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-

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(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]

TABLE I

Acetone,[a] M	$NaBH_4$, M total	pH	Yield[b] of N^6-isopropyllysine, %
2.4[c]	0.4[d]	4.1–4.7	4
2.4[c]	0.9[d]	4.1–4.7	15
2.4[c]	1.8[d]	4.1–4.7	34
2.4[c]	3.6[d]	4.1–4.7	46
2.4[c]	7.2[d]	4.1–4.7	50
0.6[c]	2.1[d]	4.1–4.7	8
1.1[c]	2.0[d]	4.1–4.7	26
4.1[c]	1.5[d]	4.1–4.7	53
2.4[e]	1.8[d]	6.1 (initial)	6
2.4[f]	1.8[f]	6.3–6.7	55
2.4[g]	1.8[g]	11	20

[a] Lysine 0.4 M, 0°. [b] Yield estimated from ninhydrin colors; see Experimental. [c] Sodium acetate buffer 4.2 M. [d] Solid added in small amounts over 10 min. [e] Sodium phosphate buffer 4.2 M. [f] Imidazolium chloride buffer 4.2 M. Boron hydride added in 10 min., allowed to react 10 min. more. [g] In water, pH 11 established by borohydride and sodium borate. Borohydride added at once, and allowed to react for 30 min.

lysine which was isolated in very low yield as the methyl ester dihydrobromide. As indicated in Table I, the yield of N^6-isopropyllysine is relatively insensitive to pH, but increases with increasing concentrations of borohydride and of the carbonyl compound.

Probably the Schiff base salt or tertiary iminium salt, formed from the reactants,[6] is actually reduced by BH_4^-; this hypothesis[7] may account for the rapid reduction under relatively acidic conditions, as compared to the relatively slow reduction of isolated Schiff bases.[3] Simple calculations reveal that the reduction of Schiff base salts must be several orders of magnitude faster than the reduction of acetone, which is pH independent.[8] And of course, acid-catalyzed decomposition of the borohydride[9] competes with the reduction.

The following additional amines were prepared: N-isopropylalanine methyl ester, N-benzylaniline, N-isopropylaniline, N-isopropylbutylamine, and N-ethylpiperidine. Paper chromatographic evidence was obtained for the reductive coupling of the N^6-amino group of lysine with acetaldehyde, benzaldehyde, and cyclohexanone to form the ethyl, diethyl, benzyl, and cyclohexyl derivatives. The reaction is most successful with reactive carbonyls and primary amines, since acetophenone and benzophenone apparently failed to form lysine derivatives, and piperidine failed to react with cyclohexanone or acetone, although it did form N-ethylpiperidine in the reaction with acetaldehyde.

Experimental

All melting points unless otherwise noted were taken with the Fisher-Johns apparatus and are corrected. Confirmatory evidence for the structures of the products was obtained from infrared spectra.

N^6-Isopropyllysine Methyl Ester Dihydrobromide.—N^2-Carbobenzyloxy-L-lysine (Cyclo Chemical Co., 1.72 g., 6.14 mmoles), 5 ml. of glacial acetic acid, 2.5 g., of sodium acetate trihydrate, 10 ml. of water, and 5 ml. of acetone were placed in a stirred vessel at 0°. Sodium borohydride (4 g.) was added in 30-mg. lots over a 30-min. period, interrupted by the addition of 5 ml. more of acetone after the first 15 min. The final pH was 7. The mixture was evaporated to dryness *in vacuo* at 100°, taken up in methanol (100 ml.), saturated with dry hydrogen bromide, and allowed to stand 12 hr. at room temperature. The hydrogen bromide and methanol simultaneously esterified the amino acid and removed the carbobenzyloxy group. The mixture was made alkaline, and the amine extracted with ether and washed. The dihydrobromide was obtained by adding methanol and hydrogen bromide to the ether solution and evaporating to dryness. The product was recrystallized from methanol–ether; yield, 1.22 g. (55%); m.p. 156.5–157.5°.

Anal. Calcd. for $C_{10}H_{24}O_2N_2Br_2$: Br, 43.89. Found: Br, 43.11.

N^6-Isopropyllysine methyl ester dihydrobromide had been synthesized previously by Dr. Burt Zerner.[10] The melting point, mixture melting point, and infrared spectrum of the compound prepared by the two methods are identical. Acid hydrolysis of the ester gave N^6-isopropyllysine, which, on ascending paper chromatography with Whatman No. 1 paper and the system 1-propanol 550, water 300, and ammonium hydroxide 100, gave a single spot after treatment with ninhydrin[11] with an R_f of 0.63. Similar reactions with lysine were analyzed by paper chromatography (Table I); the only ninhydrin positive spots found corresponded to lysine (R_f 0.46) and N^6-isopropyllysine. The yield of product reported in Table I was determined as follows: the two ninhydrin positive spots were cut out and eluted with 5:1 acetone–ammonia. The absorbance at 575 mμ of the eluates was determined, and the per cent yield was taken as the absorbance of the product eluate divided by that of the total eluates. Comparison of the total absorbance of aliquots before and after the reaction indicated that most of the starting lysine was accounted for as lysine and N^6-isopropyllysine.

In similar experiments acetaldehyde gave two ninhydrin positive derivatives of lysine, a major product with R_f 0.63, and a minor one of R_f 0.69. These are presumably the N^6-ethyl and N^6,N^6-diethyllysine. (N^2-alkyllysines do not give the purple ninhydrin color.) Cyclohexanone and benzaldehyde each gave only a single derivative with R_f 0.79 and 0.75, respectively. Acetophenone and benzophenone gave only the spot corresponding to lysine.

N^2,N^6-Diisopropyllysine Methyl Ester Dihydrobromide.—This preparation was similar to but on a larger initial scale than that of the N^6-derivative described previously, with L-lysine hydrochloride, 3.65 g. (20 mmoles), in place of N^2-carbobenzyloxylysine, and the other reagents in proportion. The product was crystallized from ether–methanol–hydrogen bromide, yield 0.32 g. (4%), m.p. 186.5–188.5°. Proton n.m.r. at 60 Mc. of the salt (previously exchanged with deuterioxide) in deuterioxide revealed the methyls of the two isopropyls (split with J = 6 c.p.s.) nearly coincident at $-\delta$ = 1.40 p.p.m. (tetramethylsilane external standard) and the ester methyl at $-\delta$ = 3.95 p.p.m., with proper ratios of the peak areas of all the protons.

Anal. Calcd. for $C_{13}H_{30}O_2N_2Br_2$: Br, 39.35. Found: Br, 39.37.

N-Isopropylalanine Methyl Ester Hydrobromide.—Identical to the synthesis of N^6-isopropyllysine methyl ester, with DL-alanine 0.9 g. (10 mmoles) as the amine. The product, 0.52 g. (23%) had m.p. 150–151.7°.

Anal. Calcd. for $C_7H_{16}NO_2Br$: Br, 35.34. Found: Br, 35.38.

N-Isopropylbutylamine.—Sodium borohydride (2 g.) was added in 30-mg. portions over a 10-min. period to a stirred solution of *n*-butylamine (1 ml., 10.1 mmoles), sodium acetate trihydrate (2.7 g.), acetic acid (8.4 ml.), acetone (5 ml.), and water (25 ml.), at 0°. The mixture was made alkaline and the product was extracted with ether, washed, and crystallized as the hydrochloride. The yield was 0.96 g. (63%), m.p. 197–197.8°, lit.[12] 195–196°.

N-Isopropylaniline.—The procedure was similar to the preparation of N-isopropylbutylamine, with aniline as amine, and eth-

(6) This is analogous to other carbonyl amine condensation: J. B. Conant and P. D. Bartlett, *J. Am. Chem. Soc.*, **54**, 2881 (1932); E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 4319 (1962).

(7) This mechanism was suggested by Professor F. H. Westheimer. An example of the reduction of a Schiff base salt by borohydride in a complex molecule is given in the synthesis of reserpine by R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstad, *Tetrahedron*, **2**, 1 (1958).

(8) H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **83**, 4372 (1961).

(9) R. E. Davis and C. G. Swain, *ibid.*, **82**, 5949 (1960).

(10) This synthesis was achieved by alkylation of N^2-carbobenzyloxylysine with isopropyl bromide, esterification, and removal of the carbobenzyloxy group with methanol and hydrogen bromide, and crystallization of N^6-isopropyllysine methyl ester dihydrobromide from chloroform. N^6-Isopropyllysine was obtained from the ester by acid hydrolysis.

(11) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., Revised, D. C. Heath and Co., Boston, Mass., 1957, p. 136.

(12) K. N. Campbell, A. H. Sommers, and B. K. Campbell, *J. Am. Chem. Soc.*, **66**, 82 (1944).

anol (6 ml.) added to dissolve the aniline. The yield of amine was 1.35 g. (91%). Benzamide had m.p. 62–65°, lit.[13] 63–65°.

N-Benzylaniline.—The method was similar to the previous with aniline and benzaldehyde (5 ml.), and ethanol (20 ml.). The yield was 1.67 g., (83%), m.p. 36–37.2°, lit.[14] 37–38°.

N-Ethylpiperidine.—The method was similar to the previous with piperidine, 1.0 ml. (10.1 mmoles), and acetaldehyde (10 ml.). The borohydride was added over 30 min.; half of the acetaldehyde was added at the beginning, and the remainder after 15 min. The product was crystallized as the hydrochloride. The yield was 0.81 g. (53%) m.p. (evacuated capillary, uncor.) 225–227°, lit.[15] 225°. The picrate was also prepared, m.p. 165–167.5°, lit.[16] 167–168°. Corresponding synthetic attempts with acetone and cyclohexanone in place of acetaldehyde gave no detectable tertiary amine.

(13) W. S. Emerson and C. A. Uraneck, *J. Am. Chem. Soc.*, **63**, 749 (1941).
(14) K. Brand, *Ber.*, **42**, 3460 (1909).
(15) R. Lukes and J. Pliml, *Chem. Listy*, **50**, 557 (1956).
(16) R. Dulou, E. Elkik, and A. Veillard, *Bull. soc. chim. France*, 967 (1960).

The Reduction of Esters with Sodium Borohydride[1]

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It is generally accepted that sodium borohydride, a powerful reducing agent for aldehydes and ketones, will not reduce carboxylic esters. However, cases are reported in the literature in which reduction of esters to primary alcohols has been observed, and Schenker[3] has included many of these in his excellent review on the uses of complex borohydrides in organic chemistry. Also, instances of reduction of lactones and carbon–carbon double bonds, generally resistant to sodium borohydride, are given. Many of the compounds which undergo such "abnormal" reduction contain neighboring functional groups,[4] and Schenker implies that these groups may, in some way, take part in the reductions, although no suggestion is made as to the mechanism of this effect. We have now found that esters of simple heterocyclic, aromatic, and aliphatic acids are reduced to varying degrees by a large excess of sodium borohydride in methanol. Thus, it is evident that esters are not resistant to reduction by sodium borohydride, although the rate of reduction is much slower than for aldehydes and ketones.

For synthetic purposes, we were interested in preparing 3-(4′-pyrimidyl)-1-propanol.[5] Lithium aluminum hydride reduction of methyl 3-(4′-pyrimidyl)-propenoate or the corresponding saturated ester was complicated by simultaneous reduction of the pyrimidine ring. Therefore, in view of the suggestive reports cited, reduction of the unsaturated ester by sodium borohydride was attempted. A 77% yield of the desired propanol was obtained from the reduction carried out in methanol with a tenfold excess of sodium borohydride.

The reductions of several other unsaturated esters were then investigated, and the results are presented in Table I. The 3-(4′-pyridyl)propenoate, reduced with a tenfold excess of borohydride, behaved similarly to the pyrimidyl compound, giving mostly the saturated alcohol along with small amounts of the saturated ester and the unsaturated alcohol. With lesser amounts of reducing agent, larger amounts of saturated ester, unsaturated alcohol, and recovered starting material were obtained. The 3-(2′-quinolyl)propenoate, with a 16-fold excess of borohydride, surprisingly gave a mixture of products, although it might have been expected to be analogous to the pyridyl and pyrimidyl compounds. Methyl cinnamate and methyl 2-nonenoate also gave mixtures of reduction products and unaffected ester on treatment with a tenfold excess of reducing agent.

The reduction of several other esters with excess borohydride then was investigated, giving the results shown in Table I. The pyridine esters, methyl 4-pyridinepropanoate, ethyl 4-pyridineacetate, and methyl nicotinate, were reduced in high yields to the corresponding alcohols by a 20-fold excess of sodium borohydride in methanol. When less borohydride was used for the reduction of methyl nicotinate, some ester was recovered. Analogous phenyl esters, methyl hydrocinnamate, methyl phenylacetate, and methyl benzoate, also were substantially reduced by a 20-fold excess of borohydride, but not as cleanly as the pyridine esters, 10 to 15% of the ester being recovered. With lesser amounts of borohydride, methyl benzoate followed the same trend as methyl nicotinate, but in each corresponding case, less reduction was observed with the benzoate. One aliphatic ester, methyl nonanoate, was examined, and it was reduced to a lesser extent than the pyridine or phenyl esters, 57% of the ester being recovered.

From these results, it is obvious that no special structural features are necessary for reduction of esters by sodium borohydride to occur at least to some extent. However, such features may, indeed, enhance the reactivity in some manner, as is evident in going from aliphatic to phenyl to pyridine esters, and by the fact that many of the esters previously reported as being reduced contain proximate keto and hydroxyl groups.[3,4] Clearly, the solvent has an influence on the rate of reduction, as Chaikin and Brown[6] found that ethyl butyrate or ethyl phenylacetate, when heated with a suspension of sodium borohydride in dioxane or diethyl carbitol for one hour, showed no evidence of reduction. It was observed[7] that a mixture of ethyl benzoate and sodium borohydride in isopropyl alcohol lost but 12% of the available active hydrogen in six hours at 75°, and a similar mixture in diglyme lost less than 10% of the available hydrogen in twenty-four hours at 75°. In agreement with this behavior of esters is the fact that aldehydes and ketones are also reduced more slowly in these solvents than in

(1) Supported in part by the U. S. Army Research Office, Durham, N. C.
(2) Miller Research Fellow.
(3) E. Schenker, *Angew. Chem.*, **73**, 81 (1961).
(4) *E.g.*, V. Boekelheide and R. J. Windgassen, Jr., *J. Am. Chem. Soc.*, **81**, 1456 (1959), and J. E. G. Barnett and P. W. Kent, *J. Chem. Soc.*, 2743 (1963), for the borohydride reduction of some keto and hydroxy esters to diols.
(5) This has been successfully converted to 6-azapyrrocoline [$\lambda_{max}^{CH_3OH}$ 229 mμ (ε 30,100), 272 (7000), 283 (7800), 345 (900)]. Details will be reported in a forthcoming publication.
(6) S. W. Chaikin and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 122 (1949).
(7) H. C. Brown, E. J. Mead, and B. C. Subba Rao, *ibid.*, **75**, 6209 (1955).