Pa.), equipped with a Dispersomax stirrer, a heating mantle, and cooling coils. Instruments for measuring oxygen absorption and formation of carbon dioxide and carbon monoxide were employed to monitor the reaction. Molecular oxygen was used as the oxidant, introduced into the autoclave through a medium porosity, 2-in. o.d. stainless steel sparger. In the closed system, oxygen was supplied at the rate at which it was consumed. In the continuous system, exit gases were removed at about 1 l./hr.

In a typical experiment (expt 3, Table I), 157 g of *n*-butane was charged into the autoclave together with a solution of 20 g of cobaltous acetate tetrahydrate in 280 g of glacial acetic acid as well as 20 g of MEK. This mixture was agitated for 2 hr at 110° and 24 atm of total pressure. The autoclave was then cooled and depressured through a series of Dry Ice–acetone traps, and the product was withdrawn. A total of 615.7 g of material was recovered from the autoclave and an additional 20.3 g of butane from the traps. Analysis was carried out employing standard procedures such as vpc, titration, and distillation. Water of reaction and nonacidic oxygenated products were determined by vpc on a 4-ft Porapak Q column, programmed from 75 to 250° at 10°/min using acetone as the internal standard. Propionic and *n*-butyric acids were chromatographed on a 10-ft 20% sebacic acid column at 135° using isobutyric acid as internal standard. Total acidity was obtained by titration, obtaining the yield of acetic acid by difference. Results were verified by actual isolation of products by distillation. Approximately 5 g of butane was unaccounted for and was assumed to be lost during the venting operation.

Registry No.—Co(III), 22541-63-5; acetic acid, 64-19-7.

Selective Reductions. XVIII. The Fast Reaction of Primary, Secondary, and Tertiary Amides with Diborane. A Simple, Convenient Procedure for the Conversion of Amides to the Corresponding Amines

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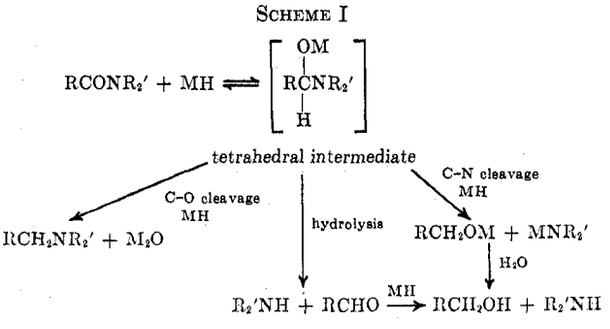
Primary, secondary, and tertiary amide derivatives of both aliphatic and aromatic carboxylic acids were reduced rapidly and quantitatively into the corresponding amines by excess diborane in refluxing tetrahydrofuran. Highly reactive tertiary amides, such as *N*,*N*-dimethylpivalamide, were reduced at moderate rates even at room temperature. The ease of reduction of the different amide functions, as revealed by the rate studies, follows the order tertiary amide ≥ secondary amide ≫ primary amide. Primary aliphatic amides are reduced at faster rates than primary aromatic amides. Unlike lithium aluminum hydride reductions, the tendency for C–N bond cleavage to yield alcohol is completely absent. The mildness of the reagent, diborane, permits the presence of other substituents less susceptible to the reducing action of the reagent, such as nitro, ester groups, halogen, etc. This reaction provides a convenient synthetic procedure for the selective reduction of amides where this is required in synthetic operations.

Reduction of carboxylic acid amides to the corresponding amines has been examined with a variety of complex metal hydrides and metal hydrides such as lithium aluminum hydride, lithium trimethoxyaluminohydride, aluminum hydride, etc.[2] The most common reagent, lithium aluminum hydride, has been widely applied to such reductions. However, it is very well known that the reaction of lithium aluminum hydride with primary amides is extraordinarily slow and incomplete,[2c] whereas with hindered tertiary amides the yield of the corresponding amine is always quite low owing to side reactions. The tetrahedral intermediate formed initially (Scheme I) undergoes both carbon–oxygen bond rupture leading to the amine, and carbon–nitrogen bond rupture leading to the alcohol. The relative importance of these two pathways depend on (a) steric and electronic characteristics of the amide structure, (b) nature of the reducing agent. Finally, lithium aluminum hydride, lithium trimethoxyaluminohydride, and, to a certain extent, aluminum hydride are exceedingly powerful reducing agents, capable of

SCHEME I



reducing almost all of the functional groups in an organic molecule. Consequently, this introduces severe limitation in the utility of these reagents for the selective reduction of amides to amines in the presence of other reducible functional groups in a multifunctional substrate.

We recently reported an extensive investigation of the approximate rates and stoichiometry of the reaction of diborane with organic compounds containing representative functional groups in tetrahydrofuran at 0°.[3] During the course of that investigation, it was observed that primary, secondary, and especially tertiary amides (both aliphatic and aromatic) are reduced by diborane to the corresponding amines rapidly and quantitatively under relatively mild conditions[4] (eq 1).

(1) Postdoctorate Research Associate, 1962–1964, on research grants supported by the Atomic Energy Commission, AT(11-1)-70, and the National Institutes of Health, GM 10937.

(2) (a) For a summary of the literature, see N. G. Gaylord, "Reductions with Complex Metal Hydrides," Interscience, New York, N. Y., 1956, pp 544–592. (b) For a recent review, see J. Zabicky, "The Chemistry of Amides," Interscience, New York, N. Y., 1970, pp 795–801. (c) H. C. Brown, P. M. Weissman, and N. M. Yoon, *J. Amer. Chem. Soc.*, **88**, 1458 (1966); H. Uffer and E. Schlitter, *Helv. Chim. Acta*, **31**, 1397 (1948); V. M. Mićović and M. L. Mihailović, *J. Org. Chem.*, **18**, 1190 (1953). (d) H. C. Brown and P. M. Weissman, *J. Amer. Chem. Soc.*, **87**, 5614 (1965). (e) H. C. Brown and N. M. Yoon, *ibid.*, **88**, 1464 (1966). (f) N. M. Yoon and H. C. Brown, *ibid.*, **90**, 2927 (1968).

(3) H. C. Brown, P. Heim, and N. M. Yoon, *ibid.*, **92**, 1637 (1970).

(4) For a preliminary communication on this reaction, see H. C. Brown and P. Heim, *ibid.*, **86**, 3566 (1964).

$$RCNR_2' \xrightarrow[THF]{BH_3} RCH_2NR_2' \quad 83\text{–}97\% \qquad (1)$$

R = alkyl or aryl
R′ = alkyl or hydrogen

The unique reduction characteristics of diborane permit the reduction of tertiary amides to amines in the presence of a variety of other less reactive functional groups. Encouraged by the results of our preliminary exploratory studies, we undertook a detailed study of the scope of the reaction and the influence of the electronic and steric characteristics of the amide structure on the rate of reaction. The results of these investigations are reported in the present paper.

Results and Discussion

Stoichiometry.—Primary amides, such as hexanamide, would require a total of seven "active hydrides"[5] for the reduction to amine, two hydrides for the reaction with "active hydrogen" present on the nitrogen, two hydrides for the reduction, and three hydrides (1 mol of borane) tied down to the resulting amine as the amine–borane complex.

In the case of secondary amides, such as *N*-methylpivalamide, a total of six "active hydrides" (one for reaction with active hydrogen present in the molecule, two for the reduction, and the remaining three for the complex formation with the resulting amine) would be required for the smooth reduction.

Finally, tertiary amides, such as *N*,*N*-dimethylpivalamide, where there is no active hydrogen present, would need a total of five "active hydrides" (two for reduction and three for the complex formation) for complete reduction.

General Procedure for Rate and Stoichiometry Studies.—In order to understand the influence of the amide structure on the rate of this reaction, a series of tertiary amides was prepared and their reactivity toward diborane was measured. Tertiary amides were the substrate of choice because of the absence of any complication due to active hydrogen present on nitrogen as in primary and secondary amides.

The general procedure adopted was to add 20 mmol of N,N-disubstituted amide to 20 mmol of borane solution in sufficient tetrahydrofuran (THF) to give 20 ml of solution. This makes the reaction mixture 1.0 *M* in BH_3 and 1.0 *M* in substrate.[6] The solutions were maintained at constant temperature (*ca.* 25°) and aliquots were removed at appropriate intervals of time and analyzed for "residual hydride" by hydrolysis in a mixture of concentrated hydrochloric acid–THF.

Effect of Structure of the Amide on the Reactivity.—

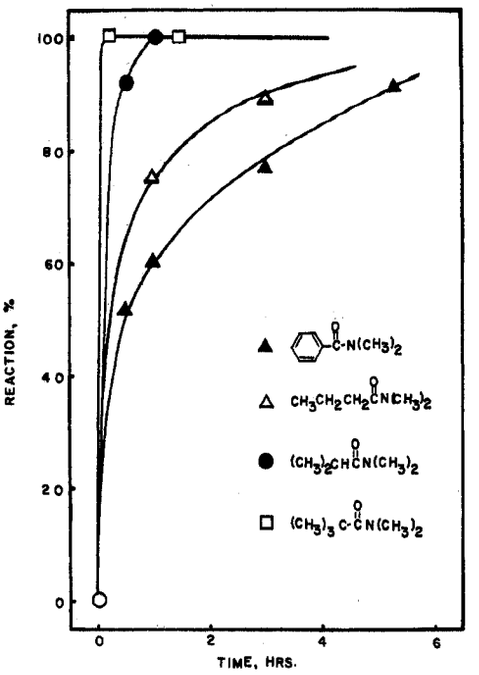
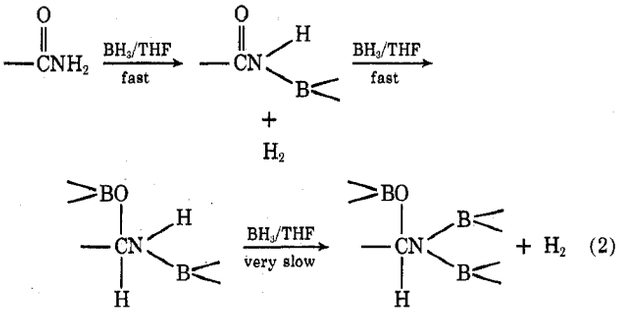


Figure 1.—Rates of reduction of the *N*,*N*-dimethylamides with borane in tetrahydrofuran at 25° (both reagents 1.0 *M*).

Primary amides react relatively rapidly to evolve their active hydrogen, but such hydrogen evolution stops well before 2 mol are realized (1.1 mmol of hydrogen per mmol of compound was observed for hexanamide and 1.4 mmol for benzamide at room temperature). The incomplete hydrogen evolution in the case of primary amides might be due to a simultaneous attack by the diborane on the carbonyl group. The adduct would resemble an amine and would cease to evolve hydrogen further with diborane (eq 2).



They are also reduced very slowly, far slower than secondary and tertiary amides. Secondary amides, such as *N*-methylpivalamide, liberate 1 mol of hydrogen per mol of substance, as expected, and are also reduced faster than primary amides. Tertiary amides evolve no hydrogen and are reduced rapidly and quantitatively even at room temperature. A series of N,N-disubstituted tertiary amides were examined toward diborane to understand the influence of electronic and steric characteristics of amide group on the rate of reaction.

Increasing the branching on α carbon to the carbonyl group increases the rate of reduction, as revealed by the rates of reduction of *N*,*N*-dimethylamide derivatives of *n*-butyric, isobutyric, and pivalic acid. Aliphatic amides, such as *N*,*N*-dimethylbutyramide, are reduced faster than aromatic amides, such as *N*,*N*-dimethylbenzamide (Figure 1).

(5) It is convenient to discuss the utilization of the reagent in terms of moles of hydride taken up per mole of amide. However, it should not be confused that free "hydride" ion is the active species. An "active hydride" refers to one B–H bond.

(6) During the course of this investigation, it was realized that, in scaling up this reaction for preparative purposes, the yield of amines decreased, especially for the more reactive amides, such as *N*,*N*-dimethylpivalamide. However, the analysis of the resulting mixture indicated the presence of unreacted amide and the absence of any alcohol, indicating that the lower yield is not the result of any side reaction.

It was concluded that the tertiary amine first formed reacts with diborane to form an amine–borane complex of much lower reactivity. Alkylamine–borane reduces acyl halides, aldehydes, and ketones, but is inert to esters, carboxylic acids, and amides; see H. Nöth and H. Beyer, *Ber.*, **93**, 1078 (1960). However, this difficulty can be overcome by using additional diborane, 2 mol of borane per mol of amide.

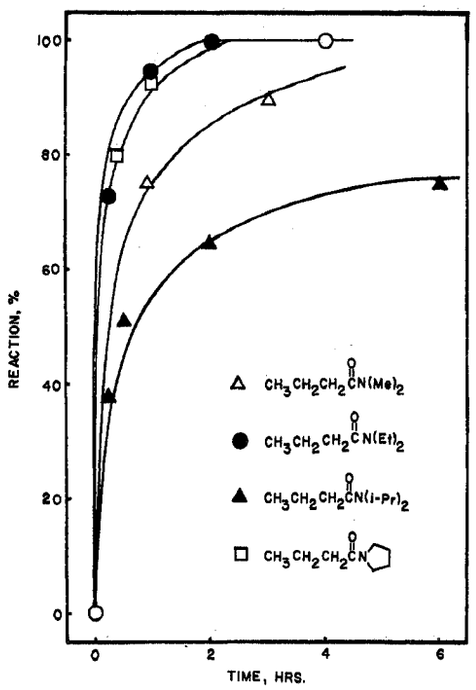


Figure 2.—Rates of reduction of the *N*,*N*-dialkylbutyramides with borane in tetrahydrofuran at 25° (both reagents 1.0 *M*).

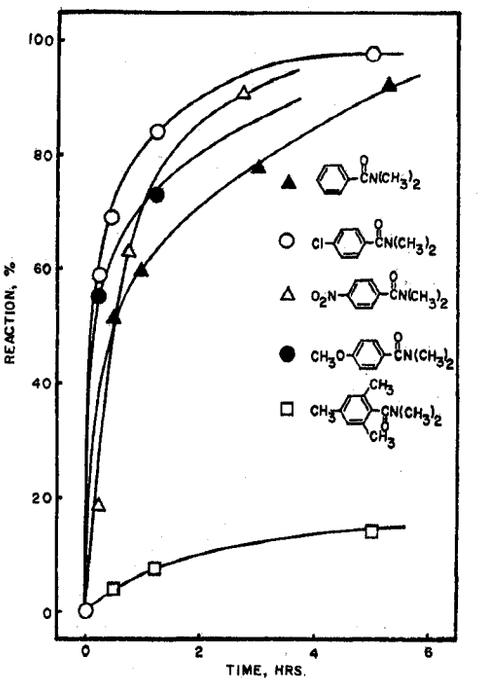


Figure 3.—Rates of reduction of the *N*,*N*-dimethylbenzamides with borane in tetrahydrofuran at 25° (both reagents 1.0 *M*).

The reaction is also sensitive to the nature of the substituent present on the nitrogen. Thus, *N*,*N*-diethylbutyramide and *N*-butyrylpyrrolidine are reduced at a faster rate than *N*,*N*-dimethylbutyramide. However, *N*,*N*-diisopropylbutyramide is reduced at a slower rate than the above-mentioned amides. This clearly indicates that the reaction is sensitive to both electronic and steric effects (Figure 2).

Introduction of polar substituents in *N*,*N*-dimethylbenzamide (both electron releasing and electron withdrawing), such as *p*-nitro, *p*-chloro, *p*-methoxy, and *p*-methyl, does not influence the rate of reduction to any appreciable extent, revealing insensitiveness of the reaction to electronic effects. However, substituents in the ortho position greatly retard the reaction, which should be attributed to the steric hindrance to the formation of the tetrahedral intermediate. Thus, *N*,*N*-dimethylmesitoic acid amide is reduced at a far slower rate than *N*,*N*-dimethylbenzamide (Figure 3).

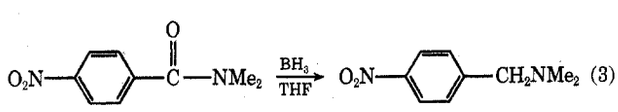
Synthetic Utility.—The rate and stoichiometric studies previously discussed indicated that for optimum rate of reduction it is desirable to use at least $1^2/_3$ mol of borane per mol of tertiary amide. In extending this procedure to primary and secondary amides, the amount of borane used was increased by $^1/_3$ for each equivalent of active hydrogen present in the amide. The amide in THF was added to borane solution at 0°. With tertiary and secondary amides, the resulting mixture was brought to reflux and maintained there for 1 hr to drive the reaction essentially to completion. In the cases of primary amides, it was found desirable to increase the reaction time at reflux to 2 hr for primary alphatic amides and to 8 hr for primary aromatic amides. Accordingly, we adopted these conditions for examining the synthetic applicability of the procedure. A critical step in the reaction is the hydrolysis of the excess hydride and the liberation of amine from amine–borane complex. A series of exploratory experiments indicated the necessity of refluxing the resulting mixture with concentrated hydrochloric acid with simultaneous distillation of the THF.

Simple primary amides, such as hexanamide and benzamide, were converted into *n*-hexylamine and benzylamine, respectively, in 87% yield.

Secondary amides, such as *N*-methylhexanamide and *N*-methylpivalamide, were converted into their corresponding secondary amines in 98 and 83% yield, respectively.

N,*N*-Diethylpivalamide was converted into diethylneopentylamine in 94% yield. Similarly, *N*,*N*-diisopropylbenzamide was converted into diisopropylbenzylamine in a yield of 98%.

Finally, *N*,*N*-dimethyl-*p*-nitrobenzamide was examined to test the utility of this procedure for selective reductions. The product, *N*,*N*-dimethyl-*p*-nitrobenzylamine, was obtained in 97% yield, confirming the value of this procedure for selective reductions (eq 3). The results are summarized in Table I.



Scope and Applicability.—It was previously established that diborane is a highly selective reducing agent. Being a Lewis acid by itself, it exhibits many unique reduction characteristics which are absent in other complex metal hydrides, such as lithium aluminum hydride. For achieving amide to amine conversion, diborane has two major advantages over the conventional reagents, such as lithium aluminum hydride: (a) the reaction is rapid, quantitative, and very clean, even in the case of tertiary amides; (b) the reaction can tolerate many functional groups such as nitro, halogen, ester, sulfone, carbamate, etc. The remarkable utility

TABLE I

REDUCTION OF REPRESENTATIVE AMIDES TO AMINES BY DIBORANE IN TETRAHYDROFURAN

Registry no.	Acid amide	Product	Yield, % Anal.[a]	Yield, % Isolated
628-02-4	Hexanoic[d]	*n*-Hexylamine	87	
3418-05-1	*N*-Methylhexanoic[c]	Methyl-*n*-hexylamine	98	
5830-30-8	*N,N*-Dimethylhexanoic[b]	Dimethyl-*n*-hexylamine	95	
754-10-9	Pivalic[d]	Neopentylamine	83	
6830-83-7	*N*-Methylpivalic[c]	Methylneopentylamine	83	
24331-71-3	*N,N*-Dimethylpivalic[b]	Dimethylneopentylamine	92	79
55-21-0	Benzoic[e]	Benzylamine	87	
611-74-5	*N,N*-Dimethylbenzoic[b]	Dimethylbenzylamine	98	
7291-01-2	*N,N*-Dimethyl-*p*-nitrobenzoic[b]	Dimethyl-*p*-nitrobenzylamine	97	84
24331-72-4	*N,N*-Diethylpivalic[b]	Diethylneopentylamine	94	81
20383-28-2	*N,N*-Diisopropylbenzoic	Diisopropylbenzylamine	98	

[a] Determined by gas chromatographic analysis, isolation as the picrate, or by titration. [b] $1^1/_3$ mol of BH_3 per mol of amide, heated under reflux in tetrahydrofuran for 1 hr. [c] 2 mol of BH_3 per mol of amide, heated under reflux for 1 hr. [d] $2^1/_3$ mol of BH_3 per mol of amide, heated under reflux for 2 hr. [e] $2^1/_3$ mol of BH_3 per mol of amide, heated under reflux for 8 hr.

of this procedure over other methods is evidenced by numerous applications of this procedure in medicinal, pharmaceutical, and biological chemistry since our preliminary communication on this reaction.

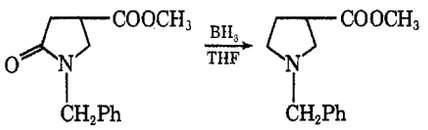
There are quite a large number of instances where the use of conventional lithium aluminum hydride has failed to achieve conversion of amide to amine in any appreciable yield. The failure has been attributed to two factors, the incomplete and slow reaction and the side reaction of C–N bond cleavage resulting in the corresponding alcohol. However, in such cases, the difficulty has often been overcome by using diborane in place of lithium aluminum hydride, resulting in rapid and essentially quantitative conversion to the desired amine.[7]

Recently diborane has been applied to the reduction of 1,2-diacylhydrazines to 1,2-dialkylhydrazines without the rupture of the nitrogen–nitrogen bond,[8] and of ketoxime acetate or tosylate to the corresponding amine.[9]

Diborane, unlike lithium aluminum hydride and its derivatives, being a mild and selective reducing agent, makes possible the presence of many other substituents less susceptible to the reducing action of the reagent.

Thus, diborane has been successfully utilized for the reduction of halogen-substituted amide derivatives to the corresponding halo-substituted amine, in excellent yield,[10] where lithium aluminum hydride causes extensive hydrogenolysis of the carbon–halogen bonds in both aromatic and aliphatic substrates.[11]

The utility of diborane for such amide reductions is further evidenced by the successful selective reduction of the amide function in the presence of carbamate, ester,[12] and sulfone[13] groups, applications where lithium aluminum hydride had failed. Thus, 1-benzyl-3-methoxycarbonyl-5-pyrolidinone was selectively reduced to methyl 1-benzyl-3-pyrolidinecarboxylate in 54% yield (eq 4). The utility of this method can be



(4)

realized by the previous three-step procedure for the preparation of this compound[14] in an overall yield of 28%.

A disadvantage of diborane for such reductions occurs with unsaturated derivatives, such as *N,N*-dimethylcinnamamide, since diborane rapidly adds to the double bonds. However, for such reductions, aluminum hydride can often be successfully applied.[15]

Experimental Section

Materials.—Tetrahydrofuran was dried with excess lithium aluminum hydride and distilled under nitrogen. Diborane solution in tetrahydrofuran was prepared from sodium borohydride and boron trifluoride etherate.[16] The borane–THF solution was standardized by hydrolyzing a known aliquot of the solution with a glycerine–water–THF mixture and measuring the hydrogen evolved. For most experiments, the concentration was approximately 2 *M* in BH_3.

Primary amides used were the commercial products of the highest purity. Secondary and tertiary amides were prepared by the method of Brown and Taukamoto.[17] In all of the cases physical constants agreed satisfactorily with constants in the literature. For further details, the thesis should be referred to.

All reduction experiments were carried out under a dry nitrogen atmosphere. Hypodermic syringes were used to transfer the solution.

Rates of Reduction of N,N-Disubstituted Acid Amides.—Reduction of *N,N*-dimethylisobutyramide is representative. A 100-ml flask was dried in an oven and cooled down in a dry nitrogen atmosphere. The flask was equipped with a rubber syringe cap and a magnetic stirring bar, and a reflux condenser was connected to an inverted gas buret *via* a Dry Ice trap. The flask was immersed in a water bath at room temperature (*ca.* 25°), and 9.7 ml (20 mmol) of 2.1 *M* borane solution in THF was introduced into the reaction flask, followed by 0.3 ml of THF. Then 20 mmol of *N,N*-dimethylbutyramide in 10 ml of THF was introduced. Now the reaction mixture was 1.0 *M* in BH_3 and amide.

At the end of 20 min, a 2.0-ml aliquot of the reaction mixture was removed with a hypodermic syringe and injected into a hydrolyzing mixture of 10 ml of concentrated hydrochloric acid and 5 ml of THF. The hydrogen evolved was measured with a gas buret. This indicated that 1.86 mmol of hydride has reacted per mmol of the amide, indicating the completion of 93% of the reduction. The reaction was monitored at 1 hr, 3 hr, etc. Reaction was essentially complete in 1 hr.

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(8) H. Feuer and F. Brown, Jr., *J. Org. Chem.*, **35**, 1468 (1970).

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(16) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963); H. C. Brown and R. L. Sharp, *J. Amer. Chem. Soc.*, **90**, 2915 (1968).

(17) H. C. Brown and A. Tsukamoto, *ibid.*, **86**, 1089 (1964); A. Tsukamoto, Ph.D. Thesis, Purdue University, Lafayette, Ind., 1959.

The results for other amides are summarized graphically in Figures 1, 2, and 3.

Procedure for Product Analysis.—For analyzing reduction products separate experiments on a 20-mmol scale were carried out. The yields were determined by titration with 1.0 *N* HCl, isolation as the picrate, or by glpc analysis on a 10% Porimene JM-T on Fluoropak. Reduction of *N,N*-diisopropylbenzamide to *N,N*-diisopropylbenzylamine is representative. The experimental setup is as in the previous experiment. A typical reaction setup was assembled. Then 33.3 mmol of borane solution (20 ml of a 1.67 *M* solution in THF) was placed in the reaction flask maintained at *ca.* 25°. To this 4.1 g (20 mmol) of *N,N*-diisopropylbenzamide in 20 ml of THF was added and the mixture was stirred well. The resulting mixture was refluxed for 1 hr. The flask was allowed to cool to room temperature and 8 ml of 6 *M* HCl was added. The tetrahydrofuran was removed by distillation at atmospheric pressure as hydrogen was evolved (1.5 l., 60 mmol) from hydrolysis of excess borane. Sodium hydroxide pellets were added to saturate the aqueous phase and the latter was extracted three times with a total of 25 ml of ether. Titration of a known aliquot of this reaction mixture with a standardized HCl solution revealed the presence of amine in 98% yield.

To 2.5 ml (1 mmol) of the ether extract of the amine, a saturated solution of picric acid in 95% ethanol was added and heated. Water was added drop by drop until the solution turned slightly milky. After cooling, yellow needles of picrate crystallized out in 98% yield, mp 134–135°. *Anal.* Calcd for $C_{19}H_{24}N_4O_7$: C, 54.27; H, 5.75; N, 13.32. Found: C, 54.42; H, 5.82; N, 13.32.

General Preparative Procedure for the Reduction of Amides to Amines.—The following general procedure illustrated for the reduction of *N,N*-dimethylpivalamide to dimethylpivalamine is suggested for the reduction of amides. (Depending upon the nature of the amide and the substituents present, the hydride to compound ratio and the time required may require an increase or decrease.)

To a solution of 200 ml (334 mmol) of 1.67 *M* borane in THF in a 500-ml flask equipped with a reflux condenser, dropping funnel, and a magnetic stirring bar maintained under nitrogen was added 25.8 g (200 mmol) of *N,N*-dimethylpivalamide in 100 ml of THF over 15 min. The temperature was maintained approximately at 0° during the addition. The colorless solution was then brought to reflux and maintained there for 1 hr. The flask was permitted to cool to room temperature and 50 ml of 6 *M* hydrochloric acid was added slowly through a dropping funnel. The THF was removed by distillation at atmospheric pressure as hydrogen was evolved (15.5 l., 0.6 mol) from the hydrolysis of the amine–borane complex. Sodium hydroxide pellets were added to saturate the aqueous phase and the latter was extracted three times with a total of 100 ml of ether. After drying with sodium sulfate, distillation yielded 18.2 g (79% yield) of dimethylneopentylamine, bp 95–96°, $n^{20}D$ 1.3982.

Similarly, *N,N*-diethylpivalamide was converted into isolated diethylneopentylamine in an isolated yield of 81%.

Selective Reduction of *N,N*-Dimethyl-*p*-nitrobenzamide to Dimethyl-*p*-nitrobenzylamine.—To a solution of 50 ml (83.3 mmol) of a 1.67 *M* solution of borane in THF in a 200-ml flask maintained at 0° under nitrogen was added 9.76 g (50 mmol) of *N,N*-dimethyl-*p*-nitrobenzamide in 4.0 ml of THF over a period of 10 min. After the addition was completed, the resulting mixture was refluxed for 1 hr. After the reaction flask was cooled, the reaction mixture was worked up as in the previous experiment and the combined ether extracts were dried over sodium sulfate. Distillation yielded 7.6 g (84%) of dimethyl-*p*-nitrobenzylamine, bp 96–98° (1.5 mm), $n^{20}D$ 1.5421.

Registry No.—Diborane, 19287-45-7.

Formation of Mercaptomethylamine as an Intermediate[1]

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Bis(aminomethyl) disulfide dihydrochloride (**2**) was hydrogenated to yield bis(aminomethyl) sulfide dihydrochloride (**3**) and hydrogen sulfide. Similarly, reaction of phthalimidomethyl aminomethyl disulfide hydrochloride (**4**) with hydrogen and palladium gave *N*-(mercaptomethyl)phthalimide (**5**), **3**, and hydrogen sulfide. These reactions indicate the formation of mercaptomethylamine hydrochloride (**1**) as an intermediate which undergoes self-condensation to yield **3** and hydrogen sulfide. Compounds **2** and **4** were prepared by the acid hydrolysis of bis(*o*-carboxybenzoylaminomethyl) disulfide (**8**), which was obtained by partial alkaline hydrolysis of bis(phthalimidomethyl) disulfide (**7**). Hydrazinolysis of **7** in liquid ammonia gave **2** directly in low yield. The sulfide **3** was independently synthesized from bis(phthalimidomethyl) sulfide (**10**) by saponification to bis(*o*-carboxybenzoylaminomethyl) sulfide (**11**) followed by acid hydrolysis. Treatment of β-mercaptoethylamine hydrochloride (**12**) with sulfur trioxide–pyridine afforded *S*-2-aminoethanethiosulfuric acid (**13**).

Chemical protection of mammals against ionizing radiation was demonstrated in 1949.[3] It was soon established that compounds showing radiation protection possessed both the amino and mercapto groups,[4] and β-mercaptoethylamine (MEA) is one of the most active of the more than 3000 compounds tested.[5]

The protective action of aminothiols has been shown to decrease with increasing separation of the functional groups.[5,6] We were therefore led to examine the synthesis and properties of the hydrochloride of mercaptomethylamine (**1**), the parent *N,S*-acetal of formaldehyde. Two *N,S*-hemiacetals of **1** containing tertiary nitrogens have been reported, 1-piperidinemethanethiol and 4-morpholinemethanethiol.[7]

In general, Bunte salts (*e.g.*, **13**) are less toxic than the corresponding thiols, and *S*-2-aminoethanethiosulfuric acid (**13**) and MEA (**12**) are equally protective at their maximum tolerated doses.[6] A new synthesis of **13** is reported and an attempt was made to extend the reaction to the preparation of *S*-aminomethanethiosulfuric acid (**14**).

Results and Discussion

Hydrogenation of Disulfides 2 and 4.—This communication reports evidence for the formation of mercaptomethylamine hydrochloride (**1**) as an inter-

(1) Presented in part at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, Abstracts, I23.

(2) Taken in part from the dissertation submitted by S. Abdou-Sabet in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Maryland, 1966; *Diss. Abstr. B*, **27**, 3028 (1967).

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