TABLE I

OXIDATION PRODUCTS

Sulfoxide	Yield	M.P. Obs.	M.P. Lit.	B.P. Obs.	B.P. Lit.
Di-*n*-propyl	59%	22–23°	24.5–25.5°	80°/2 mm.	80°/3 mm.
Di-*n*-butyl	55%	30–31°	32°	106–107°/2 mm.	—
Tetramethylene	58%	—	—	102–105°/15 mm.	105–107°/15 mm.

175° for 8–12 hr. The dimethyl sulfide was allowed to distill through a reflux condenser maintained at about 40°; its boiling point was observed to be 37° (lit. 37.30°).[4] The mixture was observed to turn yellow at first and eventually became black after 2–4 hr. Reduced pressure distillation separated the product from tarry residues and the product was redistilled.

The yields and properties of the products are given in Table I. The melting points were taken without recrystallization.

The infrared spectra of each of these compounds showed very strong absorption between 9.2 and 9.8μ, characteristic of the sulfoxide group. The spectrum of the known sample of *n*-propyl sulfoxide was identical with that of *n*-propyl sulfoxide. No bands in the 8.8μ and 7.5μ regions, characteristic of the sulfone group were observed.

Attempts to apply this oxidation to di-*t*-butyl, diisopropyldiphenyl, and pentamethylene sulfides and to 3,3-dimethyl, thietane were unsuccessful under the above conditions. Only unreacted starting materials were recovered from these reactions.

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(4) D. T. McAllan, T. V. Cullum, R. A. Dean, and F. A Fidler, *J. Am. Chem. Soc.*, **73**, 3627 (1951).

A Re-examination of Limitations of the Hofmann Reaction[1,2]

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An implicit tribute to the original study of Hofmann on the rearrangement that bears his name lies in the fact that except for theoretical interpretations, no substantial revision of his work has been made in the course of seventy years.[3] Theoretical considerations, however, led to the belief that the practical limitations of this reaction as set forth by Hofmann, were functions of his experimental conditions and might therefore be extended by variations of these.

In operating with the amides of fatty acids, Hofmann found that yields of amine fell off with the higher members because of two side reactions. From heptanoamide to capramide there was loss from formation of nitrile having one less carbon atom than the starting amide. With the still higher members, loss in yield was due mainly to formation of alkylacyl ureas. When the amide is not derived from a simple fatty acid, the limitations are somewhat different, numerous phenethyl amines being satisfactorily obtained from the corresponding hydrocinnamic amides. Here also, however, a limitation does appear. For example, the late J. S. Buck[4] recovered 3,4-diethoxy-α-methylhydrocinnamamide unchanged from an attempted Hofmann rearrangement. This result was presumably due to the lack of solubility, since the same amide was converted quantitatively to *N*-carbomethoxy-β-(3,4-diethoxyphenyl)isopropylamine by the Jeffreys modification[5] of the Hofmann. Such a solubility limitation may be expected to be general, especially when an amide is treated with preformed hypohalite, since that reagent cannot long persist after the temperature has been raised above about 40°.

It was our view that the loss from urea formation was largely due to the physical properties of the organic compounds. As molecular weight increases, the isocyanate, the proximate rearrangement product, the product amine and the earlier intermediates have an increasing tendency to extract each other from solution, whereby the isocyanate is increasingly likely to react with other substances than hydroxide ion. Such side reactions should be minimized by use of an inert co-solvent. The obvious substance for that purpose is dioxane.[6]

It also seemed likely that formation of nitrile, observed by Hofmann with amides of intermediate chain length, was due to his technique of adding bromine to a solution or mixture of the other reactants. Where the amide is added to an initially

(1) Abstracted from a thesis submitted by Ernest Magnien in partial fulfillment of the requirement for the M.S. degree at the Polytechnic Institute of Brooklyn, 1958.

(2) The authors express their gratitude to Burroughs Wellcome & Co. (U.S.A.) Inc. for permission to carry out the experimental part of this study in the Wellcome Research Laboratories.

(3) The literature on the Hofmann Reaction has been reviewed by Wallis and Lane up to 1946. [E. S. Wallis and J. F. Lane, *Org. Reactions*, **III**, 267 (1946)]. Except for special points, references are not made here to literature covered in this review.

(4) J. S. Buck, unpublished work.

(5) E. Jeffreys, *Ber.*, **30**, 898 (1897); *Am. Chem. J.*, **22**, 14 (1899).

(6) The use of dioxane as a co-solvent in Hofmann reactions was mentioned in a preparation of β-2,5-dimethoxyphenylisopropylamine. R. Baltzly and J. S. Buck, *J. Am. Chem. Soc.*, **62**, 161 (1940).

cold alkaline solution of hypohalite, conversion to a halogeno amide should be a smooth reaction and no amine would be present along with free halogen.[7] For this as for most other purposes we considered hypochlorite to be preferable to hypobromite since the dismutation to halide and halate is more facile with increasing size of the halogen.

In Table I are shown the results of a series of Hofmann reactions run with and without the addition of dioxane and with considerable variation in conditions of temperature. The yields of amine in runs I–III and VII (no dioxane present) are reasonably close to those reported by Hofmann and by Hoogewerff and Van Dorp.[3] There was no indication, however, of nitrile formation. From caprylamide through lauramide the use of dioxane as a co-solvent gave definitely improved results.[8] Above capramide the yields of amine did diminish gradually and a run with palmitamide was a complete failure.

The effect of temperature (compare runs IX–XIII) was not particularly critical but these results suggest that external heating once the reaction has commenced may be undesirable. Comparison of runs X and XI with XIII may indicate that continued stirring is advantageous.

The Jeffreys[5] modification of the Hofmann is known to afford excellent yields of amines as their carbomethoxy derivatives. Unfortunately, no general method of hydrolysis has been recognized.[9] Acid hydrolysis of these urethanes is very slow. Alkaline hydrolysis encounters difficulty whenever the urethane is insoluble or is rendered so by excessive concentration of alkali. The optimal general condition is found with relatively dilute alkali in alcoholic solution.[10] Five g. portions of methyl *N*-undecylcarbamate and methyl *N*-pentadecylcarbamate were refluxed in alcoholic alkali with the results shown in Table II.

TABLE I

RESULTS OF HOFMANN REACTIONS

Exp. No.	Amide	Solvent	Yield of Amine, %[a]	Temperature[b]
I	$C_5H_{11}CONH_2$	Water	95	A
II	$C_6H_{13}CONH_2$	Water	60	A
III	$C_7H_{15}CONH_2$	Water	53.5	B
IV	$C_7H_{15}CONH_2$	33% dioxane	67.3	C
V	$C_7H_{15}CONH_2$	33% dioxane	67.7	B
VI	$C_7H_{15}CONH_2$	33% dioxane	77.5	D
VII	$C_8H_{17}CONH_2$	Water	9.7	B
VIII	$C_8H_{17}CONH_2$	33% dioxane	63.2	D
IX	$C_9H_{19}CONH_2$	33% dioxane	63.0	E
X	$C_9H_{19}CONH_2$	33% dioxane	66.4	D
XI	$C_9H_{19}CONH_2$	33% dioxane	65.4	D
XII	$C_9H_{19}CONH_2$	33% dioxane	57.6	B
XIII	$C_9H_{19}CONH_2$	33% dioxane	59.4	D[c]
XIV	$C_{11}H_{23}CONH_2$	33% dioxane	49.0	B
XV	$C_{12}H_{25}CONH_2$	33% dioxane	45.0	B
XVI	$C_{12}H_{25}CONH_2$	33% dioxane	48.0	F

[a] The yields are calculated on the basis of dry hydrochloride isolated. In experiments I and II the amines were steam distilled out of the reaction mixture and the distillates were acidified with hydrochloric acid and evaporated *in vacuo*. In the other experiments, amine hydrochlorides were isolated by extraction procedures (see Experimental). [b] In all experiments the materials were first heated to 45° after which the following conditions were maintained: A—1 hr. at 70–80° followed by steam distillation; B—1 hr. at 40–50°, 1 hr. at 70°; C—1 hr. at 60–65°, 1 hr. at 80–85°; D—2 hr. no external heating (temp. 40–65°); E—1 hr. at 70–80°, 1 hr. at 92° (reflux); F—2 hr. at 60°. [c] No stirring after 45° attained.

TABLE II

HYDROLYSIS OF URETHANES

Urethane	Hydrolysis Medium	Reflux Time, Hr.	Yield, %[a]
$C_{11}H_{23}NHCOOCH_3$	110 cc. 90% MeOH + 10 g. NaOH	14	<36[b]
$C_{11}H_{23}NHCOOCH_3$	110 cc. 90% EtOH + 10 g. NaOH	17	93
$C_{11}H_{23}NHCOOCH_3$	110 cc. 90% EtOH + 5 g. NaOH	17	65.5
$C_{15}H_{31}NHCOOCH_3$	110 cc. 90% EtOH + 10 g. NaOH	17	94

[a] Yield based on amine hydrochloride isolated. [b] 64% urethane recovered.

The conversions found in the second and third runs are in good agreement with the expected bimolecular reaction kinetics. It is also to be presumed that even less soluble amides could be hydrolyzed satisfactorily in solutions containing less water or a higher-boiling alcohol such as glycol.

Reduction of these urethanes by lithium aluminum hydride affords a convenient and satisfactory preparation of the corresponding secondary amines.

EXPERIMENTAL

Preparation of amides. The amides used have all been characterized previously. The carboxylic acids (Eastman Kodak materials) were converted to the acid chlorides and the latter were added dropwise to stirred solutions of iced concentrated ammonium hydroxide solution. The amides were collected and recrystallized to constant melting point from alcohol or aqueous alcohol.

The experiments whose results are recorded in Table I were all run with 0.1 mole portions of amides. For each of

(7) An indication that this might be so was provided by Hoogewerff and Van Dorp [S. Hoogewerff and W. A. Van Dorp, *Rec. Trav. chim.*, **6**, 373 (1887)] who introduced the use of preformed hypobromite solution. Their procedure resulted in 60–65% yields of heptylamine from caprylamide but apparently failed to give an appreciable amount of octylamine from pelargonamide. In the latter case their principal product was the acyl alkyl urea. The 45% yield that has been quoted[3] for their method in this conversion was obtained by heating (presumed) *N*-bromopelargonamide with slaked lime. Hoogewerff and Van Dorp do not appear to have investigated nitrile formation but it can be inferred that little nitrile was formed in their experiments.

(8) For any individual case, the proportion of dioxane used may not have been optimal.

(9) *Cf.* P. A. S. Smith in *Org. Reactions*, **III**, 380 (1946).

(10) Mayer and Sieglitz, *Ber.*, **55**, 1835 (1922).

these a standard preparation of sodium hypochlorite solution was prepared immediately before use.

Standard hypochlorite solution. In a distilling flask equipped with a dropping funnel was placed 6.7 g. of potassium permanganate. The side arm of the flask was joined by a glass-to-glass connection to a tube dipping below the surface of a solution containing 16 g. (0.4 mole) of sodium hydroxide dissolved in 110 cc. of water and cracked ice contained in a graduated cylinder. The cylinder in turn was surrounded by an ice bath. Fifty cc. of concentrated hydrochloric acid was admitted slowly through the dropping funnel so as to produce a slow stream of chlorine. When all the acid had been added, the contents of the flask were heated with a small flame until the reflux point was a little below the junction with the side arm. A Pyrex wool plug below the side arm served to prevent acid splashings from being carried over. The hypochlorite solution was then made up to 160 cc. Such solutions contain slightly over 0.1 mole of sodium hypochlorite and 0.2 mole of excess sodium hydroxide.

For the Hofmann reactions, the standard hypochlorite solutions were added to the amides contained in round-bottom flasks equipped with reflux condensers, magnetic stirrers, and thermometers. In runs I-III, and VII, the amides were present as solids; in the other runs (using 33% dioxane as solvent) the amides were dissolved in 80 cc. of dioxane (purified by 24-hour reflux over sodium followed by distillation.[11]

Amylamine (Run I). The suspension of caproamide (11.5 g.) in hypochlorite solution was warmed with stirring to 45° when the heat of reaction sufficed to maintain the temperature. When the exothermic reaction had ceased, the solution was warmed to 75° and kept at that temperature for 1 hr. The flask was then equipped for steam distillation and the reaction mixture was steam distilled into an excess of hydrochloric acid until no more base was coming over. The distillate was then evaporated to dryness *in vacuo* giving 11.7 g. (95% yield) of amylamine hydrochloride. A portion was converted to the picrate which melted at 137–139° as did a specimen prepared from commercial *n*-amylamine. Karrer *et al.*[12] give 140–142°.

Octylamine (Run VII). The suspension of pelargonamide (15.8 g., m.p. 99–100°) and hypochlorite solution was warmed with stirring to 45°. The temperature of the reaction mixture then rose by itself to 80°. After 45 min. the temperature had fallen to 57° and some colorless crystalline material had separated. The temperature was raised to 80° and maintained there for 1 hr. after which the reaction mixture was cooled (whereupon the solid reprecipitated). The reaction mixture was extracted once with ether and twice with benzene. The combined extracts were washed twice with water and then with 100 cc. of *N* hydrochloric acid. The acid extract was basified and the precipitated oil taken into ether. The ethereal solution of base was dried over sodium hydroxide pellets, filtered, and acidified with gaseous hydrogen chloride. The resultant precipitate of amine hydrochloride was collected, m.p. 197–198°,[13] wt. 1.6 g. (9.7%).

The neutral fraction (after extraction by aqueous acid) was concentrated and cooled, yielding 6.7 g. (40%) of pelargonamide, m.p. 95–97°, undepressed by admixture with starting material. The mother liquor, on evaporation of solvent, contained 4.3 g. of an oil that did not boil below 300°. Calculated as *N*-octyl-*N'*-pelargonylurea, this is equivalent to 30% of the starting amide. There was no indication of the presence of caprylic nitrile.

Nonylamine (Run X). To the capramide (17.1 g.) in 80 cc. of purified dioxane was added the hypochlorite solution and the mixture was warmed to 45° with stirring. The temperature then rose spontaneously to 65° in two minutes. Stirring was continued without external heating for 2 hr. at which time the temperature was 42°. On cooling an oil layer separated. This was removed and the aqueous layer was extracted with benzene. The first amine layer and the benzene extract were combined, water was drawn off, and the base was extracted into 100 cc. of *N* hydrochloric acid. The acid layer was basified with concentrated alkali and the liberated base was taken into benzene. The benzene extract was dried over sodium hydroxide pellets, filtered, and saturated with hydrogen chloride gas. The mixture was then concentrated to 50 cc. volume with an air stream and 50 cc. of dry ether was added. The amine hydrochloride when collected weighed 11.9 g. (66.4%), m.p. 185–186°.[14]

Methyl N-undecylcarbamate. The procedure was essentially that of Jeffreys.[5] The hypochlorite solution was made up only to 125 cc. To it was added 19.9 g. (0.1 mole) of lauramide dissolved in 200 cc. of methanol. The temperature rose to 42° in 1/2 hr. One hundred cc. more methanol was added and the solution was refluxed 1 hr. On cooling there was obtained 21.2 g. (92%) of urethane, m.p. 42–43°. The melting point was unaltered by recrystallization from absolute ethanol.

Methyl N-pentadecylcarbamate. The above procedure proved unsuitable in this case because the palmitamide was precipitated by the water of the hypochlorite solution. The following procedure proved satisfactory.

One-tenth gram-atom (2.3 g.) of sodium was dissolved in 125 cc. of methanol and 12.8 g. (0.05 mole) of palmitamide was added to the solution. Chlorine generated from 3.2 g. of potassium permanganate and 25 cc. of concentrated hydrochloric acid was passed into the cooled methanolic solution which was then warmed and refluxed 10 min. The solution was neutralized with acetic acid and most of the methanol was evaporated *in vacuo*. Water was added until precipitation was complete and the solid was filtered off. After washing with water and drying, it weighed 13.5 g. (95%) and melted at 47–58°. Two recrystallizations from aqueous methanol gave 10.9 g. melting at 58–62°. (Jeffreys[5] gives 61–62° for m.p.)

Undecylamine (by hydrolysis of methyl-N-undecylcarbamate). Five g. of methyl-*N*-undecylcarbamate was refluxed in 100 cc. of ethanol and 20 cc. of 50% sodium hydroxide solution for 17 hr. The solution was cooled and acidified with hydrochloric acid, the sodium chloride was filtered off, and the bulk of the ethanol was evaporated off on the steam bath with an air stream. The residue was basified and extracted several times with benzene. An equal volume of ether was added to the benzene to prevent emulsion formation and the base was extracted from the organic extract into an excess of dilute hydrochloric acid. The water was evaporated off on the steam bath to give 4.2 g. (93% yield) of product. This salt sintered at 180° and melted at 190°.[15]

N-methylundecylamine. In a three necked 250-ml. flask equipped with stirrer, dropping funnel, and condenser with sodium hydroxide trap, were put 1.7 g. (0.045 mole) of lithium aluminum hydride and 150 cc. of absolute ether. A solution of 6.9 g. (0.03 mole) of methylundecylurethan in about 50 cc. of absolute ether was added dropwise over a period of 15 min. The mixture was stirred and refluxed for 27.5 hr., then decomposed with the theoretical amount of water, filtered, and the cake washed thoroughly with anhydrous ether. An excess of dry hydrogen chloride was bubbled into the solution. The resulting suspension was

(11) Use of commercial dioxane resulted in a brown color in the reaction products.

(12) P. Karrer, F. Canal, K. Zohner, and R. Widner, *Helv. Chim. Acta*, 11, 1082 (1928).

(13) J. v. Braun, G. Blessing, and F. Zobel, *Ber.*, **56**, 1993 (1923) give 198°.

(14) B. L. Murr and C. T. Lester, *J. Am. Chem. Soc.*, **77**, 1684 (1955).

(15) C. Naegeli, L. Grüntuch, and P. Leudorff, *Helv. Chim. Acta*, 12, 240 (1929). Murr and Lester[14] give 190–192°.

cooled and filtered to give 5.6 g. of colorless material of m.p. 150–154° (84.5% yield).

Anal. Calcd. for $C_{12}H_{28}NCl$: Cl^-, 16.0. Found: Cl^-, 15.9.

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Reaction of Hydrazine with Acetic Acid at 25°[1]

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While studying the oxidation of hydrazine in glacial acetic acid, it was noted that the basicity of the solution of hydrazine in acetic acid decreased with time. No record was found for the rate of reaction of hydrazine with acetic acid at room temperatures. The following work was undertaken to determine if a standard solution of hydrazine in acetic acid was stable.

Hydrazine can effectively disappear from solution in acetic acid by the following scheme:

$$NH_2NH_2 + CH_3COOH \longrightarrow CH_3CONHNH_2 + H_2O \quad (1)$$

$$CH_3CONHNH_2 + CH_3COOH \longrightarrow CH_3CONHNHCOCH_3 + H_2O \quad (2)$$

The acethydrazide formed initially can disproportionate[2] as indicated, regenerating hydrazine and forming symmetrical diacethydrazide. The disappearance of hydrazine function measured in the present work does not correspond to reaction 1

$$2CH_3CONHNH_2 \longrightarrow NH_2NH_2 + CH_3CONHNHCOCH_3 \quad (3)$$

alone, but to Reaction 1 counterbalanced somewhat by the hydrazine regeneration *via* step 3. It is thus necessary to follow the disappearance of both hydrazine and acethydrazide.

A review of the literature yielded no methods for the determination of hydrazine in the presence of acethydrazide and diacethydrazide in acetic acid as the solvent. Grammaticakis[3] reported the formation of disalicylalhydrazine on treatment of hydrazine with freshly distilled salicylaldehyde. This reaction was found to occur rapidly in acetic acid at room temperature and to yield a yellow solution or precipitate. The spectrum for a solution containing 0.2 mg. per ml. of hydrazinium acetate is shown in Fig. 1. An analytical procedure based on this color formation is decribed below.

The analytical results for the reaction of acetic acid with hydrazine are summarized in Fig. 2A and

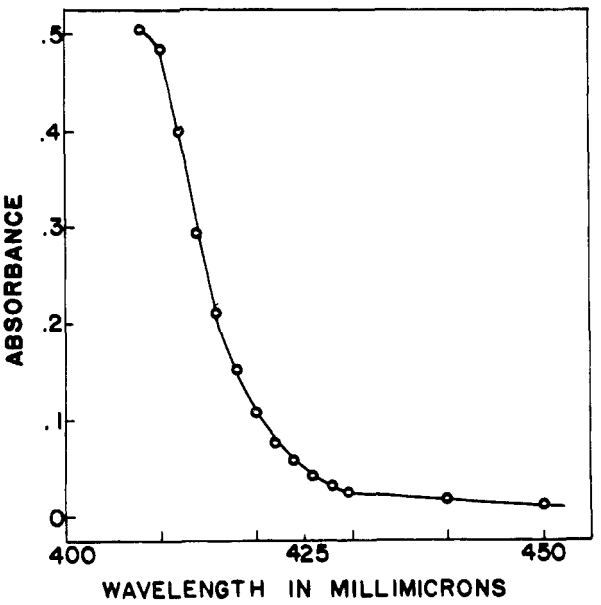

Fig. 1. Visible spectrum for disalicylalhydrazine

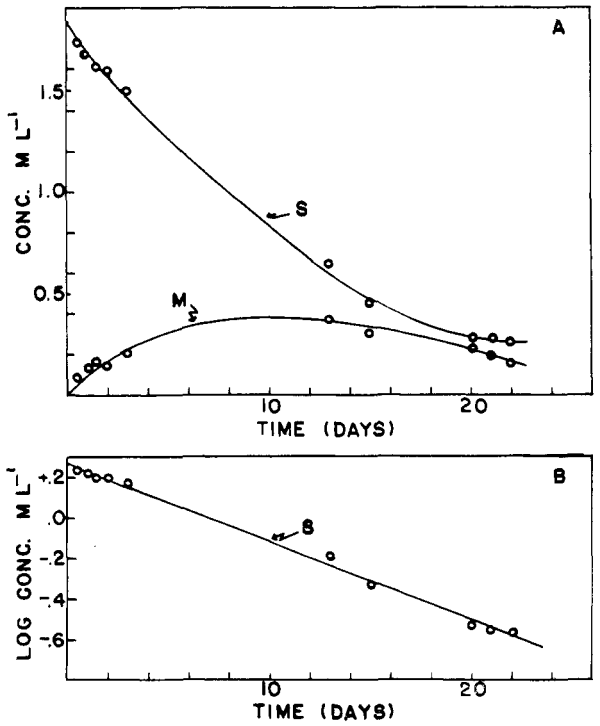

Fig. 2. A. Hydrazine–acetic acid reaction. S—salt concentration, M—acethydrazide concentration. B. First order plot for hydrazine acetate

those for the disproportionation of acethydrazide in Fig. 3A.[4] In both cases the concentration unit is moles per liter. From these results it appears that both reactions must be considered as occurring but that the rates are very different so pseudo rate constants are not too much in error.

The disproportionation of acethydrazide (Equation 3) is a moderately fast reaction which is second

(1) Abstracted from the Ph.D. thesis submitted by William C. Harris to the School for Advanced Graduate Studies, Michigan State University.

(2) W. Autenrieth and P. Spiess, *Ber.*, **34**, 187 (1901).

(3) P. Grammaticakis, *Bull. soc. chim., France*, 690 (1950).

(4) Detailed experimental data are available on request.