piperidine hydrochloride (VII). A reaction mixture consisting of 60.0 g. (0.402 mole) of bromocyclopentane, 61.6 g. (0.335 mole) of piperidine-3-(*N*,*N*-diethylcarboxamide) (II),[2] 62.0 g. (0.449 mole) of anhydrous potassium carbonate, and 150 ml. of anhydrous benzene was heated at reflux temperature, with mechanical agitation, for a total of 124 hr. Upon cooling, the solid constituents of the reaction mixture were filtered off, the filtrate was washed with aqueous 40% potassium hydroxide, and dried over anhydrous magnesium sulfate. The dry benzene solution was filtered, the benzene was removed, and the residue was fractionated under reduced pressure. The base was converted to the hydrochloride by treating it with anhydrous HCl in anhydrous ethyl ether. The salt was purified by recrystallization from ethanol-ethyl acetate.

Procedure D: 1-Methyl-1,2,5,6-tetrahydro-3-(N,N-dimethylcarboxamido)pyridine hydrochloride (III). 1-Methyl-1,2,5,6-tetrahydropyridine-3-carboxylic acid was prepared from arecoline according to Jahns' procedure.[3] To 30.0 g. (0.213 mole) of the acid, 245.7 g. (2.065 moles) of thionyl chloride was added, the mixture was heated gradually to reflux temperature, and the resulting solution was refluxed for 16 min. The excess thionyl chloride was removed under reduced pressure (max. pot temp. 40°). The residual thionyl chloride was removed from the reaction product by azeotropic distillation under reduced pressure with two 400 ml. portions of anhydrous benzene. Then 200 ml. of anhydrous benzene was introduced into the reaction vessel, and the solid acid chloride was finely dispersed with mechanical agitation. To this dispersion, a solution of 100 g. (2.219 moles) of dimethylamine in 200 ml. of anhydrous benzene was added gradually, while the reaction mixture was maintained at room temperature. After the addition, the mixture was stirred an additional 2 hr. at room temperature and an additional 5 hr. at 50–55°. The resulting slurry was treated with aqueous 40% sodium hydroxide and the base extracted with benzene. The combined benzene extracts were dried over anhydrous sodium sulfate, filtered, the benzene was removed, and the residue was fractionated under reduced pressure. The base was converted to the hydrochloride by treating it with anhydrous HCl in anhydrous ethyl ether. The salt was purified by recrystallization from ethanol-ethyl acetate.

The following monoalkylcarboxamido derivatives were prepared by Procedure D: *1-Methyl-3-(N-methylcarboxamido)-1,2,5,6-tetrahydropyridine hydrochloride (XIV)*. The base distilled at 129–131°/0.5 mm. Hg; n_D^{27} 1.5197 (yield 41.0%). The compound melted at 184.0–185.0°.

Anal. Calcd. for $C_8H_{15}ClN_2O$: C, 50.39; H, 7.93; Cl, 18.60; N, 14.70. Found: C, 50.40; H, 8.00; Cl, 18.55; N, 14.70.

1-Methyl-3-(N-ethylcarboxamido)-1,2,5,6-tetrahydropyridine hydrochloride (XV). The base distilled at 128–132°/0.09 mm. Hg; n_D^{27} 1.5107 (yield 42.2%). The compound melted at 163.0–164.0°,

Anal. Calcd. for $C_9H_{17}ClN_2O$: C, 52.80; H, 8.37; Cl, 17.32; N, 13.69. Found: C, 52.96; H, 8.39; Cl, 17.3; N, 13.8.

In tests on blood pressure and upon the autonomic nervous system as defined by changes in response to acetylcholine, epinephrine, tetramethylammonium bromide, and carotid occlusion (in chloralose anesthetized dogs), several compounds induced ganglionic blockade, some adrenergic blockade, and some effected hypotension of an as yet undetermined nature. The pharmacological evaluation is not complete at the time of this writing.

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[3] E. Jahns, *Arch. Pharm.*, **229**, 680 (1891).

Nitriles in Nuclear Heterocyclic Syntheses. I. Dihydro-1,3-oxazines[1]

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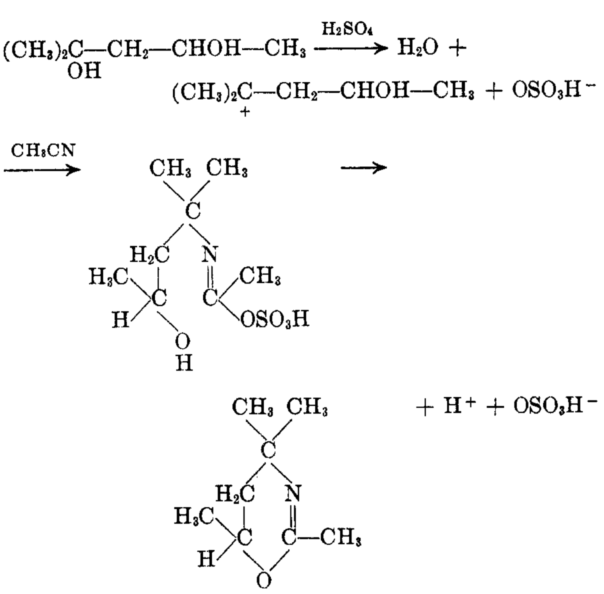
Received January 21, 1957

The acid-catalyzed reaction of secondary and tertiary alcohols with nitriles has been shown to result in formation of a variety of *N*-substituted amides.[2] Interaction of 2-methyl-2,4-pentanediol with acetonitrile has now been found to yield a dihydro oxazine instead of the expected diamide. It is suggested that primary reaction of a tertiary carbonium ion with the nitrile in the ordinary manner is followed by cyclization with displacement of $—OSO_3H$ as follows:



Confirmation of the identity of the product was obtained by comparison with authentic 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine.[3] Further proof consisted in comparison of the caprylate of the amine resulting from alkaline cleavage of this dihydro oxazine with that of an authentic specimen of 4-amino-4-methyl-2-pentanol.

Two additional dihydro oxazines, 4,4,6-trimethyl-2-phenyl-5,6-dihydro-1,3-oxazine and 4,4,6-trimethyl-2-benzyl-5,6-dihydro-1,3-oxazine were prepared in the same manner by substituting benzo-

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[1] Abstracted from part of a thesis submitted by Emma-June Tillmanns to the Graduate Faculty of New York University in partial fulfilment of the requirements for the degree of Doctor of Philosophy, February 1954.

[2] J. J. Ritter and J. Kalish, *J. Am. Chem. Soc.*, **70**, 4048 (1948); F. R. Benson and J. J. Ritter, *J. Am. Chem. Soc.*, **71**, 4128 (1949); L. W. Hartzel and J. J. Ritter, *J. Am. Chem. Soc.*, **71**, 4130 (1949); H. Plaut and J. J. Ritter, *J. Am. Chem. Soc.*, **73**, 4076 (1951).

[3] M. E. Smith and H. Adkins, *J. Am. Chem. Soc.*, **60**, 407 (1938).

nitrile and phenylacetonitrile respectively for acetonitrile.

This novel variant of the alkene-nitrile reaction has since been extended to the synthesis of Δ^1-pyrrolines, dihydropyridines, and other *N*-heterocyclic systems which will be reported in the near future.

EXPERIMENTAL

2,4,4,6-Tetramethyl-5,6-dihydro-1,3-oxazine(I). Acetonitrile (55 ml., 1.05 mole) was added dropwise with stirring to 500 g. of 92% sulfuric acid at 6–7° during 0.5 hr. Then 128 ml. (118.2 g., 1 mole) of 2-methyl-2,4-pentanediol was added dropwise with stirring over 4 hr. at 8–10°. The resulting solution was poured with stirring on 1 kg. of cracked ice and the mixture was half-neutralized with 40% sodium hydroxide solution, then extracted with several portions of chloroform. The acid layer was then made alkaline with 40% sodium hydroxide and the basic oil which separated was extracted with several portions of ether. The combined ether extracts were dried over anhydrous potassium carbonate, and after removal of the ether the residual oil was distilled through a 30-cm. vacuum-jacketed Vigreux column. There was obtained 61.4 g. (44%) of a water-soluble colorless liquid with ammoniacal odor, b.p. 56°/24 mm. (146–147°/750 mm.), n_D^{25} 1.4370; reported[3] b.p. 146.8–147°, n_D^{25} 1.4358.

Anal. Calcd. for $C_8H_{15}ON$: N, 9.93. Found, 9.95. The picrate melted at 153–154° (uncorr.); reported,[3] 152–153°.

Alkaline cleavage of I. The method of Smith and Adkins[3] was used to treat 24 g. (0.17 mole) of I. A colorless amine(II) was obtained in 75% yield (15 g.), b.p. 174–175°, n_D^{20} 1.4350. A specimen of 4-amino-4-methyl-2-pentanol[4] distilled at atmospheric pressure at 174–175°, n_D^{20} 1.4340. The caprylates of II and 4-amino-4-methyl-2-pentanol were prepared by mixing 1 mmole of each with 1 mmole of caprylic acid. The mixtures solidified almost immediately and the resulting solids were recrystallized twice from dry acetone. The melting point of each was 84–85° and the mixed melt showed no depression.

4,4,6-Trimethyl-2-phenyl-5,6-dihydro-1,3-oxazine. Benzonitrile (20.6 g., 0.2 mole) was added dropwise with stirring to 100 g. of 92% sulfuric acid at 2–4° over 20 min. Then 23.6 g. (0.2 mole) of 2-methyl-2,4-pentanediol was added dropwise with stirring at 3–6° during 2 hr. The product was isolated in the same manner as for I. A pale yellow oil (19.1 g., 47%), b.p. 103–106°/3 mm. was obtained. Two recrystallizations from ethanol-water (the compound was dissolved at room temperature and the solution was then strongly cooled) gave colorless crystals, m.p. 34–35° (reported,[5] 32°).

Anal. Calcd. for $C_{13}H_{17}ON$: N, 6.90. Found, 7.01. The picrate melted at 159–161° (corr.); reported,[5] 162.5–164°.

4,4,6-Trimethyl-2-benzyl-5,6-dihydro-1,3-oxazine. The procedure for this preparation was similar to the one above. Phenylacetonitrile (11.7 g., 0.1 mole) was added to 50 g. of 92% sulfuric acid followed by 11.8 g. (0.1 mole) of 2-methyl-2,4-pentanediol. A yellow oil (5.7 g., 26%) was obtained, b.p. 116–119°/5 mm., n_D^{20} 1.5125.

Anal. Calcd. for $C_{14}H_{19}ON$: N, 6.45; found, 6.39. The picrate melted at 125–126°.

Acknowledgment. The authors wish to thank Dr. Clayton W. Ferry for permission to use the Burroughs-Wellcome and Co. laboratory facilities for this work.

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(5) M. Kahan, *Ber.*, **30**, 1319 (1897).

Amines. III. Characterization of Some Aliphatic Tertiary Amines[1]

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Received January 21, 1957

The literature on simple aliphatic tertiary amines and their characterization is surprisingly sparse. Even the commercially available triethylamine[3] has not been reported characterized by such common derivatives as the methiodide or the methotosylate. Frequently when methiodide derivatives have been prepared and reported—there are at least five references to the methiodide of *N*-ethyldimethylamine,[4] two each for that of *N,N*-diethylmethylamine[4a,4b] and of *N*-isopropyldimethylamine[4a,5] and one for that derivable from *N*-*tert*-butyldimethylamine[6]—no melting data were given. The present investigation was undertaken to provide systematic and comparative characterization of a series of closely related simple aliphatic tertiary amines. This included the fully *N*-methylated ethyl-, diethyl-, isopropyl-, diisopropyl-, and *tert*-butylamines, and triethylamine. Although the *tert*-butyldimethylamine is the only new compound, the other amines, except for triethylamine, have been poorly characterized in the literature.

The tertiary methylamines were prepared by the Eschweiler-Clarke method.[7] The preparative data are presented in Table I. Physical constants, including freezing points, refractive indices, densities, molar refractivities, and Eykman constants are summarized in Table II. The chemical derivatives are listed in Tables III and IV.

EXPERIMENTAL

Eschweiler-Clarke N-methylation. Reactions were carried out in a magnetically stirred glass system closed except for a gas effluent tube which carried off the evolved carbon dioxide

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(1) Previous paper, J. Radell, L. Spialter, and J. Hollander, *J. Org. Chem.*, **21**, 1051 (1956).

(2) Dr. Joseph A. Pappalardo, of the University of Dayton, worked on this investigation under the Summer Expert Employment Program of the Wright Air Development Center.

(3) Available from Union Carbide Chemicals Co., 30 East 42nd Street, New York 17, N. Y.

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