with a small volume of benzene, and dried.

In another experiment the same proportions of the reactants were refluxed in 40 ml. of 2-methyl-2-butanol for 6 hr. The solution was evaporated to an oily residue *in vacuo* and worked up as described above.

Attempts at reductive hydroxyethylations. A solution of 1.80 g. of glycolaldehyde (0.03 mole) in 15 ml. of 95% ethanol containing 1.95 g. of ethyl *p*-nitrobenzoate with 1.0 ml. of glacial acetic acid as a condensing agent was hydrogenated at room temperature in the presence of 0.1 g. of platinum oxide catalyst. In a similar manner the reaction was attempted only using 1.65 g. of ethyl *p*-aminobenzoate instead of the nitro compound with 120 mg. of anhydrous sodium acetate as the condensing substance. In both cases only ethyl *p*-aminobenzoate could be isolated.

Preparation of p-[di(2-chloro-C^{14}-ethyl)amino]-L-phenylalanine. *p*-Amino-*N*-phthaloyl-L-phenylalanine ethyl ester (I) prepared according to the method of Bergel and Stock[9] was used as starting material. All subsequent chemical transformations leading to the crude C^{14}-labelled phenylalanine mustard were performed in the same tared flask to avoid possible losses in material transfers.

In a 100-ml. one neck flask a solution of 3.073 g. (I) (9.1 mmoles m.p., 108°–109°) in 15 ml. of glacial acetic acid was maintained nearly at its freezing point. The long shaped ampule, containing 0.434 g. of ethylene-1,2-C^{14} oxide[24] (10 mmoles, specific activity 0.203 millicurie/mmole) in its bulb, was inserted in a one hole rubber stopper in such a position that the top of it would be submerged about 5 mm. under the surface of the acetic acid solution if the stopper were placed into the neck of the flask. Keeping the oxyalkylating agent in the bulb in solid state with liquid nitrogen the top of the ampule was opened. Then the ampule, by means of the stopper, was placed into position in the flask. The ethylene oxide was quantitatively transferred into the cold acetic acid solution by allowing the bulb to warm up slowly to room temperature. The ampule was rinsed by controlled warming and subsequent cooling of the flask. After completing this transfer, the solution was kept stoppered at room temperature for 18 hr. with occasional shaking. Then under the same conditions, the solution was treated with an additional 10 ml. of inactive ethylene oxide (0.2 mole) for 24 hr. in order to complete the hydroxyethylation. Finally, the mixture was concentrated and dried as a sirup in vacuo.

Without any further purification, the hydroxyethylated amine ester was dissolved in 50 ml. of benzene and the solution distilled until about 15 ml. of distillate was collected. The residual benzene solution was gently refluxed with 12 ml. of freshly distilled phosphorus oxychloride for 25 min. and then concentrated to an orange brown gum *in vacuo.* The gum was dissolved in 40 ml. of a benzene-ethanol mixture (1:1) and the solution evaporated to dryness at low temperatures. This procedure was repeated again to remove residual phosphorus oxychloride.

The residue obtained in the chlorination was dried over sodium hydroxide *in vacuo* and subsequently refluxed in 40 ml. of 6*N* hydrochloric acid for 3 hr. The hydrolysis mixture was cooled for several hours, filtered on a tared fritted glass funnel, and dried. The weight of the precipitated phthalic acid was determined in order to check the completeness of the hydrolysis. Then 100 ml. of a saturated sodium acetate solution was added in small portions to the cold filtrate. The precipitated crude L-phenylalanine mustard was collected, washed with a small amount of cold saturated sodium acetate solution, and dried, yielding 2.172 g. (73% based on the amount of I) of the impure compound. The crude substance was recrystallized from methanol by concentrating a 250 ml. alcoholic solution to a volume of 50 ml. 1.190 g. (43% yield) of *p*-[di(2-chloro-C^{14} ethyl)amino]-L-phenylalanine (m.p. 181°–184°, $[\alpha]^{25}_{D}$ +9.5 ± 0.6°, *c*, 0.93 g./100 ml. in 1*N* hydrochloric acid) having a specific activity of 0.213 mc./mmole was obtained. Based on the specific activity of the oxyalkylating agent, the utilization of ethylene-1,2-C^{14} oxide was 41%.

Distribution of C^{14}-labelled melphalan between aqueous and lipid phases. Approximately 2 mg. of the C^{14}-labelled L-phenylalanine mustard was partitioned between 50 ml. of an aqueous potassium dihydrogen phosphate buffer (*p*H 7.18) and 50 ml. of benzene or chloroform. After separation of the two phases, several 0.05 ml. quantities of each layer were plated and counted. Distribution coefficients found are 103 for aqueous/benzene and 116 for aqueous/chloroform.

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(24) New England Nuclear Corporation, Boston, Mass.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Reaction of Ammonia with an Aromatic Aldehyde in Dilute Solution

RICHARD K. McLEOD AND THOMAS I. CROWELL

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The reaction of *p*-dimethylaminobenzaldehyde, at very low concentrations, with ammonia in methanol is similar in many respects to its reaction with primary amines to yield Schiff bases. The rate of the reaction is determined at 0° and 25° and the energy and entropy of activation calculated. The formation of a simple imine is inferred.

The action of ammonia on aromatic aldehydes is generally complex and usually results in the formation of hydrobenzamides,[1] the kinetics of which were investigated by Dobler[2] as early as 1922. By passing gaseous hydrogen chloride into a solution of hydrobenzamide in ethanol, Busch[3] was able to

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(1)(a) M. A. Laurent, *Ann.*, 21, 130 (1837). (b) F. Sachs and P. Steinert, *Ber.*, **37**, 1733 (1904).

(2) F. Dobler, *Z. Physik. Chem.* (*Leipzig*), **101**, 1 (1922).

(3) M. Busch, *Ber.*, **29**, 2143 (1896).

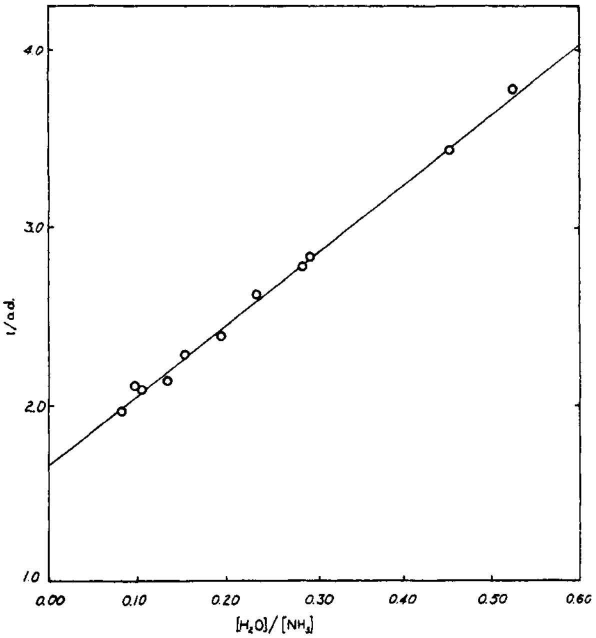

Fig. 1. Reciprocal of optical density of equilibrium mixture plotted against $[H_2O]/[NH_3]$

isolate the hydrochloride of benzylidenimine. This unstable imine was itself isolated from a solution of hydrobenzamide in liquid ammonia[4] and also as a product of the catalytic reduction of benzonitrile under vacuum.[5] No rate studies have been made of the formation of this imine or its analogs.

p-Dimethylaminobenzaldehyde was chosen as a reactant because of its particular suitability for spectrophotometric study. Since the rate of formation of products resulting from the combination of two or more aldehyde molecules with ammonia should be very small at low aldehyde concentrations, it seemed possible that the reaction might go no farther than the formation of *p*-dimethylaminobenzylidenimine. We therefore sought evidence for the reaction,

$$\text{ArCHO} + NH_3 \rightleftharpoons \text{ArCH}{=}\text{NH} + H_2O \qquad (1)$$

by employing the spectrophotometric techniques already used for the investigation of Schiff base formation.[6]

EXPERIMENTAL

Materials. Eastman white label *p*-dimethylaminobenzaldehyde was recrystallized twice from water. A methanolic ammonia solution was prepared by passing ammonia, evolved from boiling ammonium hydroxide, through a drying column and into methanol. The solvent for the kinetic runs was reagent grade methanol.

Rate measurements. For each group of runs, a standard solution of *p*-dimethylaminobenzaldehyde was pipetted into 50-ml. volumetric flasks containing solutions of methanolic ammonia. After dilution to the mark, samples were periodically withdrawn and diluted 1:25 into a solution of hydrochloric acid in methanol. The acid served to convert the *p*-dimethylaminobenzylidenimine to its conjugate acid and the unchanged aldehyde to the acetal. The imine concentration was then determined from the ultraviolet absorption peak of the imine conjugate acid at 386 mμ, the absorption of the acetal being negligible at this wave length. The imine conjugate acid was found to undergo rapid decomposition which necessitated extrapolation of a plot of optical density *vs.* time in order to determine the value at the moment of dilution.

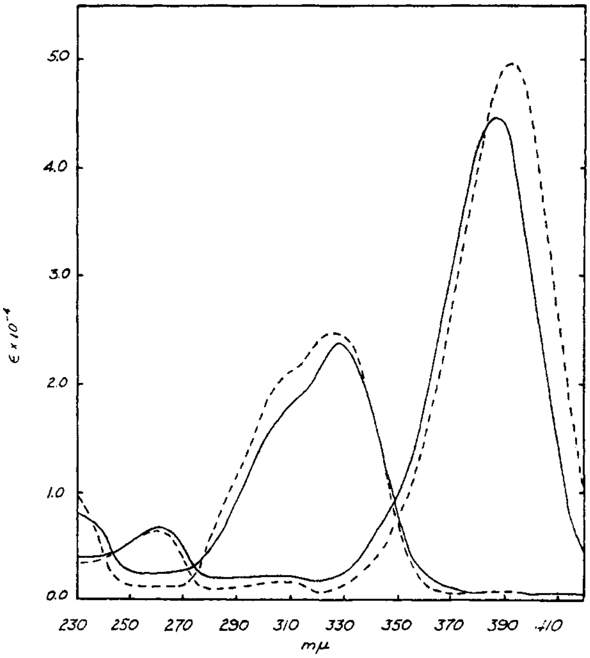

Fig. 2. Extinction coefficients *vs.* wave length for *p*-dimethylaminobenzylidenimine (solid line) and *N*-(*p*-dimethylaminobenzylidene)-*n*-butylamine (broken line). The curves with maxima near 330 mμ are for the pure compounds; those with maxima near 390 mμ are for the conjugate acids

Determination of extinction coefficient and equilibrium constant. The extinction coefficient, ε, of the conjugate acid of the imine at 386 mμ and the equilibrium constant for the reaction 1 were obtained at 24.85° from equilibrium determinations of the water and ammonia concentrations and measurements of the optical density at the conjugate acid peak. The failure of the reaction to go 100% to completion at feasible ammonia concentrations precluded obtaining the extinction coefficient directly from the spectrum after complete reaction.

From the equilibrium expression, $K = [\text{ArCH}{=}\text{NH}][H_2O]/[\text{ArCHO}][NH_3]$, the following equation may be derived:

$$\frac{1}{(\text{o.d.})} = \frac{25}{Ka\epsilon} \cdot \frac{[H_2O]}{[NH_3]} + \frac{25}{a\epsilon} \qquad (2)$$

where (o.d.) is the optical density of the acidified equilibrium mixture, K is the equilibrium constant, a is the initial aldehyde concentration, and 25 is the dilution factor. The intercept and slope of a plot of 1/(o.d.) against $[H_2O]/[NH_3]$ gave ε and K, as shown in Fig. 1, after correction for slightly unequal aldehyde concentrations. The values obtained were $\epsilon_{386} = 4.46 \times 10^4$ and $K_{25} = 0.416$.

The water concentrations in the reaction flasks were determined by titration with Karl Fischer reagent and the ammonia concentrations by titration with standard hydrochloric acid to a methyl red end point.

A solution of *N*-(*p*-dimethylaminobenzylidene)-*n*-butyla-

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[4] H. H. Strain, *J. Am. Chem. Soc.*, 49, 1558 (1927).

[5] R. Escourreau, *Bull. soc. chim. France*, 45, 735 (1929).

[6] (a) T. I. Crowell and D. W. Peck, *J. Am. Chem. Soc.*, 75, 1075 (1953). (b) G. M. Santerre, C. J. Hansrote, Jr., and T. I. Crowell, *J. Am. Chem. Soc.*, 80, 1254 (1958).

TABLE I

[ArCHO] M	[NH_3] M	[H_2O] M	10^5k_2 L. Mole^{-1}. Sec^{-1}	K
		TEMPERATURE 24.85°		
3.31×10^{-4}	0.504	0.118	4.45	0.416[a]
	0.500	0.049	4.53	
	1.003	0.083	4.00	
	1.005	0.104	4.12	
6.63×10^{-4}	1.007	0.048	4.13	
3.38×10^{-4}	0.248	0.112	4.60[b]	
	0.494	0.096	4.58[b]	
	0.495	0.066	4.55[b]	
3.38×10^{-4}	0.250		4.17[c]	
	0.497		4.17[c]	
	0.992		3.78[c]	
3.29×10^{-4}	0.247		4.55	
	0.494		4.58	
	0.971		4.38	
			Av. 4.41 ± .18	
		TEMPERATURE 0.00°		
3.29×10^{-4}	0.247	0.078	0.862	0.644[d]
	0.486	0.120	0.825	0.688[d]
	0.978	0.179	0.767	0.720[d]
6.57×10^{-4}	0.479	0.170	0.830	0.693[d]
			Av. 0.831 ± .027	0.686 ± .021

[a] The equilibrium constant at 25° was determined graphically. [b] Measured in 0.0074M sodium methoxide. [c] Measured in 0.1374M sodium methoxide. These values were not considered in the average. [d] Obtained directly from spectrophotometric and titrimetric measurements of the different species present at equilibrium.

mine was prepared by allowing *p*-dimethylaminobenzaldehyde to react with excess *n*-butylamine in methanol.[6b]

RESULTS AND DISCUSSION

The reaction of *p*-dimethylaminobenzaldehyde with ammonia shows second-order kinetics as previously observed in the reaction of this and other aldehydes with amines.[6,7] The reaction was carried out in a large excess of ammonia and the resulting data treated as a pseudo first-order reversible reaction. The sum of the forward and reverse first-order rate constants, $k_1 + k_{-1}$, was easily obtained from the slope, λ, of the line resulting from the usual plot of such data. Since the water and ammonia concentrations remained essentially constant throughout the reaction, the forward and reverse second-order rate constants, k_2 and k_{-2}, may be expressed as $k_2 = k_1/[NH_3]$ and $k_{-2} = k_{-1}/[H_2O]$. Since $k_1 + k_{-1} = 2.303\,\lambda$ and $k_{-2}\,[H_2O] = k_2[H_2O]/K$, where K is the equilibrium constant, the expression for the forward second-order rate constant becomes

$$k_2 = \frac{2.303\lambda}{[NH_3] + [H_2O]/K} \qquad (3)$$

or

$$k_2 = \frac{2.303\lambda}{[NH_3] + [ArCHO]_e[NH_3]/[ArCH{=}NH]_e} \qquad (4)$$

The values of k_2 listed in Table I were calculated by means of equation 4. Each k_2 is the result of from five to eight kinetic measurements; the average deviation from the mean is 4% for the rate constants obtained at 25° and 3% for those obtained at 0°.

The results shown in Table II are typical. This was one of six runs to which sodium methoxide was added in order to rule out the possibility of base catalysis or catalysis by traces of acid.

TABLE II

REACTION OF *p*-DIMETHYLAMINOBENZALDEHYDE WITH AMMONIA AT 25°

(a = $3.38 \times 10^{-4}M$, [NH_3] = 0.495M, [$NaOCH_3$] = 0.0074M, [H_2O] = 0.0657M)

t, Sec.	10^4x, M	$\text{Log}\,\frac{x_0-x_e}{x-x_e}$	$10^5\,(k_1 + k_{-1})$, Sec.$^{-1}$	$10^5\,k_2$, L./Mole^{-1} Sec.$^{-1}$
2880	0.207	0.0358	2.86	4.48
6540	.462	.0842	2.96	4.64
10260	.675	.129	2.90	4.54
14100	.874	.176	2.88	4.51
17580	1.05	.222	2.91	4.55
23580	1.29	.297	2.90	4.53
27600	1.45	.349	2.91	4.56
∞	2.62	—	—	—

Average k_2: 4.54×10^{-5} l. mole^{-1} sec.$^{-1}$

The spectrum of the conjugate acid of the imine was obtained with a Beckman recording spectrophotometer. Although the conjugate acid decomposed at a measurable rate, a medium scanning speed reproduced the spectrum with an error of no more than 1%. In an acidified solution of the reaction mixture, the only absorbing species was the conjugate acid; in the basic solution, however, two absorbing species were present: the imine and the aldehyde. Since the concentration of the imine present was known from the ab-

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(7) R. L. Hill and T. I. Crowell, *J. Am. Chem. Soc.*, **78**, 2284, 6425 (1956).

sorption of its conjugate acid, the absorption of the aldehyde remaining in the basic solution could be calculated and subtracted from the spectrum of the aldehyde-imine mixture, leaving the spectrum of the imine. The conclusion that the imine is obtained as the product of the reaction of ammonia with a very dilute aldehyde solution appears further borne out by the comparison of these spectra with the spectra of *N*-(*p*-dimethylaminobenzylidene)-*n*-butylamine and its conjugate acid as shown in Fig. 2.

The mean values of k_2 at 0° and 25°, given in Table I, were used in calculating the energy and entropy of activation for the reaction, with the result that $E_a = 10.9$ kcal./mole and $\Delta S^{\ddagger} = -43.7$ e.u. The close correspondence with the values for the reaction of this same aldehyde with *n*-butylamine (8.0 kcal./mole and -41.9 e.u.)[6b] and *t*-butylamine (10.3 kcal./mole and -41.7 e.u.)[8] is one more indication that imine formation is taking place.

Acknowledgment. We are grateful for the support of the National Science Foundation.

CHARLOTTESVILLE, VA.

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(8) Unpublished work by C. E. Bell, Jr., and T. I. Crowell.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ISRAEL INSTITUTE OF TECHNOLOGY]

The Reactions of Carbobenzoxyamino Acid Amides with Carbonyl Compounds

URI ZEHAVI[2] AND DOV BEN-ISHAI

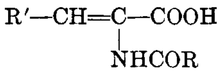
Received August 4, 1960

Amides of carbobenzoxyglycine, carbobenzoxyalanine, and carbobenzoxyphenylalanine have been found to react with carbonyl compounds (isobutyraldehyde, benzaldehyde, and cyclohexanone), in the presence of a sulfonic acid catalyst, to give two types of products: 1-carbobenzoxy-4-imidazolidinones (III) and carbobenzoxyamino acid 1-isobutenylamides (IV). The structure of the products is predetermined by the structure of the amide and that of the carbonyl component.

Primary amides and primary urethanes are known to react with aldehydes under acidic conditions to give alkylidenebisamides[3] (I) and alkylidenebisurethans (I,R = OR′).[4] In the case of α-keto acids two types of reaction products are known, the bis-adduct (type I) and α-acylaminoacrylic acids (II)[5]:

$R'CH(NHCOR)_2$

I

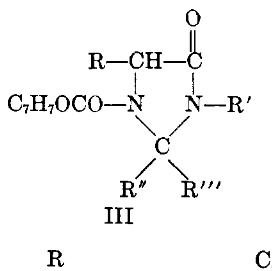


$$R'-CH{=}\underset{\displaystyle NHCOR}{C}-COOH$$

II

If additional functional groups are present in the amide or urethan component, intramolecular cyclization may occur, leading to cyclic products. Thus, asparagine affords upon treatment with formaldehyde, 6-hydroxytetrahydropyrimidine-4-carboxylic acid,[6] and carbobenzoxyamino acids,[7] or β-hydroxyalkylcarbamates[8] afford on reacting with carbonyl compounds oxazolidine derivatives.

In the present paper the reactions of primary and secondary carbobenzoxyamino acid amides with isobutyraldehyde, benzaldehyde, and cyclohexanone are described. Refluxing benzene solutions of carbobenzoxyglycineamide, carbobenzoxyalanineamide, and carbobenzoxyphenylalanineamide with benzaldehyde or cyclohexanone in the presence of a sulfonic acid catalyst affords crystalline 1-carbobenzoxy-4-imidazolidinone (III. R′ = H) under identical experimental conditions the same primary amides react with isobutyraldehyde to give open chain products of the ene-amide type, *i.e.* carbobenzoxyamino acid 1-isobutenylamides (IV):



III

$$C_7H_7OCONH\overset{\displaystyle R}{C}H-CONH-CH{=}\overset{\displaystyle CH_3}{C}-CH_3$$

IV

Carbobenzoxyamino acid methylamides (secondary amides) do not react with cyclohexanone and their reactions with isobutyraldehyde and benzaldehyde are much slower than those of the corresponding primary amides. With the methylamides only 1-carbobenzoxy-4-imidazolidinones (III. R′ = CH_3) were obtained even with isobutyraldehyde.

The structures assigned to the reaction products are based upon their infrared spectra and chemical behavior. The carbobenzoxyimidazolidinones lack the NH absorptions of the starting materials in the 1500–1600 cm.$^{-1}$ region (cyclic lactams). The two

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(1) Presented at the 26th meeting of the Israel Chemical Society, Jerusalem, April, 1960.

(2) From a thesis submitted for the M.Sc. degree by U. Zehavi, Israel Institute of Technology, Haifa, 1960.

(3) W. A. Noyes and D. B. Forman, *J. Am. Chem. Soc.*, **55**, 3493 (1933).

(4) W. M. Kraft and R. M. Herbst, *J. Org. Chem.*, **10**, 483 (1945).

(5) A. E. Martel and R. M. Herbst, *J. Org. Chem.*, **6**, 878 (1941).

(6) D. French and J. T. Edsall, *Advances in Protein Chemistry*, **2**, 306 (1945).

(7) D. Ben-Ishai, *J. Am. Chem. Soc.*, **79**, 5736 (1957). F. Micheel and W. Meckstroth, *Ber.*, **92**, 1675 (1959).

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