ene according to the procedure described by Robinson and Ryldon.[14]

The identities of the reaction products were confirmed by their inability to depress the melting points of authentic samples. The yields in Table I refer to compounds whose boiling points or melting points are given in the same table.

Method A.—To a solution of 0.01 mole of starting material in 20 ml. of benzene containing a catalytic amount of benzoyl peroxide, was added 0.01 mole of TMAT. The mixture was stirred at room temperature for the specified reaction period, which was determined by the disappearance of the tribromide and the cessation of hydrogen bromide evolution. The colorless tetramethylammonium bromide was dissolved by adding water. The organic layer was separated, washed with water and aqueous sodium carbonate in succession, dried over sodium sulfate, and the solvent removed. The reaction product was isolated by recrystallization, distillation, or by both procedures.

Method B.—A solution of 0.01 mole of the starting material and 0.01 mole of TMAT in 30 ml. of acetic acid was refluxed for the specified reaction time until the bromide color disappeared and no more hydrogen bromide was evolved. The cold reaction mixture was poured into water to dissolve the precipitated tetramethylammonium bromide, and the aqueous solution was then extracted with ether. The organic layer was treated, and the product isolated, as described in method A.

Benzyl Bromide.—A mixture of 0.921 g. (0.01 mole) of toluene, 6.27 g. (0.02 mole) of TMAT, and a trace of benzoyl peroxide was heated under reflux for 15 min. The cold reaction mixture was treated as described in method B to yield 1.00 g. (59%), b.p. 194–198° (lit.[15] b.p. 198°).

Benzoic acid was obtained on oxidation of the reaction product with potassium permanganate in aqueous sodium carbonate solution at reflux temperature.

***p*-Bromotoluene.**—A mixture of toluene (35 ml.), anhydrous ferric chloride (13.85 g.), and TMAT (21.55 g.) was stirred at 60° for 6 hr. The mixture was poured into water and extracted with ether. The organic layer was washed with dilute hydrochloric acid, followed by sodium carbonate solution. After removing the solvent, the residue was fractionated to afford 7.12 g. (72% yield), b.p. 184–186° (lit.[16] b.p 184°).

Oxidation of the reaction product with dilute nitric acid gave *p*-bromobenzoic acid.

Acknowledgment.—The authors are indebted to Prof. I. A. Kaye from Brooklyn College, Brooklyn, New York, for helpful discussions in the preparation of the manuscript.

(14) R. Robinson and H. N. Ryldon, *J. Chem. Soc.*, 1394 (1939).

(15) I. Heilbron, "Dictionary of Organic Compounds," Vol. I, Eyre and Spottiswoode, London, 1953, p. 271.

(16) Ref. 15, p. 374.

The Reaction of Secondary Amines with Formaldehyde

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The reaction of secondary amines with formaldehyde can lead to two products: aminomethylols (I) and methylenebisamines (II).[1] Although many examples of II

$$R_2NH + HCHO \longrightarrow \underset{\text{I}}{R_2NCH_2OH} \xrightarrow{R_2NH} \underset{\text{II}}{R_2NCH_2NR_2} + H_2O$$

have been reported, only a few examples of I have been isolated. Usually the methylols are unstable and form none of the derivatives of alcohols or amines.[2]

(1) E. C. Wagner, *J. Org. Chem.*, **19**, 1862 (1954).

Since aminomethylols have never been isolated in these reactions, and only weak evidence has been presented for their existence,[3] we wished to learn if they indeed exist in any significant amount in this reaction. Our evidence suggests that in the cases studied the methylenebisamine is the predominant product.

We used the following approach. One mole of formaldehyde was added to two moles of amine and the temperature rise ΔT_1 measured in a simple Nernst type calorimeter.[4] A second mole of formaldehyde was then added to this mixture and ΔT_2 measured. The data presented in Table I are corrected for heats of dilution of amine in water. Since alleged preparations of aminomethylols were reported at 0–5°,[2,3,5,6] we made determinations at that temperature and at room temperature. The ΔT_1 and ΔT_2 values are readily explained by considering the equilibria involved.

$$R_2NH + HCHO \rightleftharpoons R_2NCH_2OH \overset{R_2NH}{\rightleftharpoons} R_2NCH_2NR_2 + H_2O$$

On addition of the first equivalent of formaldehyde, equilibrium is established. If the equilibrium greatly favors the aminomethylol, then there is still one equivalent of amine left to react with the second equivalent of formaldehyde. The addition of this second portion of formaldehyde, then, results in a ΔT_2 which is nearly equal to ΔT_1. If, however, the equilibrium greatly favors the methylenebisamine, then there is no unchanged amine left to react with the second portion of formaldehyde and $\Delta T_1 > \Delta T_2$. If there is no aminomethylol at equilibrium after addition of the first portion of formaldehyde, ΔT_2 is zero except for heat of dilution of formaldehyde, which in these experiments can only account for temperature rises of less than 0.05.[7]

The data of Table I indicate that in most cases equilibrium favors the methylenebisamine at both temperatures. Moreover, in nearly all the cases studied the ratio $\Delta T_1/\Delta T_2$ (Table I) was greater at 30° than at 5°. This is explained by the greater stability of methylene bisamines over aminomethylols.

Two of the compounds which exhibited low ratios of $\Delta T_1/\Delta T_2$ are N-ethylethanolamine and diethanolamine which form the oxazolidine on reaction with formaldehyde.

$$RNHCH_2CH_2CH + HCHO \longrightarrow \underset{CH_2CH_2}{\overset{CH_2}{RN\diagup\quad\diagdown O}} + H_2O$$

(2) K. Bodendorf and G. Koralewski, *Arch. Pharm.*, **271**, 101 (1933).

(3) E. R. Alexander and E. J. Underhill *J. Am. Chem. Soc.*, **71**, 4014 (1949). The only evidence heretofore that aminomethylols are present at equilibrium was offered by these authors who stated that the dimethylaminomethylol which they prepared had only a weak infrared band in the OH region. We have examined the infrared spectrum of dimethylaminoethanol which has a strong OH band. This compound, because of a greater possibility of intramolecular hydrogen bonding, should have a weaker absorption in this region. This leads us to believe that the concentration of dimethylaminomethylol was probably small in the reference cited.

(4) J. M. Sturdevant, "Calorimetry, Technique of Organic Chemistry," Vol. I (1), 3rd Ed., A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1959, p. 572.

(5) M. Zief and J. P. Mason, *J. Org. Chem.*, **8**, 1 (1943).

(6) H. G. Johnson, *J. Am. Chem. Soc.*, **68**, 12 (1946).

(7) J. F. Walker, "Formaldehyde," Reinhold Publishing Corp., New York, N. Y., 1953, p. 90.

TABLE I[a]

ΔT[b] FOR THE REACTION OF FORMALDEHYDE WITH R_2NH[c]

Amine	5° ΔT_1	5° ΔT_2	30° ΔT_1	30° ΔT_2	References[d]
Morpholine	2.12	0.50	1.54	−0.02	*e, f*
Dibutylamine	0.93	0.45	0.83	0.26	*g*
N-Ethylethanolamine	0.33	0.17	0.56	0.16	New compound
Piperidine	1.29	0.67	1.06	0.26	*c*
Diallylamine	1.23	0.07	1.28	0.07	*h*
Dibenzylamine	0.28	0.05	0.52	−0.05	*i*
Diethanolamine	0.81	0.31	0.45	0.23	*j*
Diethylamine	1.07	0.10	0.83	0.07	*k*

[a] Due to the high concentrations used and the resulting large errors due to large solute–solute interactions and to differences in the specific heat of the contents of the calorimeter, these data are probably of limited value as true thermochemical quantities. [b] The standard deviation is 0.17°. [c] See ref. 6. [d] References to the reaction with formaldehyde. [e] See ref. 5. [f] U. S. Patent 2,388,058 (October 30, 1945). [g] H. Brintzinger and B. Hesse, *Kolloid-Z.*, **111**, 156 (1948). [h] N. Lewis, Ph.D. thesis, University of Florida, 1951. [i] S. V. Lieberman and E. C. Wagner, *J. Org. Chem.*, **14**, 1001 (1949). [j] See ref. 8. [k] L. Henry, *Bull. acad. roy. med. Belg.*, [3] **26**, 200 (1893); **29**, 355 (1895).

We found that these compounds formed readily under the conditions of our experiments.

Dibenzylamine is the only other amine which does not exhibit a large difference between ΔT_1 and ΔT_2. The low values of ΔT_1 for this compound made it impossible to decide whether this compound forms predominantly the methylenebisamine or the aminomethylol.

Experimental

Materials.—The chemicals used and their sources or methods of purification are stated. All distillations were through a 20-in. column packed with nichrome wire. Temperatures are uncorrected.

Formaldehyde, Merck and Co., C.P. 37% aqueous solution, standardized by the sodium sulfite method[7]; morpholine, b.p. 128.5° (760 mm.); dibutylamine, b.p. 159–160° (760 mm.); N-ethylethanolamine, b.p. 166–166.5° (760 mm.); piperidine, b.p. 106° (760 mm.); diallylamine, b.p. 109° (760 mm.); dibenzylamine, Eastman "White Label," used as received; diethanolamine, b.p. 132–135° (3.0–3.2 mm.); diethylamine, b.p. 55.5° (760 mm.).

Apparatus.—The calorimeter consisted of a 1-l. dewar flask fitted with a Beckmann differential thermometer, mechanical stirrer, and 2.5 × 14 cm. thin-walled copper test tube. The test tube was fitted with a thermometer, and glass loop stirrer through a rubber stopper, and was held in place in the dewar flask by a large rubber stopper. Water, 750 ml., was used as the calorimeter fluid. The pure amine was added to the copper tube through a funnel which was replaced with a long stem buret for slow addition of the aqueous 37% formaldehyde. The latter was added at such a rate that the temperature of the reaction mixture remained always near the bath temperature. In the low temperature runs the entire calorimeter was immersed in an ice–water bath to minimize heat loss. The temperature changes, ΔT_1, were corrected for external heat gain by preparing plots of time *vs.* temperature for the low temperature runs. To correct for heat of dilution, runs were made in which the formaldehyde was replaced by equivalent amounts of water.

3-(β-Hydroxyethyl)oxazolidine[8] was distilled from the benzene extract of an equimolar mixture of diethanolamine and formalin after it had stood for several hours, b.p. 93°(4.7 mm.), $n^{30}D$ 1.4753; lit.[8] b.p. 68°(0.5 mm.), $n^{25}D$ 1.4775.

3-Ethyloxazolidine was prepared by the same procedure as for 3-(β-hydroxyethyl)oxazolidine, b.p. 122°, $n^{22}D$ 1.4322.

Anal. Calcd. for $C_5H_{11}NO$: C, 59.4; H, 11.0; N, 13.9. Found: C, 59.0; H, 11.9; N, 13.2.

(8) Miles Laboratories, Inc., British Patent 839,289 (June 30, 1960).

The Synthesis of Secondary and Tertiary Amines by Borohydride Reduction[1]

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The preparation of secondary amines by the reduction of Schiff bases with lithium aluminum hydride or with borohydrides has been well established in earlier literature.[3] This note concerns the generality of the synthesis of secondary and tertiary amines by the action of sodium borohydride at 0° on the neutral aqueous solutions of amine salts and carbonyl compounds; reactions of this type were first reported for a special case (the preparation of dimethylamino acids) by Biemann and co-workers.[4] The process is advantageous, since it occurs rapidly without prior isolation of the Schiff bases, and even occurs in some instances where the equilibrium for the formation of the Schiff base is too unfavorable to permit its ready isolation. This synthesis, unlike previous catalytic reductions of Schiff bases formed *in situ*, may be used in the preparation of amines containing nitro or other groups sensitive to catalytic hydrogenation.

The formation of N^6-isopropyllysine[5] from lysine and acetone under various experimental conditions is reported in Table I. The primary α-amino acids could be easily identified with ninhydrin after paper chromatography. The reaction also gave N^2,N^6-diisopropyl-

(1) Supported by National Institutes of Health Research Grant GM-04712 to Professor F. H. Westheimer, whose help is gratefully acknowledged.

(2) National Institutes of Health Postdoctoral Fellow, 1960–1963; Department of Physiological Chemistry, The Johns Hopkins University School of Medicine, Baltimore, Md.

(3) J. H. Billman and J. W. McDowell, *J. Org. Chem.*, **27**, 2640 (1962), and earlier papers of this series.

(4) K. Biemann, "Mass Spectrometry Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 358.

(5) The separation of "modified" lysine (probably N^6-isopropyllysine) has been reported by H. Fasold, G. Gundlach, and F. Turba, *Biochem. Z.*, **334**, 255 (1961), from the hydrolyzate of borohydride reduced chymotrypsin to which acetone had been added to destroy excess borohydride. The isolation of N^6-isopropyllysine from a reduction with very low concentrations of acetone and borohydride has been achieved in these laboratories by Dr. B. Zerner and Dr. F. H. Westheimer with acetoacetate decarboxylase; the compound was identified by an independent synthesis.[10]