Conversion of Carboxylic Acids to Amines and Their Derivatives[1]

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Received December 27, 1963

A convenient new synthesis of aromatic amines involves heating aromatic carboxylic acids with nitromethane in polyphosphoric acid. The reaction apparently involves a Lossen rearrangement, and hydroxamic acids are formed as intermediates. With higher primary nitro alkanes, such as nitroethane, the products are generally amidoximes rather than amines. Aliphatic amines and aromatic amines containing electron-withdrawing groups are better prepared by a different procedure starting with acid derivatives and hydroxylamine. Both procedures avoid isolation of intermediate products, although hydroxamic acids, O-acylated hydroxamic acids, isocyanates, and ureas are readily obtained by minor changes in procedure. Mechanistic considerations are discussed, and the influence of the structure of the acid on yields of amines is explained.

When benzoic acid is heated with nitromethane in polyphosphoric acid (PPA), aniline is formed in good yield along with carbon monoxide and carbon dioxide. The course of this remarkable oxidative amination is revealed in part by interrupting the process before it is complete and isolating the intermediate dibenzhydroxamic acid, $C_6H_5CONHOCOC_6H_5$. Formation of this acid suggests that the synthesis is proceeding by way of a Lossen rearrangement[3,4] with the nitromethane serving as a source of hydroxylamine. This procedure will hereafter be referred to as the acidic procedure.

The new synthesis of amines works well with aromatic acids containing electron-supplying groups, but fails or gives poor yields with aliphatic acids and with aromatic acids containing electron-withdrawing groups. The reasons for these failures became apparent only after a rational scheme of intermediate reactions was devised and tested in a stepwise fashion.

$$CH_3NO_2 \xrightarrow{PPA} NH_2OH + CO \qquad (1)$$

$$RCOOH \overset{PPA}{\rightleftharpoons} [RC(OH)_2]^+ \qquad (2)$$

$$[RC(OH)_2]^+ + NH_2OH \rightleftharpoons RCONHOH + H_3O^+ \qquad (3)$$

$$RCONHOH + [RC(OH)_2]^+ \rightleftharpoons RCONHOCOR + H_3O^+ \qquad (4)$$

$$RCONHOCOR \longrightarrow RN{=}C{=}O + RCOOH \qquad (5)$$

$$RN{=}C{=}O + H_3O^+ \longrightarrow RNH_3^+ + CO_2 \qquad (6)$$

Since reactions 1 and 6 are too well known to doubt their occurrence under the conditions of this synthesis, attention was directed at the remaining reactions starting with 5. Dilaurohydroxamic acid was synthesized by an independent method and heated in PPA. Only a little undecylamine was formed and much lauric acid was recovered. Furthermore, monolaurohydroxamic acid heated in PPA gave no amine and much lauric acid. These results indicate that reactions 4 and 3 and probably 2 also are reversible. With lauric acid, 4 and 3 are apparently reversed before 5 can occur to more than a very limited extent. Reaction 5 occurs readily enough if R′ in RCONHOCOR′ is made more strongly electron withdrawing. Thus, sodium laurohydroxamate reacts with benzoyl chloride in dioxane to give undecylamine (as N,N′-diundecylurea) in 68% yield. However, if a mixture of lauric and benzoic acids is reacted with nitromethane in PPA, the only amine isolated is aniline, the lauric acid being recovered unchanged. With *p*-nitrobenzoic acid and other benzoic acids with electron-withdrawing substituents, the equilibrium in eq. 2 lies far to the left preventing the occurrence of 3 or 4. *p*-Nitrobenzoic acid dissolves to only a very limited extent in PPA. Upon these relationships depend the failures of the acid synthesis.

Reversal of reactions 4 and 3 can be prevented by operating under basic conditions, not only because the attacking species H_3O^+ is destroyed, but also because the mono- and dilaurohydroxamic acids are stabilized by conversion to salts by bases. However, base also destroys the protonated form of the carboxylic acid, $RC(OH)_2^+$, and hence does not favor reactions 2, 3, or 4 in the forward direction. The synthetic dilemma presented by these facts can be resolved by employing a different type of acylating agent, *e.g.*, an ester or an acid chloride, which will acylate under basic conditions. If potassium hydroxide flakes and then methyl laurate are added to a cold pyridine solution of hydroxylamine hydrochloride, the mixture is stirred for an hour, then benzoyl chloride is added, and the mixture is refluxed until gas evolution ceases, undecylamine is obtained as the diundecylurea in 45–50% yield. In a similar fashion and in similar yield *p*-nitroaniline is obtained using *p*-nitrobenzoyl chloride instead of methyl laurate. This procedure will be referred to as the basic procedure.

The Lossen synthesis of amines has never attained the popularity of the Hofmann[3,5] and the Curtius syntheses,[3] probably because the Lossen synthesis fails with so many acids and because it usually involves the isolation of two or more intermediates. Both of the two new procedures (acidic and basic) developed in this research are essentially one-pot syntheses; they do not require the isolation of any intermediate. Furthermore, one or the other of them can be applied to the synthesis of any kind of amine which does not contain substituent groups sensitive to the reagents employed.

Slight alterations in the acidic or basic procedures described permit the preparation of mono- or diacylated hydroxylamines, O-(carbamyl)hydroxamic acids, symmetrical ureas, or isocyanates from carboxylic

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(1) From the Ph.D. Thesis of J. E. Goldmacher, Purdue University, June, 1963.

(2) This investigation was supported in part by a Public Health Service Fellowship (GPM-13,873-C1) from the National Institute of Health, Public Health Service.

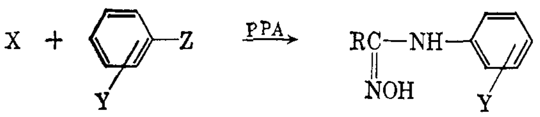
(3) W. Lossen, *Ann.*, **161**, 347 (1872).

(4) See also P. A. S. Smith, "Molecular Rearrangements," Part One, Interscience Division of John Wiley and Sons, Inc., New York, N. Y., 1963, p. 528, for a recent review of the Lossen, Hofmann, and Curtius rearrangements. H. R. Snyder, C. T. Elston, and D. B. Kellom [*J. Am. Chem. Soc.*, **75**, 2014 (1953)] developed a one-pot method for converting a carboxylic acid to an amine *via* the Lossen rearrangement in PPA using hydroxylamine instead of nitromethane. They also found that their method was poor with aliphatic acids but good with most benzoic acids.

(5) E. S. Wallis and J. F. Lane, *Org. Reactions*, **3**, 267 (1946).

TABLE I

AMIDE OXIMES

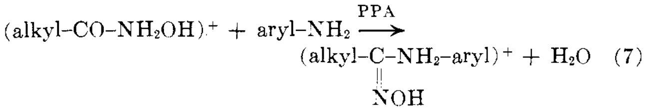


Reactants			M.p., °C.[b]	Products, % conversion	C, %		H, %		N, %		Cl, %	
X[a]	Y	Z			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
NE	p-Cl	CO_2H	130	47	51.85	51.22	4.87	4.88	15.20	15.68	19.30	19.83
NP	p-Cl	CO_2H	117	17	54.41	54.21	5.58	5.55	14.13	13.85	17.85	18.05
NB	p-Cl	CO_2H	. . .	Trace								
AHA	p-Cl	NH_2	130	54								
NE	p-CH_3	CO_2H	127	63	65.83	65.60	7.37	7.22	17.06	16.91		
AHA	p-CH_3	NH_2	127	46								
NE	p-OCH_3	CO_2H	145	63	59.98	59.25	6.71	6.77	15.55	14.59		
NE	None	NH_2	119[c]	41								
AHA	None	NH_2	119[c]	40								

[a] NE, nitroethane; NP, 1-nitropropane; NB, 1-nitrobutane; AHA, acethydroxamic acid. [b] Uncorrected. [c] See ref. 14.

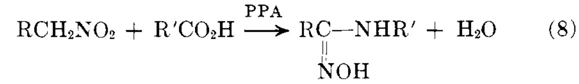
acids. The basic procedure is the more versatile in this respect. If this is interrupted before the benzoyl chloride is added, the mixture is filtered, and the solid is washed with water to remove soluble inorganic substances, an excellent yield of hydroxamic acid salt is obtained. It may be recrystallized from aqueous alcohol. Diacylated hydroxylamines are readily obtained by reaction of these hydroxamic acid salts with acid chlorides in an inert solvent such as dioxane.[6] Symmetrical ureas are the direct products of the basic procedure and must be hydrolyzed to obtain the corresponding amines. Heating the salts of hydroxamic acids with 2 moles of thionyl chloride in dioxane yields the corresponding isocyanates. With 1 mole equiv. of thionyl chloride, the product is an O-(carbamyl)-hydroxamic acid, RCONHOCONHR. Detailed procedures for all of these syntheses are given in the Experimental part.

Amidoximes.—Since all primary nitro alkanes yield hydroxylamine on acid-catalyzed hydrolysis, it was anticipated that nitroethane should convert benzoic acid to aniline in PPA as readily as does nitromethane. This was indeed found to be the case, but when substituted benzoic acids were used with nitroethane, 1-nitropropane, or 1-nitrobutane in PPA, entirely different products were obtained instead of the expected aryl amines. These were eventually identified as N-aryl amidoximes. The essential step in their formation is believed to be represented by eq. 7.



$$(\text{alkyl-CO-NH}_2\text{OH})^+ + \text{aryl-NH}_2 \xrightarrow{\text{PPA}} (\text{alkyl-}\underset{\text{NOH}}{\underset{\|}{\text{C}}}\text{-NH}_2\text{-aryl})^+ + H_2O \quad (7)$$

The protonated aliphatic hydroxamic acid is formed by rearrrangement of the nitro alkane; the aryl amine is formed by a Lossen rearrangement of a diaroylhydroxylamine, formed in turn from the aromatic carboxylic acid (as in eq. 2–6). In accord with this belief, it has been found that aryl amines can be successfully substituted for aromatic carboxylic acids and aliphatic hydroxamic acids can be substituted for nitro alkanes in the synthesis of N-aryl amidoximes. In the generalized equation (8), the nature of R′ is of the utmost importance for two reasons. In the first place, R′ must be such as to permit the formation of an amine under these acidic conditions; *i.e.*, it must be aryl- or aryl-substituted by electron-supplying groups. If R′ does not fulfill this requirement, the amidoxime can still be prepared by employing the aromatic amine, R′NH$_2$, in the synthesis instead of the aromatic carboxylic acid. Thus N-phenylacetamidoxime itself is obtained when aniline is heated with either nitroethane or acethydroxamic acid in PPA. In the second place R′ must be such as to promote reaction with the hydroxamic acid. Thus, amines such as hexylamine, urea, phenylhydrazine, and glycine do not give amidoximes with either acethydroxamic acid or nitroethane in PPA. They also do not give amidoximes under neutral or basic conditions, suggesting that the reaction requires the more reactive protonated form of the hydroxamic acid as indicated in eq. 7. Results of these experiments are summarized in Table I.



$$RCH_2NO_2 + R'CO_2H \xrightarrow{\text{PPA}} \underset{\text{NOH}}{\underset{\|}{\text{RC}}}\text{—NHR}' + H_2O \quad (8)$$

N-Aryl amidoximes are remarkably stable to hydrolysis in either acidic or basic media. We were unable to hydrolyze N-phenylacetamidoxime in 50% aqueous alkali, concentrated hydrochloric acid, or concentrated hydrobromic acid in acetic acid. This is all the more remarkable in view of the fact that unsubstituted amidoximes hydrolyze rather easily.

Amines from HOS.—Numerous attempts were made to prepare amines in high yields by reaction of carboxylic acids or their derivatives with hydroxylamine-O-sulfonic acid (HOS). This reagent is now readily available[7] and would seem to be an excellent starting material for amine synthesis. The best results (20–25% conversions to amyl amine) were obtained by heating caproic acid or its anhydride with equimolar amounts of HOS in mineral oil to 160–180° until gas

$$RCO_2H + NH_2OSO_3H \longrightarrow RCONHOSO_3H + H_2O \quad (9)$$

$$RCONHOSO_3H \xrightarrow{\text{heat}} RNCO + H_2SO_4 \quad (10)$$

$$RNCO + H_2O \longrightarrow RNH_2 + CO_2 \quad (11)$$

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(6) W. B. Renfrow, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **59**, 2308 (1937).

(7) H. J. Matsuguma and L. F. Audrieth, "Inorganic Synthesis," Vol. 5, McGraw-Hill Book Co., Inc., New York, N. Y., 1957, p. 122.

evolution ceased. Poorer results were obtained in PPA and other solvents.

Experimental

The following experiments illustrate the procedures employed. All reactions were run in a three-necked flask equipped with a mechanical stirrer, reflux condenser, and thermometer unless otherwise stated.

_p_-Chloroaniline. Reaction of _p_-Chlorobenzoic Acid with Nitromethane.—A mixture of 100 g. of PPA, 12.52 g. (0.08 mole) of _p_-chlorobenzoic acid and 9.76 g. (0.16 mole) of nitromethane was heated with stirring at 115° for 90 min. (or until gas evolution ceased), poured into 200 g. of crushed ice, stirred, and filtered. _p_-Chlorobenzoic acid, 3.1 g., was recovered. The filtrate was then made strongly alkaline with KOH, cooled for 2 hr. at 0°, and filtered. _p_-Chloroaniline, m.p. 69°, 6.1 g. (60% conversion, 80% yield), was isolated; lit.[8] m.p. 70°. A mixture melting point with an authentic sample of _p_-chloroaniline showed no depression. The infrared spectrum was superimposable on that of an authentic sample of _p_-chloroaniline.

In a similar fashion the following amines were prepared in the indicated yields from the corresponding carboxylic acids: aniline (68%), _p_-toluidine (73%), and _o_-toluidine (19%). The low yield from _o_-toluic acid may be attributed to steric inhibition of resonance caused by the _o_-methyl group and resulting in decreased protonation of the carboxyl group.

Use of benzoyl chloride instead of benzoic acid gave aniline in about the same yield (71%) but in a shorter time. Use of nitroethane instead of nitromethane gave aniline in 53% yield from benzoic acid. Use of 2-nitropropane instead of nitromethane gave oxides of nitrogen but no aniline.

N,N′-Diundecylurea and Undecylamine. A. From Methyl Laurate.—To a solution of 13.90 g. (0.2 mole) of hydroxylamine hydrochloride in 200 ml. of pyridine was added powdered potassium hydroxide, 28 g. (0.5 mole), all at once at 0° with stirring. After 15 min., 21.4 g. (0.1 mole) of methyl laurate was added all at once. The mixture was stirred for 1 hr. at room temperature. Then 56 g. (0.4 mole) of benzoyl chloride was slowly added at 0° and stirred for 0.5 hr. at ambient temperature. The mixture was refluxed for 2 hr. (or until gas evolution ceased), poured into 700 g. of crushed ice, stirred, and cooled at −10° overnight. After filtering, 8.7 g. (47% yield) of N,N′-diundecylurea, m.p. 100°, was isolated; lit.[9] m.p. 103°. A mixture melting point with an authentic sample gave no depression. The infrared spectrum was superimposable on that of an authentic sample. Acid hydrolysis gave undecylamine hydrochloride and treatment of this with base gave the free amine, benzoyl derivative, m.p. 59°; lit.[10] m.p. 60°.

The importance of the strongly basic character of KOH in the above procedure is evident from the results of similar experiments in which triethylamine replaced the KOH and all or part of the pyridine. Yields of 15–20% of ethylamine were obtained from propionyl chloride.

Using _p_-nitrobenzoyl chloride in place of methyl laurate in the basic procedure gave _p_-nitroaniline directly (not the urea) in 49% yield. Similarly, dimethyl terephthalate in place of methyl laurate gave a polymeric urea (m.p. >340°) which upon hydrolysis in concentrated hydrochloric acid gave _p_-phenylenediamine in 13% yield.

B. From Sodium Laurohydroxamate.—A mixture of 75 ml. of dioxane, 11.8 g. (0.05 mole) of sodium laurohydroxamate, and 7.2 g. (0.05 mole) of benzoyl chloride was refluxed for 24 hr., poured into 500 ml. of ice-water, and filtered. N,N′-Diundecylurea, 6.1 g. (68% yield), m.p. 102°, was obtained.

Hydroxamic Acids. Preparation of Benzhydroxamic Acid.—To a mixture of 19.6 g. (0.35 mole) of powdered potassium hydroxide suspended in 120 ml. of pyridine were added a solution of 13.90 g. (0.2 mole) of hydroxylamine hydrochloride in 100 ml. of pyridine at 0–5°, then 15 mg. (0.1 mole) of ethyl benzoate. The mixture was stirred vigorously for 6 hr. at room temperature and filtered. If the solid isolated was washed with water to dissolve the inorganic by-products and recrystallized from aqueous ethanol, a 94% yield of potassium benzhydroxamate was isolated. This salt was converted to the free benzhydroxamic acid by triturating with cold 0.01 _N_ hydrochloric acid. Benzhydroxamic acid, 12.5 g. (92% yield), m.p. 131° (from aqueous alcohol), was obtained. A mixture melting point with an authentic sample gave no depression. Laurohydroxamic acid was prepared in quantitative yield from methyl laurate by a similar experiment. _p_-Nitrobenzhydroxamic acid, m.p. 174–176°, was obtained in 17% yield.

Heating pure benzhydroxamic acid in PPA until gas evolution ceased gave aniline in 64% yield. Similarly _p_-nitrobenzhydroxamic acid gave _p_-nitroaniline in 20% yield and _p_-nitrobenzoic acid in 69% recovery.

Amyl Amine. Reaction of Caproic Acid with HOS.—A mixture of 12.0 g. (0.1 mole) of HOS, 11.6 g. (0.1 mole) of caproic acid, and 200 ml. of mineral oil was heated for 2.5 hr. at 170–180°, cooled, and filtered. The resulting black solid, about 14.5 g., was suspended in excess KOH solution and steam distilled. The distillate was saturated with potassium carbonate, extracted with four 50-ml. portions of ether, dried, concentrated, and distilled. Amyl amine, 1.98 g. (23% yield), b.p. 35–36° (87 mm.), was obtained. The infrared spectrum was superimposable on that of an authentic sample. The thiourea derivative, m.p. 69°, was prepared. A mixture melting point with an authentic sample of the thiourea derivative gave no depression.

Undecyl Isocyanate. Reaction of Potassium Laurohydroxamate with Thionyl Chloride.—A mixture of 25.3 g. (0.1 mole) of potassium laurohydroxamate, 23.6 g. (0.2 mole) of thionyl chloride, and 200 ml. of dioxane were refluxed for 4.5 hr., filtered concentrated, and distilled _in vacuo_. A forerun of 30 ml. of material, b.p. 58–63° (8.5–9 mm.), which appeared to be an adduct of thionyl chloride and dioxane was obtained. Undecyl isocyanate, 10.9 g. (62% yield), b.p. 160–162° (18–19 mm.) with decomposition, was obtained; lit.[11] b.p. 103° (3 mm.). The isocyanate was characterized by conversion to N,N′-diundecylurea, m.p. 102°, by treatment with aqueous base at room temperature. A mixture melting point with an authentic sample gave no depression.

Dibenzhydroxamic Acid.—A mixture of 20 g. (0.164 mole) of benzoic acid, 40 g. (0.64 mole) of nitromethane, and 140 g. of PPA was heated with stirring for 3 hr. at 90–100° in a nitrogen atmosphere, poured into crushed ice, and filtered. Dibenzhydroxamic acid, m.p. 160°, 6.0 g. (30.5% yield), was obtained along with aniline, 3.1 g. (20% yield). The dibenzhydroxamic acid was characterized by a mixture melting point with an authentic sample and by its infrared spectrum which was identical with that of an authentic sample.

Heating dibenzhydroxamic acid, 2.5 g. (0.0115 mole), in 30 g. of PPA gave an 81% yield of aniline.

O,N-Diacylhydroxamic Acids. Dilaurohydroxamic Acid. Reaction of Sodium Laurohydroxamate with Lauroyl Chloride.—In a 1-l. round-bottom flask equipped with a condenser were placed a mixture of 25.3 g. (0.106 mole) of sodium laurohydroxamate, 150 ml. of dioxane, and 26.5 g. (0.1 mole) of lauroyl chloride. The mixture was refluxed for 4 hr., cooled, and poured into 500 ml. of ice-water. The white precipitate which settled was filtered with suction, washed with cold (−15°) absolute alcohol, and recrystallized from hot alcohol. Dilaurohydroxamic acid, m.p. 93–94°, 17 g. (42% yield), was obtained.

Anal. Calcd. for $C_{24}H_{47}NO_3$: C, 72.49; H, 11.91; N, 3.52. Found: C, 72.79; H, 12.00; N, 3.52.

O-(Carbamyl)hydroxamic Acids. Reaction of Equimolar Amounts of Sodium Laurohydroxamate and Thionyl Chloride in Dioxane.—A mixture of 11.8 g. (0.05 mole) of sodium laurohydroxamate, 5.95 g. (0.05 mole) of thionyl chloride, and 50 ml. of dioxane were refluxed for 1 hr., poured into 200 ml. of ice-water, and filtered. Laurylcarbamyl laurohydroxamate, 5.7 g. (59% yield), m.p. 65° (from ethanol), was obtained. It decomposed at its melting point and in part during recrystallization with evolution of carbon dioxide and was converted to N,N′-diundecylurea, m.p. 102°.

Due to the difficulty of obtaining the O-(carbamyl)hydroxamic acid analytically pure, it was identified by its infrared spectrum. The NH absorption was at 3310 cm.$^{-1}$ and carbonyl absorption at 1522, 1578, 1680, and 1738 cm.$^{-1}$. Carbonyl absorption for

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(8) R. L. Shriner and R. C. Fuson, "Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 292.

(9) T. Curtius, _J. prakt. Chem._, [2]**89**, 518 (1914).

(10) M. Frankel and S. Patai, "Tables for Identification of Organic Compounds," Chemical Rubber Publishing Co., Cleveland, Ohio, 1960, p. 160.

(11) C. F. H. Allen and A. Bell, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 846.

urethanes is reported[12] to be in the range 1736–1700 cm.$^{-1}$, and carbonyl absorption for an O-acylated hydroxamic acid is reported[13] to be at 1520, 1588, 1610, and 1653 cm.$^{-1}$.

Amidoximes A. Reaction of *p*-Toluic Acid with Nitroethane.—A mixture of 11.5 g. (0.084 mole) of *p*-toluic acid, 10 g. (0.134 mole) of nitroethane and 35 g. of PPA was heated at 115–125° for 2 hr., poured into 100 g. of crushed ice, stirred, and filtered. *p*-Toluic acid, 1.0 g., was recovered. The filtrate was basified with KOH, cooled for 2 hr. at 5°, and filtered. N-(*p*-Tolyl)acetamidoxime, m.p. 127°, 7.0 g. (63% yield), was obtained. The material required recrystallization from water to give a pure product.

B. Reaction of *p*-Chloroaniline with Acethydroxamic Acid.—A mixture of 12.75 g. (0.1 mole) of *p*-chloroaniline, 7.5 g. (0.1 mole), of acethydroxamic acid, and 70 g. of PPA was heated for 90 min. at 110–115°, poured into crushed ice, basified with KOH, and filtered. N-(*p*-Chlorophenyl)acetamidoxime, m.p. 130° (from water), 10.1 g. (54% yield), was obtained. The infrared spectrum was superimposable on the product from the reaction of *p*-chlorobenzoic acid and nitroethane.

An attempt to react aniline with *p*-nitrobenzhydroxamic acid gave none of the expected N-phenyl-*p*-nitrobenzamidoxime. Instead, rearrangement of the starting acid to *p*-nitroaniline (12% yield) and hydrolysis to *p*-nitrobenzoic acid (63% yield) occurred.

C. Reaction of Aniline with Nitroethane.—A mixture of 9.3 g. (0.1 mole) of aniline, 7.5 g. (0.1 mole) of nitroethane, and 100 g. of PPA was heated for 10 hr. at 120–130°, poured into 100 g. of crushed ice, basified with KOH, cooled at −10° overnight, and filtered. N-Phenylacetamidoxime, 6.1 g. (41% yield), m.p. 121° (from water), was obtained; lit.[14] m.p. 120–121°.

A similar experiment with *p*-nitroaniline instead of aniline gave no amidoxime. Similarly, *p*-cresol and *p*-thiocresol failed to give the corresponding O-aryl and S-aryl hydroxamic acids. These three compounds are probably too weakly nucleophilic to react with hydroxamic acids.

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(12) L. J. Bellamy, "Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 221.

(13) E. M. Usova and E. M. Voroshin, *Dokl. Akad. Nauk SSSR*, **113**, 1306 (1957).

(14) E. Nordmann, *Ber.*, **17**, 2746 (1884).

Enamine Chemistry. VIII.[1] Reactions with Miscellaneous Carbonyl and Active Hydrogen Compounds[2]

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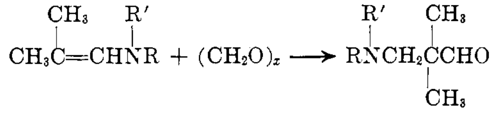
Received February 24, 1964

The reactions of enamines with a number of carbonyl and active hydrogen compounds are reported. Enamines derived from isobutyraldehyde react with paraformaldehyde to give Mannich-type products, with 2 moles of chloral to give 2,6-bis(trichloromethyl)-4-(dialkylamino)-5,5-dimethyl-*m*-dioxanes, with diethyl malonate to give a mixture of diethyl isobutylidenemalonate and diethyl isobutenylmalonate, and with acetamide to give N-[1-(dimethylamino)-2-methylpropyl]acetamide. Enamines derived from isobutyraldehyde and butyraldehyde react with *p*-benzoquinone to give substituted dihydrobenzofuranols.

Enamines have been shown to behave as nucleophilic reagents in many of their reactions. Since there is a large segment of organic chemistry which involves interactions of carbonyl compounds with nucleophiles, we have undertaken a survey of the reactions of enamines (most of which are derived from isobutyraldehyde) with several reactive carbonyl compounds. A logical starting point was the reaction with formaldehyde, the simplest carbonyl compound, at least in the structure of its monomer.

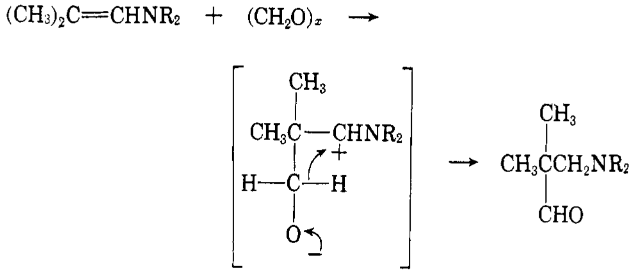
Reaction with Formaldehyde.—We found that heating N,N-dimethylisobutenylamine or 1-isobutenylpiperidine with paraformaldehyde produced substituted aminopivalaldehydes which have also been obtained by the Mannich reaction of isobutyraldehyde, formaldehyde, and the appropriate amine.[3]



$$\mathrm{CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH\overset{\displaystyle R'}{\overset{|}{N}}R + (CH_2O)_x \longrightarrow R\overset{\displaystyle R'}{\overset{|}{N}}CH_2\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}CHO}$$

1, R = CH_3; R′ = CH_3
2, R = R′ = $—CH_2(CH_2)_3CH_2—$

One possible course of the reaction is that the small amount of water present in paraformaldehyde hydrolyzes a part of the enamine and the reaction then proceeds as a simple Mannich reaction with recycling of the water. Another reaction path considered involved intermediate 3, which could form the observed product by a 1,3-hydride transfer.



$$\mathrm{(CH_3)_2C{=}CHNR_2 + (CH_2O)_x \longrightarrow \left[\,CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}\text{—}\overset{+}{C}HNR_2 \;/\; H\text{—}\underset{\displaystyle O^-}{C}\text{—}H\,\right] \longrightarrow CH_3\underset{\displaystyle CHO}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}CH_2NR_2}$$

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If the reaction were carried out using formaldehyde-d_2 as a reactant, the distribution of deuterium atoms in the products would show whether the latter route is feasible.

As a check, a Mannich reaction of isobutyraldehyde, dimethylamine, and formaldehyde was carried out using a large molar excess of deuterium oxide as solvent. The product, as expected, showed no detectable amount of deuterium present when checked by n.m.r. and infrared spectroscopy. Thus, no "scrambling" of deuterium should occur in a Mannich reaction using formaldehyde-d_2. A reaction of N,N-dimethylisobutenylamine with formaldehyde-d_2 was carried out, and in the n.m.r. spectrum of the product no peak assignable to N-methylene hydrogens was present, but a peak of

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(1) Paper VII of this series: K. C. Brannock, R. D. Burpitt, and J. G. Thweatt, *J. Org. Chem.*, **29**, 940 (1964).

(2) A portion of the material in this paper was presented at the Southeast Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., Nov. 1–3, 1962.

(3) C. Mannich, *Ber.*, **65**, 378 (1932).