

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, COLUMBIA UNIVERSITY]

The Action of Formaldehyde on Amines and Amino Acids¹

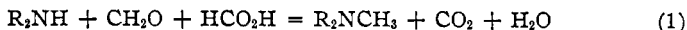
BY H. T. CLARKE, H. B. GILLESPIE AND S. Z. WEISSHAUS

The convenient method due to Sommelet and Ferrand² for the preparation of trimethylamine from ammonium formate, formaldehyde and formic acid, though its usefulness has recently been demonstrated³ in the case of anabesine, appears not to have attained general recognition as a means for the methylation of amines.

This process furnishes excellent yields of tertiary bases from simple primary and secondary aliphatic amines, including piperidine. Its ready applicability is illustrated by the complete methylation of tetramethylenediamine, the hydrochloride of which is extensively decomposed by heating at 125° with aqueous formaldehyde,⁴ and yields the tetramethyl derivative only when heated to 200° with dry paraformaldehyde.⁵

The reaction appears to be specific for formaldehyde, in contrast to its homologs, which apparently require higher temperatures⁶ for corresponding changes to take place. Thus, a mixture of acetaldehyde, formic acid and ammonium formate yielded no carbon dioxide on heating on the steam-bath, and from the resulting bases only 2-methyl-5-ethylpyridine could be isolated. The reaction also fails with compounds in which strongly polar groups are attached to nitrogen, such as amides, urea, guanidine and hydroxylamine; these appear to yield hydroxymethyl derivatives only. Moreover, it cannot be applied successfully to the methylation of aniline, which on warming with formaldehyde in formic acid solution is converted into condensation products of high molecular weight.⁷ On the other hand, 2,4,6-tribromoaniline, in which the sensitive positions in the benzene nucleus are occupied, is smoothly converted into its dimethyl derivative.

In the production of tertiary amines in this way, one molecular proportion (or slightly more) of formaldehyde has been found sufficient for each methyl group introduced. It is therefore mainly the formic acid which supplies the hydrogen involved in the reduction



This is confirmed by the behavior of hexamethylenetetramine, in which only one-half of the amount of formaldehyde necessary for the formation of trimethylamine is potentially present. In the final mixture of products 70–80% of the methylene carbon reappears as methyl group, mainly in the

(1) This work was aided by a grant from The Chemical Foundation.

(2) Sommelet and Ferrand, *Bull. soc. chim.*, [4] **35**, 446 (1924).

(3) Orechoff and Norkina, *Ber.*, **65**, 724 (1932).

(4) Clarke, *J. Chem. Soc.*, **103**, 1700 (1913).

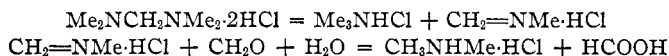
(5) Keil, *Z. physiol. Chem.*, **196**, 81 (1931).

(6) Wallach, *Ann.*, **343**, 54 (1905).

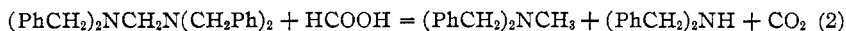
(7) Cf. Wagner, *THIS JOURNAL*, **55**, 724 (1933).

form of trimethylamine, as has been demonstrated by Sommelet and Ferrand.⁸ The deficiency of carbon must be due to the participation in the reduction of some of the formaldehyde liberated by hydrolysis, and not to the escape of formaldehyde nor to the production of methyl alcohol, for these have been shown not to occur to a significant extent. Moreover, less than 70% of the calculated amount of carbon dioxide is produced; this appears to be general in methylation reactions involving formaldehyde and formic acid, and furnishes a contrast to the theoretical yield⁹ obtainable in the reaction between formic acid and triphenylcarbinol.¹⁰ The hydrogen-donating function of formaldehyde, which constitutes an important feature in the Plöchl process¹¹ for methylation with formaldehyde alone, finds a counterpart in the behavior of the carbinol group in ethyl- α -pyrrolidylcarbinol and similar compounds;¹² this is converted into carbonyl during methylation by formaldehyde alone, but remains unaffected when the reaction is carried out in the presence of formic acid.

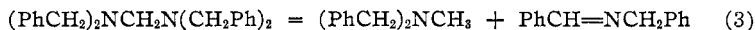
Werner's¹³ explanation of the production of trimethylamine by the action of formaldehyde upon ammonium chloride involves the scission of tetramethyldiaminomethane into trimethylamine and methylenemethylamine, which in turn accepts hydrogen from formaldehyde



In the methylation of simple amines by formaldehyde in formic acid this type of disruption appears not to occur, for secondary amines other than dimethylamine are converted, in excellent yields, into their N-methyl derivatives. Of those studied, the least favorable results were given by dibenzylamine, from which 75% of the amount of methyl dibenzylamine anticipated according to Reaction 1 was secured. Tetrabenzyl diaminomethane reacts with formic acid to yield equivalent amounts of methyl dibenzylamine and dibenzylamine



Were the preponderating reaction of the type analogous to that described by Werner, the primary products would have been methyl dibenzylamine and benzalbenzylamine



and the latter would, as we have found by experiment, immediately be hydrolyzed by the formic acid.¹⁴ Benzaldehyde is not formed to any

(8) Sommelet and Ferrand, *Bull. soc. chim.*, [4] **25**, 457 (1919); **35**, 446 (1924).

(9) A 99.1% yield of carbon dioxide was secured in this reaction when carried out under the conditions adopted for the present experiments.

(10) Kauffmann and Pannwitz, *Ber.*, **45**, 766 (1912); Kovache, *Ann. chim.*, [9] **10**, 184 (1918).

(11) Plöchl, *Ber.*, **21**, 2117 (1888).

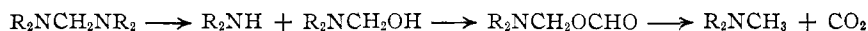
(12) Hess, *ibid.*, **46**, 4104 (1913); Hess, Merck and Ubrig, *ibid.*, **48**, 1886 (1915).

(13) Werner, *J. Chem. Soc.*, **111**, 844 (1917).

(14) Benzaldehyde is also hydrolyzed on warming with formic acid, no evolution of carbon dioxide nor reduction to methylbenzylamine taking place.

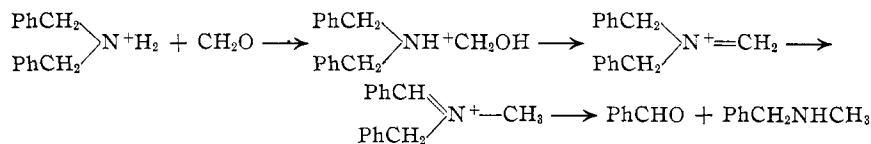
appreciable extent. Methylenedipiperidine also furnishes a clear-cut example of the type of Reaction 2.

It therefore appears reasonable to suppose that in the above case, as in that of simple amines, the main methylation reaction consists in the formation and subsequent reduction of a methylol derivative by the formic acid. As has been suggested by Emde,¹⁵ this possibly involves the thermal decomposition of the formic ester



The analogous formation of saturated hydrocarbons by pyrolysis of formic esters appears to be a general reaction.¹⁶ The ease with which it can take place probably depends upon the degree of polarity of the groups attached to the carbinol carbon atom; thus, triphenylcarbinol is reduced by formic acid at temperatures below 100°.

Among the products of the reaction of dibenzylamine with excess of formaldehyde in formic acid there occurs 6–12% of a more volatile base, probably dimethylbenzylamine, and a corresponding amount of benzaldehyde. Since, as above stated, benzaldehyde is barely detectable among the products of the action of formic acid upon tetrabenzylidiaminomethane, its formation cannot be explained along the lines of Reaction 3, but rather as a result of a rearrangement of a methylene derivative of an ammonium ion



The shift of unsaturation may be ascribed to the polar character of the phenyl groups, which favor the formation of conjugated double bonds. Slightly less benzaldehyde and somewhat more of the more volatile base were obtained when the formic acid was replaced by acetic acid.

A similar effect of unsaturation (in this case of the carbonyl group) has been observed¹⁷ in the conversion of aminocamphor hydrochloride into camphorquinone by heating with formaldehyde.

The behavior of aliphatic amino acids toward formaldehyde similarly displays the effect of the unsaturation inherent in the carboxyl group. Zeleny and Gortner¹⁸ have recently shown that when alanine, glutamic acid, tyrosine and cystine are boiled with an excess of formaldehyde in 20% hydrochloric acid, as much as 40% of the nitrogen is eliminated as methylamine. We find analogous decompositions to take place on warming amino acids with formaldehyde in formic and acetic acids. Glycine under

(15) Emde, *Apoth. Zeit.*, **44**, 1125 (1929); Emde and Hornemann, *Helv. Chim. Acta*, **14**, 892 (1931).

(16) Bayer & Co., German Patent 296,741 (*Chem. Zentr.*, [1] 611 (1917)).

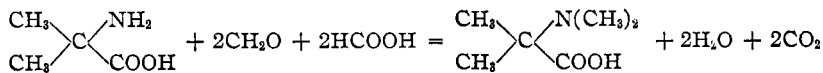
(17) Rupe, Buxtor and Flatt, *Helv. Chim. Acta*, **13**, 1026 (1930).

(18) Zeleny and Gortner, *J. Biol. Chem.*, **90**, 427 (1931).

these conditions yields 60–70% of dimethylglycine, but at the same time considerable amounts of more complex, non-crystallizable products, as well as 6% of volatile base (mostly trimethylamine) are formed in the reaction. β -Aminopropionic acid behaves in much the same way, though the yield of the dimethyl derivative is distinctly lower.

With alanine, on the other hand, none of the dimethyl derivative could be secured; a complex mixture was formed, and 36% of the nitrogen was converted into methylamines. Similar results were obtained with leucine, α -aminocaprylic acid and glutamic acid, in all of which an even greater proportion of the nitrogen was split off. When the formic acid was replaced by acetic acid, volatile bases were produced, but definitely less carbon dioxide was liberated.

The view that the deamination is associated with migration of unsaturated linkages is supported by the observation that α -aminoisobutyric acid, in which such migration is clearly impossible without decarboxylation, is converted into its dimethyl derivative in 80% yield



In this reaction over 88% of the theoretical amount of carbon dioxide was recovered, and only 5% of the nitrogen was detached.

α -Aminophenylacetic acid on treatment with formaldehyde and formic acid gave up over 50% of its nitrogen, together with an appreciable quantity of benzaldehyde. Inasmuch as benzylamine yields little or no benzaldehyde under these conditions, the disruptive effect must here be ascribed to the combined influence of the phenyl and carboxyl groups. With acetic acid in place of formic acid, benzaldehyde was likewise found, and a notable proportion of the nitrogen was released as volatile base; the yield of carbon dioxide was much lower. It is difficult to avoid speculation as to an analogy between this reaction and the formation of acetyl-amino ketones from amino acids and acetic anhydride in presence of pyridine.¹⁹ The possibility that at least a part of the carbon dioxide was derived from the carboxyl group is supported by the observation that α -aminophenylacetic acid yields benzylamine as the sole volatile base on heating in acetic acid solution with heptaldehyde. The formation of benzaldehyde is undoubtedly due to a secondary reaction which invites comparison with the "oxidative deamination" reaction between α -amino acids and furfural²⁰ or methylglyoxal.²¹

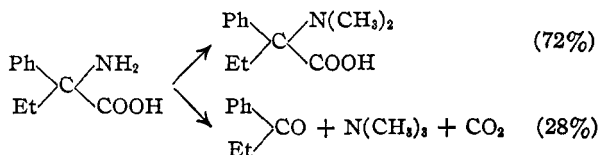
α -Phenyl- α -aminobutyric acid with formaldehyde in formic acid gave a 72% yield of its dimethyl derivative, 10–16% of the nitrogen appearing in volatile form. The yield of carbon dioxide closely approximated the

(19) Dakin and West, *J. Biol. Chem.*, **78**, 91, 745 (1928).

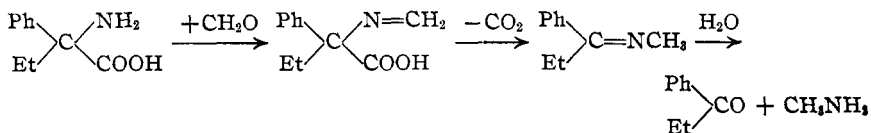
(20) Akabori, *Ber.*, **66**, 143 (1933).

(21) Kisch, *Biochem. Z.*, **257**, 334 (1933).

theoretical value, an effect which may reasonably be ascribed to the promotion of decarboxylation under the influence of the phenyl group. This hypothesis is supported by the isolation of 28% of propiophenone

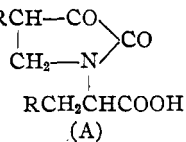


The side reaction, resulting in the formation of the ketone, probably takes the course

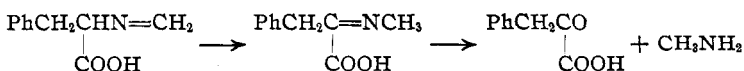


With amino acids of higher molecular weight, treatment with formaldehyde in either formic or acetic acid generally resulted in the formation of neutral nitrogenous products which were soluble in ether. This was also observed in the reactions with heptaldehyde. The physical character of these products, however, stood in the way of their detailed study.

dl-Phenylalanine with formaldehyde, in either formic acid or acetic acid solution, yielded a crystalline acid having the composition $\text{C}_{19}\text{H}_{17}\text{O}_4\text{N}$. An optically active variety of this acid was prepared from *l*-phenylalanine, and an optically active dimethoxy analog was obtained from *l-p*-methoxyphenylalanine.²² These compounds are derivatives of pyrrolidinedione; the evidence for the structure (A) is presented in the experimental part of this report. Like the triphenylpyrrolidinedione prepared by Borsche²³ from phenylpyruvic acid, benzaldehyde and aniline, they react exclusively in the enolic form, yielding green colors²⁴ with ferric chloride in alcohol and failing to yield hydrazones and similar ketonic derivatives under the usual conditions.



The formation of pyrrolidinedione from phenylalanine apparently involves the rearrangement of a methylene derivative, followed by hydrolysis to phenylpyruvic acid and methylamine



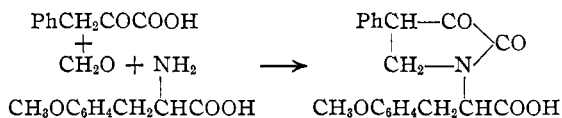
The phenylpyruvic acid then condenses with formaldehyde and a second molecule of phenylalanine, in analogy with the syntheses of triphenyl-

(22) Behr and Clarke, *THIS JOURNAL*, **54**, 1630 (1932).

(23) Borsche, *Ber.*, **41**, 3884 (1908); **42**, 4072 (1909).

(24) We have found that triphenylpyrrolidinedione in alcoholic solution develops with ferric chloride a green color resembling that obtained with phenylpyruvic acid.

pyrrolidinedione and of β -amino ketones.²⁵ The same product is equally readily formed from phenylalanine and formaldehyde in acetic acid solution; in this case the nitrogen eliminated in the reaction reappears almost entirely as methylamine. A similar yield was obtained on replacing half of the phenylalanine by a semi-equivalent amount of phenylpyruvic acid, when much less volatile base was formed. Even stronger evidence for the correctness of the above view is furnished by the formation, in excellent yield, of the corresponding monomethoxy derivative from phenylpyruvic acid, formaldehyde and *p*-methoxyphenylalanine



Since, as above stated, the volatile bases formed by the action of formaldehyde upon alanine in acetic acid likewise consist principally of monomethylamine, it seems logical to attribute the partial deamination of other amino acids by formaldehyde to a similar series of reactions.

Experimental

Methylation of Simple Amines.—One mole of the primary amine was added, with cooling, to 5 moles of formic acid (90%); 2.2 moles of formaldehyde (35% solution) was added. For secondary amines, half these quantities of acid and aldehyde were taken, though in either case excess does no harm. The mixture was heated on the steam-bath under reflux for two to four hours after evolution of gas had ceased (eight to twelve hours in all). Slightly more than one mole of hydrochloric acid was then added, and the formic acid and any excess formaldehyde were evaporated on the steam-bath. The colorless residue was dissolved in water, rendered alkaline with excess of 25% sodium hydroxide solution, and the base distilled out. The distillate was saturated with potassium hydroxide, the oil was separated, dried by heating with solid potassium hydroxide and distilled over sodium. In this way the following bases were obtained in yields of over 80%; dimethyl-*n*-butylamine, b. p. 94°; dimethylbenzylamine, b. p. 176–180°; methylpiperidine, b. p. 106°.

1,4-Tetramethyldiaminobutane.—To a solution of 4.6 g. of sodium bicarbonate in 18 cc. of 95% formic acid were added 4.0 g. of 1,4-diaminobutane hydrochloride and 10 cc. of formalin. The mixture was boiled under reflux for thirty-five hours, diluted with an equal volume of water containing 6 cc. of 10 *N* hydrochloric acid, and evaporated to dryness. The residue was redissolved in water, and the base isolated as above described, when 3.3 g. (92% of the theoretical amount) of the pure 1,4-tetramethyldiaminobutane, b. p. 167°, was secured. The picrate melted at 198–199°.

Aromatic Amines.—Treatment of aniline in formic acid with formalin led to the formation of a viscous oil, practically none of which was volatile with steam. With 2,4,6-tribromoaniline, on the other hand, methylation proceeded smoothly: a solution of 10 g. of the amine in 150 cc. of 90% formic acid and 10 cc. of formalin was boiled under reflux for two hours. After the addition of 3–5 cc. of concentrated hydrochloric acid and removal of most of the formic acid under reduced pressure, the residue was made alkaline and distilled with steam. The heavy oil which passed over was collected and

(25) Mannich, *Arch. Pharm.*, **255**, 261 (1917); *Ber.*, **53**, 1874 (1920); Bodendorf and Koralewski, *Arch. Pharm.*, **271**, 101 (1933).

redistilled; it boiled at 295–300° (uncorr.). The yield was 9.3 g. (77% of the calculated amount). As no rise in temperature was observed on adding acetic anhydride (with which the oil is only sparingly miscible) the product consists of a tertiary amine. It was definitely identified in the form of the perbromide²⁶ which melted at 124–125° with evolution of gas.

Dibenzylamine and Formaldehyde.—A mixture of 19.7 g. of dibenzylamine (0.1 mole), 25 cc. of 90% formic acid and 12 cc. of formalin was heated on the steam-bath for eighteen hours; it was then treated with 120 cc. of normal sulfuric acid and distilled in a current of steam. Benzaldehyde was extracted with chloroform from the distillate and yielded 1.87 g. of the phenylhydrazone (m. p. 155–157°). According to control experiments carried out in the presence of comparable amounts of formic acid and formaldehyde, this corresponds to about 12 millimoles of benzaldehyde. The residual acid solution was rendered alkaline and distilled at constant volume in a current of steam: seven successive 50–55 cc. fractions, collected and titrated separately, showed the presence of 11.8, 5.0, 3.1, 2.6, 2.2, 2.2, 2.2 milliequivalents of base, respectively. Neglecting the retention of methyl-dibenzylamine in the first four fractions due to the presence of a more volatile base, the amount of the latter (undoubtedly dimethylbenzylamine) may be inferred to have been about 13 m. eq. The less volatile methyl-dibenzylamine which had distilled, therefore, amounted to 16 m. eq.; the undistilled balance was isolated from the residue in a yield of 13.0 g. (61 m. eq.); after the removal of 2.5 m. eq. of base which reacted with acetic anhydride, it boiled at 146–147° (7 mm.) and contained 6.62% of N (calcd., 6.60).

In a parallel experiment with 7.1 g. (36 m. eq.) of dibenzylamine and 4.5 cc. of formalin in 11 cc. of acetic acid, 0.370 g. of benzaldehyde-phenylhydrazone (1.84 millimoles) was secured, while the presence of 9.4 m. eq. of more volatile bases was indicated by the distillation procedure.

Action of Formic Acid on Tetrabenzyl-diaminomethane and on Methylenedipiperidine.—A solution of 3.344 g. of tetrabenzyl-diaminomethane²⁷ (m. p. 99–101°) in 30 cc. of 90% formic acid was heated on the steam-bath under reflux for eight hours. After the addition of 3 cc. of concentrated hydrochloric acid, the mixture was distilled in a current of steam; the distillate contained only a trace of benzaldehyde, detected by a very faint odor. The residue was diluted to 500 cc. and an aliquot portion treated with alkali and benzenesulfochloride, then acidified and filtered free of benzenesulfonyl compounds. The filtrate contained 45.6% of the nitrogen in the form of tertiary amines.

An analogous experiment with 13.4 g. of methylenedipiperidine in 40 cc. of 90% formic acid gave 52.1% of the nitrogen as crystalline benzenesulfonylpiperidine and 45.3% as methylpiperidine.

Action of Formic Acid on Benzalbenzylamine.—A solution of 10 cc. of benzaldehyde in 5 cc. of alcohol was added to 10 cc. of benzylamine in 50 cc. of water. The heavy oil which separated, with evolution of heat, was collected and distilled²⁸ (b. p. 143–144° (5 mm.)).

Anal. Calcd. for $C_{14}H_{13}N$: N, 7.18. Found: N, 6.98.

On adding 2.05 g. of this product to 10 cc. of 90% formic acid the temperature rose slightly, and the odor of benzaldehyde at once appeared. The mixture was heated on the steam-bath for forty-four hours without appreciable evolution of carbon dioxide; on distilling in a current of steam, benzaldehyde passed over, and benzylamine was recovered from the residual solution.

Action of Formic Acid on Hexamethylenetetramine.—A solution of 0.560 g. (4 millimoles) of hexamethylenetetramine in 25 cc. of 90% formic acid (freed of dissolved

(26) Fries, *Ann.*, **346**, 200 (1906).

(27) Von Braun and Röver, *Ber.*, **36**, 1196 (1903).

(28) Mason and Winder, *J. Chem. Soc.*, **65**, 91 (1894), report b. p. 200–202° (10–20 mm.).

carbon dioxide) was boiled under reflux in a slow current of nitrogen for ten hours. The carbon dioxide evolved during the reaction was collected in barium hydroxide and estimated by titrating the precipitated barium carbonate with standard acid; it amounted to 33.6 m. eq. or 68.9% of the quantity theoretically obtainable. The residual solution was treated with excess of hydrochloric acid and freed of formic acid by evaporation; the residue was treated with alkali and the volatile bases again distilled out and converted into their hydrochlorides. These were dried as completely as possible and repeatedly extracted with boiling chloroform, which dissolved the salts of dimethylamine and trimethylamine. The amounts of these were determined on aliquot portions by estimating the volatile bases before and after treatment in dilute alkaline solution with benzenesulfochloride. The chloroform-insoluble residue, containing the hydrochlorides of ammonia and methylamine, was treated in dilute alkaline solution with mercuric oxide according to the method of Weber and Wilson²⁹ for the separation of these two bases. The values for the nitrogen distribution: NH_3 , 9.28; CH_3NH_2 , 0.85; $(\text{CH}_3)_2\text{NH}$, 0.70; $(\text{CH}_3)_3\text{N}$, 5.09—total, 15.92 m. eq.—correspond to 99.5% of the calculated amount of nitrogen but to only 73% of the carbon in the hexamethylenetetramine taken.

That the deficiency of carbon is not due to the escape of formaldehyde nor to the formation of methyl alcohol (or formate) was proved by boiling a solution of 10 g. of hexamethylenetetramine in 80 cc. of formic acid for six hours, collecting the evolved carbon dioxide in cold aqueous sodium hydroxide, and then distilling 6.5 cc. of the residual mixture. The distillate was rendered alkaline, united with the absorption liquid, and again distilled. Oxidation of an aliquot portion of the resulting distillate by standard dichromate indicated the presence of less than 10 mg. of methyl alcohol; *i. e.*, less than 0.1% of the amount corresponding to the carbon content of the hexamethylenetetramine. Formaldehyde was not detectable by ammoniacal silver nitrate.

Action of Acetaldehyde on Ammonia in Formic Acid.—To a cold mixture of 167 cc. of 90% formic acid and 11 cc. of 28% aqueous ammonia (0.2 mole) was added 33 cc. of acetaldehyde (0.6 mole). The whole was gently warmed on the steam-bath under reflux. Carbon dioxide was not evolved. After forty-two hours of heating the basic products were isolated; these consisted of ammonia and 2.5 cc. of a weakly basic oil which yielded 3.0 g. of 2-methyl-5-ethylpyridine picrate of m. p. 162–164°.

Action of Formaldehyde and Heptaldehyde on Amino Acids.—Two series of preliminary experiments were run with amino acids (2–5 millimoles), using rather more than twice the equivalent quantities of formaldehyde and carbon dioxide-free formic acid and acetic acid, respectively, as reaction media. Varying the proportions of the latter within wide limits had no apparent effect on the relative amounts of volatile base and carbon dioxide produced. Boiling was continued until the reaction had come to an end (three to eight hours).

The results are presented in Tables I and II. To these may be added a few points of detail. In the reaction of leucine with formaldehyde and formic acid, a neutral ether-soluble oil was formed; a similar product was obtained from α -aminocaprylic acid, and was found to contain 44.6% of the nitrogen. α -Aminophenylacetic acid also yielded an ether-soluble fraction containing 6.5% of the nitrogen; at the same time an appreciable quantity of benzaldehyde was formed. This occurred also in acetic acid; analysis of the volatile bases (25.1% of the nitrogen) produced in a parallel experiment in acetic acid, showed the nitrogen distribution to be 18.6% ammonia, 51.2% primary amines, and 30.2% di- and trimethylamines.

A few similar experiments were carried out with heptaldehyde in formic acid and acetic acid. To the information reported in Table III should be added the following: in Expt. 1 practically all of the non-volatile nitrogen in the aqueous solution was found to be in the primary amino form. In Expt. 2 the neutral ethereal extract was separated

(29) Weber and Wilson, *J. Biol. Chem.*, **35**, 385 (1918).

TABLE I

AMINO ACIDS WITH FORMALDEHYDE IN FORMIC ACID		
Amino acid	CO ₂ , moles per amino group	Volatile bases, % of total N
Glycine	1.55	5.7
Alanine	1.10	36.4
β -Aminopropionic	1.75	8.3
α -Aminoisobutyric	1.77	5.3
Leucine	..	25.5
Glutamic	1.43	51.4
α -Aminocaprylic	..	32.3
α -Aminophenyl-acetic	1.34	53.9
Phenylalanine	1.30	51.8
α -Amino- α -phenyl-butyric	1.99	10.6
Cystine	1.67	31.4

TABLE II

AMINO ACIDS WITH FORMALDEHYDE IN ACETIC ACID		
Amino acid	CO ₂ , moles per amino group	Volatile bases, % of total N
Glycine	0.49	15.1
Alanine	.41	13.2
β -Aminopropionic	.52	23.6
α -Aminoisobutyric	.81	29.8
α -Aminophenyl-acetic	.80	43.0
Phenylalanine	.60	26.0
Cystine	1.29	23.1

into two fractions, (a) soluble in petroleum ether, 5.834 g. containing 7.6 m. eq. of nitrogen (15.2%), and (b) insoluble in petroleum ether but soluble in benzene, 1.526 g. containing 4.75 m. eq. of nitrogen (9.5%). In Expt. 3 one-half of the nitrogen in the ether extract was in the primary amino form, while all of that in the water solution was amino nitrogen. In Expt. 4 the volatile base consisted entirely of benzylamine, b. p. 180–190°, identified as dibenzylamide, m. p. 216°. The oily ether-soluble fraction, weighing 7.1 g., was distilled under reduced pressure, when about half of it passed over at 180–190° (10 mm.) before decomposition set in. The distillate partially crystallized on cooling, yielding colorless leaflets, m. p. 57°, very soluble in alcohol and ether, but sparingly in petroleum ether, and containing: C, 72.82; H, 7.55; N, 8.3. It is doubtful if the product was homogeneous; the amount available was too small for further study.

TABLE III

ACTION OF HEPTALDEHYDE ON AMINO ACIDS

Expt.	Amino acid	Acid	Time and temp. of heating		Volatile N, %	Ether-soluble N, %	Water-soluble N, %
			Hours	t, °C.			
1	Alanine	HCOOH	16	90	1.3	2.65	95
2	Alanine	AcOH	40	115	7.4	24.7	56
3	α -Aminophenylacetic	HCOOH	16	90	13.8	46.3	36
4	α -Aminophenylacetic	AcOH	21	115	13.6	61.4	..

In several instances the reaction with formaldehyde was investigated more closely on a larger scale; the more significant of such experiments are reported in detail.

Dimethylglycine Hydrochloride.—A mixture of 22.5 g. (0.3 mole) of glycine, 75 cc. of 90% formic acid and 60 cc. of formalin was gently boiled under reflux for seventeen hours; 30 cc. of concentrated hydrochloric acid was added, and the solution was evaporated to a sirup under reduced pressure. The crystals which separated on cooling were collected, washed with acetic acid, dried and recrystallized from water. The mother liquor yielded 27–28 g. (64–67% of the calculated quantity) of dimethylglycine hydrochloride as needles of m. p. 189–190° (uncorr.), readily soluble in water and alcohol, sparingly soluble in cold but readily in warm acetic acid, insoluble in chloroform and acetone.

Anal. Calcd. for $C_4H_{10}O_2NCl$: C, 34.5; H, 7.17; N, 10.03; Cl, 25.4. Found: C, 34.70, 34.56; H, 7.11, 6.81; N, 10.02; Cl, 25.36.

The free dimethylglycine was prepared as an extremely hygroscopic solid by treating a cold aqueous solution with an exactly equivalent quantity³⁰ of freshly-precipitated silver oxide, filtering and evaporating to dryness.

The ethyl ester was identical with that described by Willstätter.³¹ It boiled at 149°.

Anal. Calcd. for $C_6H_{13}O_2N$: C, 54.9; H, 9.93; N, 10.68. Found: C, 54.7, 54.9; H, 9.68, 9.63; N, 10.47.

On hydrolysis with dilute hydrochloric acid, the original hydrochloride, m. p. 189–190°, was regenerated.

The united mother liquors from an experiment which had given a 67% yield of dimethylglycine hydrochloride contained 60.5 m. eq. of nitrogen (20.2%), of which 13.8 m. eq. (4.6%) was in the form of volatile bases. After evaporation, the residue was extracted with chloroform (to remove trimethylamine hydrochloride), warmed with alcoholic hydrogen chloride in order to form ethyl esters, concentrated and extracted with ether. The ethereal solution on evaporation left 0.2–0.3 g. of a residue which contained 0.8 m. eq. of (non-basic) nitrogen. The ether-insoluble portion was rendered alkaline with potassium carbonate solution and extracted with ether, which took up slightly less than 1 g. of a product containing 9.0 m. eq. of (basic) nitrogen. The watery solution contained 48.9 m. eq. of nitrogen.

Alanine and Formaldehyde.—(1) A mixture of 8.9 g. (0.1 mole) of alanine, 15 cc. of 90% formic acid and 10 cc. of formalin was heated under reflux on the steam-bath. Rapid evolution of carbon dioxide occurred. After two hours, 10 cc. of concentrated hydrochloric acid was added, and the mixture was evaporated to dryness. The dark brown, sirupy residue, which contained 11.0 m. eq. of trimethylamine and 85.7 m. eq. of non-volatile nitrogen, was esterified by alcoholic hydrogen chloride and subjected to ether extraction from acid and alkaline solution. The ether extract from acid solution (wt. 0.1 g.) contained 0.3 m. eq. N; that after adding potassium carbonate (wt. 1 g.) contained 4.6 m. eq. N; the residual alkaline solution contained 91.0 m. eq. N. The bases extracted by ether distilled over a wide range, mainly above 220°, with decomposition.

(2) A mixture of 17.8 g. (0.2 mole) of alanine, 80 cc. of acetic acid and 36 cc. of formalin was boiled under reflux for twenty minutes; the light brown solution was treated with 100 cc. of *N* sulfuric acid and evaporated to dryness under reduced pressure. The brown, amorphous residue was dissolved in 250 cc. of water, made alkaline with 100 g. of crystallized barium hydroxide, and distilled into standard acid. The volatile bases amounted to 14.9 m. eq.; these were found to consist of 2.34 m. eq. of ammonia, 8.56 m. eq. of methylamine, and 3.93 m. eq. of di- and trimethylamine. The residual alkaline solution was diluted, freed of barium hydroxide with carbon dioxide, concentrated, filtered and treated with 800 cc. of absolute alcohol. The precipitate was redissolved in water and reprecipitated with alcohol. After drying it weighed 7.2 g.; it contained 5.8% of nitrogen and 20.2% of barium.

β -Dimethylaminopropionic Acid Hydrochloride.—A mixture of 3.56 g. of β -aminopropionic acid, 25 cc. of 90% formic acid and 5 cc. of formalin was boiled under reflux for eight hours, treated with 5 cc. of concentrated hydrochloric acid, and evaporated to complete dryness. The crystalline residue was washed with 10–15 cc. of glacial acetic acid, which removed a viscous by-product. The yield of colorless crystals, which melted at 188–191° (uncorr.), was 2.3 g. (38% of the calculated amount).

(30) Excess of silver oxide must be avoided as it rapidly oxidizes the dimethylglycine to carbon dioxide and dimethylamine, even in the cold.

(31) Willstätter, *Ber.*, **36**, 599 (1902).

Anal. Calcd. for $C_8H_{12}O_2NCl$: C, 39.0; H, 7.16; N, 9.12; Cl, 23.8. Found: C, 39.4; H, 7.74; N, 8.81; Cl, 22.4.

α -Dimethylamino-isobutyric Acid Hydrochloride.—A mixture of 5.15 g. (0.05 mole) of α -aminoisobutyric acid, 13 cc. of 90% formic acid and 10 cc. of formalin was gently warmed under reflux. At 68°, evolution of gas began; it ceased after one and one-half hours, when the temperature had risen to 107°. After two hours 6 cc. of concentrated hydrochloric acid was added and the mixture was evaporated to dryness at 90–100°. The crystalline residue was recrystallized from acetic acid; in all 6.65 g. (80% of the calculated amount) of colorless needles was secured. The product is the hydrochloride of α -dimethylaminoisobutyric acid.

Anal. Calcd. for $C_6H_{14}O_2NCl$: N, 8.36; Cl, 21.2. Found: N, 8.30, 8.10; Cl, 21.1, 21.0.

It melts with decomposition at 264° (uncorr.), is readily soluble in water, alcohol and boiling acetic acid, sparingly in cold acetic acid, but insoluble in acetone or chloroform. A similar experiment with 25.75 g. of the amino acid gave a yield of 30.0 g. (72%) of the hydrochloride.

No attempt was made to prepare the free dimethylamino acid. After long boiling with methyl alcoholic hydrogen chloride, the bulk of the original hydrochloride crystallized out unchanged; the mother liquor, on treatment with ether and saturated potassium carbonate solution, furnished a small yield (20–25%) of the methyl ester, b. p. 154–155°. This is a colorless liquid, miscible with water but insoluble in concentrated potassium carbonate.

Anal. Calcd. for $C_7H_{15}O_2N$: N, 9.66. Found: N, 9.70.

α -Dimethylamino- α -phenylbutyric Acid.—A mixture of 0.90 g. of α -amino- α -phenylbutyric acid,³² 2 cc. of formic acid and 1 cc. of formalin was boiled for forty minutes, cooled and diluted with 5 cc. of water, which caused the separation of 0.29 cc. of a neutral oil, identified as propiophenone by its semicarbazone m. p. 176–178° (uncorr.). The residual solution was evaporated and treated with acetone. The resulting needles, weighing 0.75 g., melted with decomposition at 220° (uncorr.) and were readily soluble in cold water and alcohol but insoluble in acetone.

Anal. Calcd. for $C_{12}H_{17}O_2N$: C, 69.6; H, 8.22; N, 6.77. Found: C, 69.6; H, 8.37; N, 6.57.

The mother liquor gave a 16.4% yield of volatile bases.

α -Aminophenylacetic Acid and Formaldehyde.—A mixture of 5.0 g. of α -aminophenylacetic acid, 50 cc. of acetic acid, and 5 cc. of formalin was boiled for eight hours and then distilled in a current of steam. The benzaldehyde in the distillate yielded 0.5 g. (7.6%) of the phenylhydrazone. The residual solution contained 18.1% of the original nitrogen in the form of volatile bases having the following distribution (determined by the method outlined for hexamethylenetetramine): NH_3 , 6.7; CH_3NH_2 ,³³ 46.6; $(CH_3)_2NH$, 39.4; $(CH_3)_3N$, 7.2.

Phenylalanine and Formaldehyde.—(1) A mixture of 3.3 g. of *dl*-phenylalanine, 10 cc. of 90% formic acid and 2 cc. of formalin was warmed on the steam-bath for fifteen minutes. Carbon dioxide was rapidly evolved; separation of crystals occasionally occurred. The reaction mixture was cooled and diluted with 2 cc. of water; the crystalline product was collected, washed with 5 cc. of cold alcohol, and recrystallized from 50 cc. of hot alcohol. A further small quantity was obtained from the mother liquors. The total yield was 2.2 g. of colorless hexagons or needles which melted at 245–246° (uncorr.).

(32) The authors are indebted to Dr. R. M. Herbst for this substance.

(33) This fraction included traces of other bases possessing hydrochlorides insoluble in chloroform; it melted at 210–213° (12° lower than pure methylamine hydrochloride).

Anal. Calcd. for $C_{19}H_{17}O_4N$: C, 70.59; H, 5.27; N, 4.34; mol. wt., 323. Found (different samples): C, 70.70, 70.65, 70.63, 70.47, 70.45; H, 5.47, 5.44, 5.42, 5.24, 5.25; N, 4.30, 4.42, 4.65; mol. wt. (in camphor), 319.

The combined mother liquor from several such preparations was rendered alkaline and distilled; the volatile bases consisted entirely of methylamine hydrochloride which melted at 222–227° and showed no depression when mixed with an authentic sample.

(2) A solution of 3.3 g. of *l*-phenylalanine⁸⁴ (which had $[\alpha]_D^{20} -11.7^\circ$ in water, and was therefore more than two-thirds racemized) in 12.5 cc. of formic acid and 2 cc. of formalin was heated for one hour on the steam-bath, and the product (2.1 g.) isolated as above. It melted at 250–251° (uncorr.) and, apart from its optical activity, appeared to be identical with the product from *dl*-phenylalanine.

Rotation. $[\alpha]_D^{20} -37.6^\circ$ (2.7% in *N* NaOH).

(3) To a suspension of 3.3 g. of *dl*-phenylalanine in 13 cc. of acetic acid was added 2 cc. of formalin. Solution took place readily in the cold. On boiling for one hour, no apparent evolution of gas occurred; the acetic acid was evaporated under reduced pressure and the residue recrystallized from alcohol; yield 1.00 g., m. p. 246°; m. p. of mixture with sample prepared in formic acid, 245°.

Anal. Found: C, 70.64; H, 5.58; N, 4.37; mol. wt. (in camphor), 336.

The mother liquor contained 3.7 m. eq. of volatile base, of which 3.3 m. eq. consisted of methylamine (hydrochloride m. p. 225°) and 0.4 m. eq. of di- and trimethylamines.

(4) A solution of 1.65 g. of *dl*-phenylalanine, 0.83 g. of phenylpyruvic acid and 1 cc. of formalin in 13 cc. of acetic acid was boiled under reflux for one hour. The acetic acid was evaporated under reduced pressure, and the residue crystallized from alcohol. The weight of the crude product was 1.00 g.; after one recrystallization it melted at 245°, and was identical with preparations from phenylalanine alone. The mother liquors contained 1.03 m. eq. of volatile base, which comprised 19% of ammonia, 77% of methylamine and 4% of di- and trimethylamines.

Di-*p*-methoxy Derivative of $C_{19}H_{17}O_4N$.—To a warm solution of 7.0 g. of *l-p*-methoxyphenylalanine in 15 cc. of formic acid was added 4 cc. of formalin. Evolution of gas occurred at once. After being boiled under reflux for one hour, the mixture was diluted with an equal volume of alcohol and evaporated to 20 cc. The crystalline product was collected and washed with cold alcohol; it weighed 1.2 g. and melted at 217–218°. After two recrystallizations from absolute alcohol it was obtained as prisms which melted sharply, with decomposition, at 231°. In general properties it closely resembled the product obtained from phenylalanine. Several preparations were analyzed.

Anal. Calcd. for $C_{21}H_{21}O_6N$: C, 65.8; H, 5.48; N, 3.66; OCH_3 , 16.19. Found: C, 66.0, 65.7, 66.0, 65.8; H, 5.69, 5.66, 5.41, 5.31; N, 3.85, 3.72; OCH_3 , 16.00.

Rotation. $[\alpha]_D^{21} -31.0^\circ$ (3.6% in *N* NaOH).

The filtrate from the crystals gave a 25% yield of volatile bases having nitrogen distribution: NH_3 , 0; CH_3NH_2 , 73; $(CH_3)_2NH$, 28; $(CH_3)_3N$, 5.

Mono-*p*-methoxy Derivative of $C_{19}H_{17}O_4N$.—A solution of 3.24 g. of *l-p*-methoxyphenylalanine, 2.74 g. of phenylpyruvic acid and 1.2 cc. of formalin in 20 cc. of acetic acid was boiled under reflux for one hour. To the cold mixture was added 1.6 cc. of concentrated hydrochloric acid, and the crystalline product (3.35 g.) washed first with a little cold acetic acid and then with alcohol, and recrystallized from absolute alcohol. It then melted at 239–240°; its general properties were almost identical with those of $C_{19}H_{17}O_4N$.

Anal. Calcd. for $C_{20}H_{19}O_5N$: C, 68.0; H, 5.38; N, 3.97; OCH_3 , 8.78. Found: C, 67.9; H, 5.68; N, 4.44; OCH_3 , 8.81.

(84) A sample of protein origin, generously presented by Dr. H. B. Vickery.

Rotation. $[\alpha]_D^{21.5} - 135.5^\circ$ (3.6% in *N* NaOH).

The mother liquor gave a 3.6% yield of volatile bases, of which one-third consisted of ammonia.

Constitution of $C_{19}H_{17}O_4N$

The compound is insoluble in water and in dilute acids; it readily dissolves in cold concentrated sulfuric acid, from which it is precipitated unchanged on dilution. It is soluble in ammonia and in dilute alkalis (1 equivalent of 0.1 *N*) or alkali carbonate solutions. It is moderately soluble in acetic acid and acetone, less so in alcohol, and almost insoluble in ether, benzene and carbon tetrachloride. An alcoholic solution yields an intense blue-green color with ferric chloride.

Barium Salt.—On attempting to determine the neutral equivalent, employing phenolphthalein as indicator, indefinite end-points were obtained on titration with sodium hydroxide in water solution. They were somewhat sharper in alcohol, but the observed neutral equivalents varied with the composition of the solvent; 210 in 25% alcohol, 188 in 80% alcohol. A satisfactory end-point was secured by titrating the compound in alcohol with barium hydroxide, when the barium salt precipitated; a neutral equivalent of 165.5 (calcd. 161.5) was found in this way. The barium salt (microscopic plates) was collected, washed with alcohol and dried at 100° .

Anal. Calcd. for $C_{19}H_{15}O_4N \cdot Ba \cdot 3H_2O$: C, 44.5; H, 4.10; Ba, 26.7. Found: C, 44.4; H, 4.05; Ba, 26.8.

No loss of weight occurred at 115° (sixteen hours); at 150° decomposition took place, but only 2.17% was lost in three hours.

A flocculent, alcohol-soluble silver salt was precipitated on adding silver nitrate to a solution of the ammonium salt, but this rapidly decomposed, even in the dark, with formation of metallic silver and an odor of phenylacetaldehyde.

Absence of Basic Properties.—No reaction was observed in acetone or alcohol solution with alcoholic hydrochloric acid, employing benzene-azo- α -naphthylamine as indicator. The compound formed no platinichloride, and was recovered unchanged after treatment in alkaline solution with phenyl isocyanate. It yielded no nitrogen on treatment with sodium nitrite and acetic acid.

Decarboxylation.—A 0.500-g. sample, heated at 255° in a current of hydrogen, evolved 0.068 g. of carbon dioxide, together with 0.016 g. of moisture (calcd. for loss of one COOH: CO_2 , 0.0678 g.).

Oxidation.—The compound is readily oxidized by cold, alkaline permanganate: a solution of 0.0808 g. in 5 cc. of 0.1 *N* sodium hydroxide required 30.5 cc. of 0.1 *N* potassium permanganate. The only product obtained was impure benzoic acid (m. p. 98°) which gave a green color with alcoholic ferric chloride (suggesting the presence of phenylpyruvic acid). No volatile base was formed.

Permanganate in acetone, and alkaline hypobromite are readily reduced, but bromine in acetic acid is only slowly decolorized and Fehling's solution is without action. Profound oxidation occurs on heating in water with silver oxide: 0.0808 g. of the compound, boiled with a water suspension of the freshly precipitated and washed oxide from 2 g. of silver nitrate, yielded 0.0612 g. of carbon dioxide (calcd., 0.055 g.). In a similar experiment with 4.98 g. (15.4 millimoles) of the compound and the oxide from 45 g. of silver nitrate, the volatile base amounted to 5.45 m. eq. and consisted entirely of ammonia.³⁵ The residual solution contained 1.95 m. eq. of non-volatile nitrogen; the remaining 52% was not accounted for. Benzaldehyde (identified as the phenylhydra-

(35) An investigation, in progress in this Laboratory, of the action of silver oxide upon amino acids indicates that *N*-alkyl derivatives of such acids yield, under these conditions, all of their nitrogen in the form of the corresponding alkylamine. In this case, therefore, no methyl group appears to be attached to the nitrogen atom.

zone m. p. 156–158°) was formed in small amount. The reduced silver amounted to 250 m. eq., or 90% of the quantity calculated from the equation: $C_{19}H_{17}O_4N + 9Ag_2O = 2C_6H_5CHO + 5CO_2 + NH_3 + H_2O + 18Ag$.

Hydrogen peroxide oxidized the compound: a solution of 1.00 g. (3.09 millimoles) in 16 cc. of 0.5 *N* sodium hydroxide was treated with 10 cc. of 30% hydrogen peroxide. After twenty-four hours at room temperature the mixture was acidified and extracted with ether. The extracted acids were redissolved in alkali and precipitated from a volume of 15–20 cc.; the resulting crystals melted at 122° and did not depress the melting point of pure benzoic acid. The filtrate from the benzoic acid had the odor of phenylacetic acid; it was not found possible to isolate this product, but further evidence for its presence was secured by distilling out the volatile acids (0.59 m. eq.) and boiling the distillate with silver oxide (from 2.5 g. of silver nitrate) for five hours. The odor of phenylacetic acid had then disappeared, and 0.96 m. eq. of metallic silver had formed. This corresponds to the oxidation of 0.16 m. eq. of phenylacetic acid³⁶ to benzoic acid.

Alkaline Fusion.—On fusion with alkali, ammonia is evolved, together with vapors having the odor of styrene. In a typical experiment a mixture of 0.529 g. (1.63 millimoles) of the compound, 2 g. of powdered potassium hydroxide and 0.5 cc. of a 40% solution of sodium hydroxide was heated by an oil-bath in a platinum crucible enclosed in a glass tube through which a slow current of nitrogen was passed. The issuing vapors were led through a trap surrounded by solid carbon dioxide in alcohol (to condense any styrene), and then into dilute acid. The bath was held at 280–285° for three hours. The contents of the chilled tube were treated with dilute sulfuric acid and extracted with five 10-cc. portions of chloroform. The acid layer was joined with that in the absorption vessel and the volatile base determined in the regular way. It amounted to 1.02 m. eq. (65% of the calculated quantity) and consisted almost entirely of ammonia. The chloroform layer was treated with a slight excess of bromine and evaporated at room temperature, when yellow crystals were obtained which melted at 68–70° (styrene dibromide melts at 73°). The residue in the crucible was rapidly dissolved in water and the solution acidified, when 0.2305 g. of carbon dioxide was evolved. This is 107% of the amount of carbon dioxide calculated from the equation:³⁷ $C_{19}H_{17}O_4N + 6KOH = 2C_6H_8 + NH_3 + 3K_2CO_3 + H_2O + H_2$. The acid solution remaining after the expulsion of the carbon dioxide contained a small amount of a black precipitate, but no acids extractable by ether.

Acetylation.—The compound was recovered unchanged after being boiled for forty hours with 10 parts of anhydrous formic acid—evidence of the absence of alcoholic hydroxyl groups. On the other hand, though insoluble in cold acetic anhydride, it slowly dissolves on warming, and then fails to separate on cooling. Such a solution, prepared from 0.3 g. in 3 cc. of anhydride, was allowed to evaporate in a vacuum desiccator over solid potassium hydroxide. The rather sticky, crystalline residue was recrystallized from a mixture of ethylene chloride (in which it was very soluble) and benzene (which dissolved it only sparingly), when it was obtained in the form of long, thin needles which melted at 192–194° (uncorr.). From its analysis it appears to be an internal anhydride of a monoacetyl derivative.

Anal. Calcd. for $C_{21}H_{17}O_4N$: C, 72.7; H, 4.90; N, 4.04. Found: C, 73.5; H, 5.20; N, 3.79.

A suspension of 68.0 mg. in 8 cc. of acetone was titrated with 0.1 *N* sodium hydroxide in the cold, employing phenolphthalein. When 3.3 cc. had been added, solution was complete and the pink color appeared. This soon faded on warming. The titration

(36) Unpublished results of experiments by Dr. R. M. Herbst in this Laboratory indicate the approximate correctness of this interpretation.

(37) The reaction with alkali probably involved not only decarboxylation but oxidation of the type studied by Fry and collaborators [*THIS JOURNAL*, **46**, 2268 (1924); **48**, 958 (1926); **50**, 1122 (1928)].

was continued until a permanent end-point had been reached; this occurred with 6.3 cc. of the alkali, whence the saponification equivalent was 108 (calcd., 116). The acetone was then evaporated and the residual solution acidified; the precipitate was washed with water, then with alcohol and dried. It melted at 247–248°, and obviously consisted of the original compound, $C_{19}H_{17}O_4N$.

Benzoylation.—An apparently hydrated benzoyl derivative was prepared by shaking a solution of 1.0 g. of the compound in 20 cc. of 4 *N* sodium hydroxide with 6 cc. of benzoyl chloride in two portions. The resulting solution was acidified with 5 cc. of acetic acid, the granular precipitate was filtered off at once and repeatedly extracted with warm ligroin. The heavy, pale yellow, insoluble sirup was dissolved in ethylene chloride, and the filtered solution concentrated to 3 cc. On treatment with 15 cc. of ligroin an oil was precipitated; this was washed with petroleum ether and dried *in vacuo* over phosphorus pentoxide. A friable resin weighing 1.45 g. remained. It melted at 60° after softening at a lower temperature.

Anal. Calcd. for $C_{26}H_{23}O_6N$: C, 70.2; H, 5.17; N, 3.15. Found: C, 70.4; H, 5.8; N, 2.94.

The product is readily soluble in alcohol; on adding a few drops of dilute alkali to the solution, the odor of ethyl benzoate is developed at once in the cold. The saponification equivalent, determined in the same way as described for the acetyl derivative, was 146.5 (calcd., 148.3). On acidifying after titration, the original acid was regenerated, m. p. 249° after recrystallization from acetone.

Methyl Ester.—On esterification by methyl alcoholic hydrogen chloride, only one alkyl group enters the molecule; the product consisted of prisms of m. p. 118°.

Anal. Calcd. for $C_{20}H_{19}O_4N$: C, 71.2; H, 5.64; N, 4.15; OCH_3 , 9.19. Found: C, 71.3; H, 5.78; N, 4.30; OCH_3 , 9.16.

This derivative gave the blue-green color with alcoholic ferric chloride. On titrating a cold solution in methyl alcohol with barium hydroxide, employing phenolphthalein, a neutral equivalent of 326 (calcd., 337) was obtained. No precipitate was formed until an excess of barium hydroxide was added and the mixture had been boiled. Titration of the excess of baryta after two hours of heating gave a saponification equivalent of 154 (calcd., 161.5).

Methyl Ether.—To a solution of 1.0 g. of the compound in 7 cc. of *N* sodium hydroxide was added, in several portions and with vigorous shaking, 1 cc. of methyl sulfate, further additions of sodium hydroxide being made so as to maintain alkalinity to litmus. A gummy precipitate formed; when the reaction was complete, the clear supernatant solution was decanted and acidified with hydrochloric acid. The amorphous precipitate was collected, washed with water, and dissolved in a small amount of methyl alcohol; the solution was allowed to evaporate over sulfuric acid. The amorphous residue, which melted rather indefinitely at 75–90°, was very soluble in methyl alcohol. With alcoholic ferric chloride, only a pale yellow color developed, indicating the methylation of an enolic hydroxyl group.

The barium salt of the methyl ether was precipitated on adding an excess of 0.4 *N* barium hydroxide to a solution of 0.5 g. of the ether in 5 cc. of cold methyl alcohol. It is insoluble in alcohol, but somewhat soluble in hot water, from which it separates in gelatinous form on cooling.

Anal. Calcd. for $(C_{20}H_{18}O_4N)_2Ba$: C, 59.3; H, 4.45; Ba, 16.95; OCH_3 , 7.68. Found: C, 59.2; H, 4.43; Ba, 16.93; OCH_3 , 7.69.

The anilide was prepared by heating 0.3 g. of the methyl ether with 1.5 cc. of aniline for two minutes and then distilling off the bulk of the excess aniline under reduced pressure. The oily residue was washed with dilute acetic acid and dissolved in methyl alcohol, from which it separated in rectangular prisms melting at 208° (uncorr.).

Anal. Calcd. for $C_{22}H_{25}O_3N_2$: N, 6.78; OCH_3 , 7.51. Found: N, 6.58; OCH_3 , 7.23.

Methyl Ester of Methyl Ether.—The gummy precipitate formed by the action of methyl sulfate and alkali was dissolved in a small volume of methyl alcohol and an equal volume of water was slowly added to the filtered solution. The product separated as an oil which rapidly crystallized; yield, 0.5 g. of prisms melting at 78° .

Anal. Calcd. for $C_{21}H_{21}O_4N$: C, 71.8; H, 5.98; N, 3.98; OCH_3 , 17.66; sapon. eq., 351. Found: C, 71.6; H, 6.03; N, 4.10; OCH_3 , 16.77, 16.83; sapon. eq., 357.

An alcoholic solution gave only a pale yellow color with ferric chloride. The solution obtained after saponification gave, on acidification, a product identical with the above methyl ether.

Anilide of Anil.—A suspension of 1.0 g. of $C_{18}H_{17}O_4N$ in 3 cc. of aniline was gently heated over the flame; before the boiling point of aniline was reached, solution suddenly took place with evolution of steam. After being boiled under reflux for twenty minutes the mixture was allowed to cool, and the product which separated was recrystallized from acetone; yield, 0.9 g. of prismatic needles which melt without decomposition at 215° (uncorr.).

Anal. Calcd. for $C_{31}H_{27}O_2N_2$: C, 78.6; H, 5.71; N, 8.86. Found: C, 78.9; H, 5.82; N, 9.33.

This derivative is insoluble in alkali and gives no color with ferric chloride.

Reduction of Carbonyl.—Treatment of the compound with hydrogen under pressure and an active palladium, or platinum oxide, catalyst was without effect when 0.1 *N* sodium hydroxide (2 equivalents) was employed as a solvent,³⁸ nor did reduction occur on treating an alkaline solution with sodium amalgam. Boiling with red phosphorus in a mixture of hydriodic acid and acetic anhydride led to the formation of tarry products only. A solution in acetic anhydride failed to respond to catalytic hydrogenation, using palladium; the crystalline product, after hydrolysis by alkali, yielded only the starting material.

However, zinc dust in acetic acid, with which Borsche reduced triphenylpyrrolidinedione,³⁹ brings about the desired reduction, yielding a product which neither crystallized nor yielded a crystalline barium salt. It was not analyzed, for as it gave no color with ferric chloride, there was no question as to its identity.

Hydroxylamine Derivative.—On treatment in dilute acetic acid with phenylhydrazine, *p*-nitrophenylhydrazine and semicarbazide, no reaction occurred, and unchanged material was recovered. A new compound, however, was formed with hydroxylamine: to a solution of 0.5 g. of the acid in 4 cc. of *N* sodium hydroxide was added 0.2 g. of hydroxylamine hydrochloride. An oily precipitate formed and soon became crystalline. Solution occurred on heating to 100° ; 0.2 cc. of glacial acetic acid was added, and the oily precipitate stirred until it had completely crystallized. It melted with decomposition at 185 – 186° , after becoming yellow above 160° . It was dried at 100° for analysis.

Anal. Calcd. for $C_{19}H_{18}O_4N_2$: C, 67.5; H, 5.33; N, 8.29. Found: C, 67.8; H, 5.58; N, 7.67.

This substance is appreciably soluble in cold water, readily in hot water and in alcohol. Although its analytical figures are in reasonable accord with those calculated for an oxime, its general properties indicate a less stable type of compound, in which the enolic character persists. It gives a blue-green color with ferric chloride in alcohol and readily reduces Fehling's solution. On adding, in small portions, an equal volume of *N* hydrochloric acid to a cold, concentrated alcoholic solution, the original acid (m. p. 246° dec.) crystallizes.

(38) In a control experiment with the palladium catalyst under the same conditions, α -benzoylaminocinnamic acid was smoothly reduced to benzoylphenylalanine, m. p. 182 – 183° .

(39) Borsche, *Ber.*, **42**, 4077 (1909).

Summary

Simple aliphatic amines are smoothly methylated to the corresponding tertiary amines by warming in formic acid solution with formaldehyde. Dibenzylamine, under these conditions, is mainly converted into methyl-dibenzylamine, but at the same time yields some benzaldehyde and a more volatile base (probably dimethylbenzylamine).

Tetra-alkyl-diaminomethanes, on warming with formic acid, are converted into equimolar quantities of the corresponding dialkylamine and methyldialkylamine. Hexamethylenetetramine reacts with warm formic acid yielding mainly ammonia and trimethylamine, with smaller amounts of mono- and dimethylamines; only three-quarters of the methylene carbon reappears as methyl in the final mixture.

Only about two-thirds of the anticipated amount of carbon dioxide, calculated on the assumption that the formic acid is the sole hydrogen donor, is obtained in these reactions; apparently some of the formaldehyde also contributes hydrogen.

Amino acids react with formaldehyde in warm formic or acetic acid with detachment of some of the nitrogen in the form of volatile bases. Dimethyl derivatives were isolated from the reaction in formic acid with glycine, β -aminopropionic acid, α -aminoisobutyric acid and α -amino- α -phenylbutyric acid. Other amino acids yielded breakdown and condensation products of various degrees of complexity. Benzaldehyde was isolated from α -aminophenylacetic acid, propiophenone from α -amino- α -phenylbutyric acid, and α -(4-phenyl-2,3-diketopyrrolidyl)- β -phenylpropionic acid from phenylalanine. Mechanisms by which these products may be formed are suggested.

NEW YORK CITY

RECEIVED JUNE 19, 1933
PUBLISHED NOVEMBER 7, 1933