of 2-but-3-enyl-substituted nitrile ylides does not occur.[9] This was attributed to the stereoelectronic problem of locating the p orbital of the terminal olefin in the proper position for maximum overlap with the second LUMO of the nitrile ylide. A similar explanation would also account for the absence of a 1,1-cycloaddition reaction with tetrazole **4**.
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# Reversible Interconversion of *N*-Nitroso(2-methylamino)acetonitrile and 3-Methyl-5-amino-1,2,3-oxadiazolium Chloride and Related Reactions[1]

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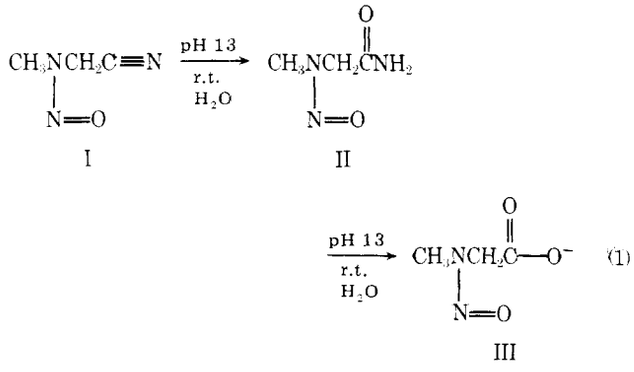
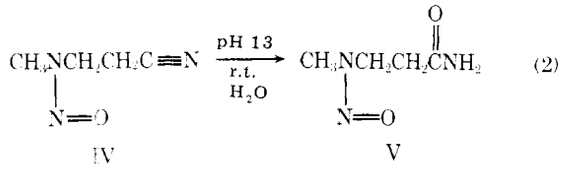
Reaction of *N*-nitroso(2-methylamino)acetonitrile (I) with gaseous hydrogen chloride in dry methanol, ethanol, or ether is a fast reaction that yields 3-methyl-5-amino-1,2,3-oxadiazolium chloride (VI) virtually quantitatively. A pathway for the conversion of I to VI involving anchimeric assistance by the nitroso group is suggested. With aqueous base at pH 8–11, VI is reversibly converted to I, but at pH 11.5–14 VI is converted to *N*-nitrososarcosine (VII). Treatment of the homologous *N*-nitroso(3-methylamino)propionitrile (IV) with hydrogen chloride in methanol is a relatively slow reaction and does not yield a cyclic product; IV is denitrosated and converted to methyl (3-methylamino)propionate hydrochloride (VIII), with concomitant formation of ammonium chloride. The unnitrosated parent amine of I, methylcyanomethylamine hydrochloride (IX), on reaction with hydrogen chloride, behaves in the same manner as IV; products are methyl(2-methylamino)acetate hydrochloride (X) and ammonium chloride. A simple denitrosation procedure for *N*-nitrosamines derived from secondary amines is also described.

In an earlier paper,[3] we reported the unexpectedly rapid hydrolysis of *N*-nitroso(2-methylamino)acetonitrile (I) in aqueous alkaline solution under mild conditions (room temperature and pH 13) to a salt of *N*-nitrososarcosine (III) via the intermediate amide (II) (eq 1). The homologous *N*-nitrosamine, *N*-nitroso(3-methylamino)propionitrile (IV), was hydrolyzed to the amide (V) under similar conditions but at a rate only about 1/500 that of I (eq 2). These results, coupled with $^{18}O$-labeling studies and determination of activation parameters, showed unequivocally that anchimeric assistance by the *N*-nitroso group plays the dominant role in the more rapid hydrolysis of I.

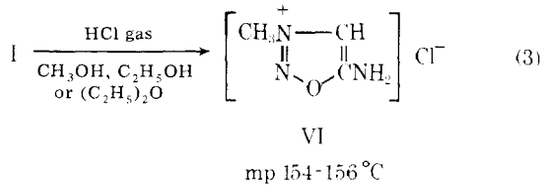



As part of our ongoing investigation of anchimeric effects of the *N*-nitroso group in conjunction with studies on structure–biological activity relationships in *N*-nitrosamines, we examined the behavior of I and IV with anhydrous hydrogen chloride in nonaqueous solvents—methanol, ethanol, and diethyl ether; the results of that study are reported here. During that investigation deuterium-exchange studies were conducted on starting materials and products with interesting results. Finally, a mild chemical denitrosation technique was developed for certain nitrosamines which should be useful in destroying carcinogenic or potentially carcinogenic nitrosamines.[4]

## Results and Discussion

Treatment of I in dry methanol with hydrogen chloride gas for 1 h followed by solvent evaporation, washing with acetone, and recrystallization from ethanol yields 3-methyl-5-amino-1,2,3-oxadiazolium chloride (VI) in high to quantitative yield (eq 3). This compound had been prepared similarly in 1962 by Daeniker and Druey.[5] Similar results are obtained using ethanol or ether as solvent.




VI

mp 154–156 °C

Compound VI undergoes (a) typically *rapid* exchange of two protons by deuterium when $D_2O$ is added to a $Me_2SO$-$d_6$ solution, (b) *slow* exchange of the vinyl proton when it remains in $D_2O$ solution overnight, (c) complete reconversion to I on treatment with aqueous base at pH 8–11, and (d) complete

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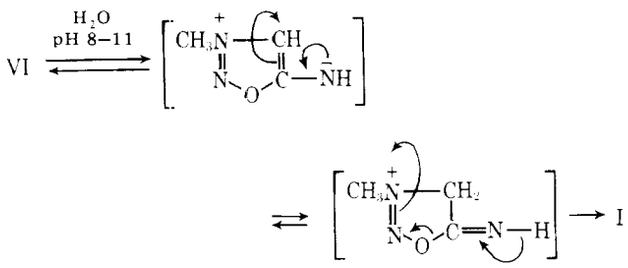
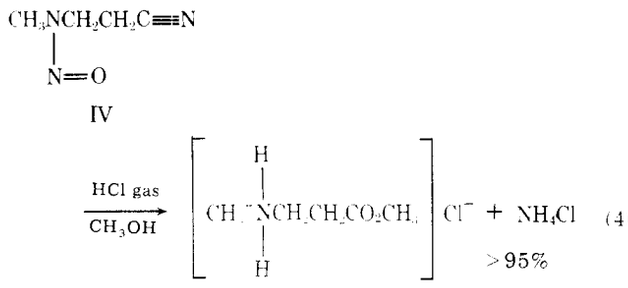
Scheme I



conversion to the sodium salt of *N*-nitrososarcosine (III) on treatment with aqueous base at pH 11.5–14. Acidification of III yields *N*-nitrososarcosine (VII). The slow exchange of the vinyl proton to yield VI-$d_3$ is characteristic of $\alpha$ protons in enols and enamines. Recoversion of VI to I at pH 8–11 is rationalized in Scheme I.

If VI is treated with NaOD–$D_2O$ at pH 8 instead of with NaOH–$H_2O$, I-$d_2$ (both methylene protons replaced) is obtained instead of I. The pathway for the conversion of VI to III at pH 11.5–14 is assumed to occur via the intermediacy of I, and has already been explained.[3] Further, I rapidly undergoes exchange of its methylene protons by neutral $D_2O$ whereas IV does not; this is a consequence of the higher acidity of the methylene protons in I.

A special feature of the conversion of I → VI by hydrogen chloride is the anchimeric assistance for the formation of a five-membered ring provided by the *N*-nitroso group. In contrast, reaction of *N*-nitroso(3-methylamino)propionitrile (IV), the next higher homologue of I, with hydrogen chloride gas in methanol under identical conditions does not yield a cyclic product. Compound IV undergoes denitrosation and the cyano group is transformed to the methyl ester. Products are methyl (3-methylamino)propionate hydrochloride (VIII) (75–95% yields) and ammonium chloride (>95% yield) (eq 4).

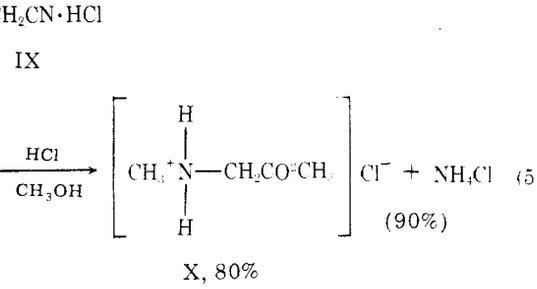


VIII, 75–95%

The additional methylene group that separates the *N*-nitroso and nitrile groups in IV is responsible for the difference in behavior of I and IV; cyclization requires the formation of a six-membered ring, a process that occurs less readily than five-membered ring formation. These results are consistent with our earlier studies and conclusions on the difference in reactivity of I and IV with aqueous base.[3]

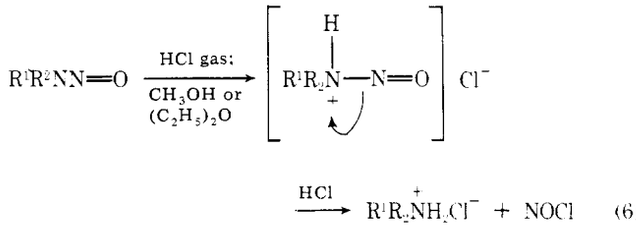
To confirm the importance of the nitroso group in directing the reaction of I with hydrogen chloride to the cyclic product VI, the unnitrosated parent amine of I [methyl cyanomethylamine hydrochloride (IX)] was also treated with hydrogen chloride gas in methanol (eq 5). Compound IX was cleanly and rapidly converted to methyl (2-methylamino)acetate hydrochloride (X) (80%) and $NH_4Cl$ (90%).

**Denitrosation Studies.** Literature methods for the destruction or deactivation of *N*-nitroso compounds are often time-consuming and complex, and results are irreproducible and equivocal.[6] These methods have been applied to nitrosoureas and nitrosamines of complex structure not related to the carcinogenic types of dialkylnitrosamines with which we are concerned. Reaction of I with hydrogen chloride gas in methanol, ethanol, or ether eliminates the nitroso function by cyclization within 30 min, the method is simple and requires no special apparatus or reagents, and products are easily isolated in pure form if desired. With IV however, denitrosation occurs, as already described, and since hydrogen chloride gas is bubbling through the solution, the nitrosonium ion is removed as a volatile species, nitrosyl chloride (see Experimental Section), requiring no scavengers and avoiding reversible renitrosation of the amine (or transnitrosation in mixtures of amines and *N*-nitrosamines[4]).



X, 80%

Denitrosation of IV with hydrogen chloride prompted us to extend the technique to dimethyl-, diethyl-, dipropyl-, and dibutylnitrosamines and *N*-nitrososarcosine. In all of these cases, denitrosation occurs within 30 min; the products are hydrochlorides of the corresponding secondary amines. When the gases leaving the reaction flasks are passed through 2,3-dimethyl-2-butene in diethyl ether, a royal blue color develops in less than 10 min, a result typical of the reaction of nitrosyl chloride with the olefin.[7] The denitrosation technique is presumed to be general for *N*-nitrosamines unable to form rings by anchimeric assistance of the nitroso group (eq 6).



## Experimental Section[8]

**3-Methyl-5-amino-1,2,3-oxadiazolium Chloride (VI) from *N*-Nitroso(2-methylamino)acetonitrile (I) and Gaseous Hydrogen Chloride.** This was prepared essentially by the method of Daeniker,[5] but instead of tetrahydrofuran as solvent, we used methanol, ethanol, or diethyl ether (90–92% yields).

NMR ($Me_2SO$-$d_6$): $CH_3$ ($\delta$ 1.86, s, 3 H); vinyl (5.53, s, 1 H); $NH_2$ (7.34, s, 2 H) ($Me_2SO$=O). Addition of 1 drop of $D_2O$ to the solution caused virtually immediate disappearance of the two amino protons. In $D_2O$, only the signals of the methyl ($\delta$ −0.03) and vinyl ($\delta$ 2.94) protons (HOD=O) were observed. The signal of the vinyl proton decayed slowly and had completely disappeared overnight. IR: moderately strong absorption at 1680 $cm^{-1}$ (C=N) and absence of absorption due to the C≡N group. UV: in ethanol, VI showed two maxima at $\lambda$ 204 and 294 m$\mu$,[5] shifted slightly in water at pH 2 to 200 and 292 m$\mu$.

**Reaction of VI with Aqueous Base.** Compound VI (2.0 g, 15 mmol) was dissolved in $H_2O$ (16 mL) and the solution was divided into two equal parts. Part 1 was adjusted to pH 8.5 with sodium hydroxide solution and stirred under a nitrogen atmosphere for 1 h. Evaporation of the water was followed by extraction of the residue with methylene chloride (4 × 10 mL) and filtration. Evaporation of the solvent from the combined extracts yielded I (0.68 g, 93%) as a yellow oil. The differential pulse polarogram in basic solution (pH ~10) showed a single well-defined peak ($E_p$ = −1.25 V vs. SCE). Addition of authentic I to the solution gave an increase in peak height without any change in peak potential. NMR spectra of the yellow oil in $Me_2SO$-$d_6$ and $D_2O$ were identical with those of an authentic sample of I.[3] An identical

study of pH 8.5 using NaOD–$D_2O$ instead of NaOH–$H_2O$ yielded I-$d_2$ (both methylene protons were replaced by deuterium).

Part 2 was adjusted to pH 13.5 with sodium hydroxide solution and stirred under a nitrogen atmosphere for 8 h. The pH was adjusted to 4.0 followed by evaporation to dryness. The residue was extracted with acetone (4 × 20 mL) and filtered. The combined acetone extracts were evaporated to dryness and the residual yellow oil was dissolved in methylene chloride (50 mL) and filtered. Evaporation of the filtrate yielded a yellow oil (0.8 g, 92%) identified by NMR, IR, and UV as VII.

**Reaction of *N*-Nitroso(3-methylamino)propionitrile (IV) with Gaseous Hydrogen Chloride.** Compound IV (5.0 g, 40 mmol) was dissolved in dry methanol (40 mL) and dry hydrogen chloride gas was passed through the solution for 2 h; a white precipitate formed. The reaction mixture was evaporated to half its volume under vacuum and the concentrate was cooled in a dry ice–acetone bath for 15 min. Filtration yielded a white solid identified as ammonium chloride (2.1 g, 89%) (sublimation temperature ca. 340 °C, evolution of $NH_3$ on treatment with NaOH). The filtrate was evaporated to dryness and washed with acetonitrile (3 × 50 mL). The second residue was also $NH_4Cl$ (0.19 g, 8%); total yield of $NH_4Cl$, 97%. The combined acetonitrile washings were evaporated to dryness to yield a white powder (6.45 g, 95%) which was recrystallized from acetone–ethyl acetate. The resulting product, methyl (3-methylamino)propionate hydrochloride (VIII), was strongly hygroscopic, making it difficult to obtain an accurate or reproducible melting point or elemental analysis. Anal. Calcd for $C_5H_{12}O_2ClN$: C, 39.1; H, 7.82; N, 9.12; Cl, 23.1. Found: C, 37.6; H, 8.45; N, 9.42; Cl, 22.5.

NMR ($Me_2SO$-$d_6$): $CH_3$ (δ 0.04, s, 3 H); $CH_2$ (0.32, t, 2 H); $CH_2$ (0.62, t, 2 H); $OCH_3$ (1.17, s, 3 H); $NH_2$ (6.80, s, 2 H) ($Me_2SO$=O). Addition of 1 drop of $D_2O$ to the solution caused the two proton signal due to $NH_2$ to disappear. IR: intense absorption at 1750 $cm^{-1}$ (C=O) and weak absorption at 3000 $cm^{-1}$ ($NH_2$).

**Reaction of Methyl Cyanomethylamine Hydrochloride (IX) with Gaseous Hydrogen Chloride.** This was conducted and worked up as described for IV. The yield of $NH_4Cl$ was 90% and that of methyl (2-methylamino)acetate hydrochloride (X) was 80%. Compound X was also exceedingly hygroscopic. Anal. Calcd for $C_4H_{10}O_2ClN$: C, 34.4; H, 7.17; N, 10.0; Cl, 25.4. Found: C, 33.8; H, 7.07; H, 9.90; Cl, 25.7.

NMR ($Me_2SO$-$d_6$): $CH_3$ (δ 0.06, s, 3 H); $OCH_3$ (1.44, s, 3 H); $CH_2$ (1.62, s, 2 H); $NH_2$ (7.20, s, 2 H) ($Me_2S$=O = 0). Addition of 1 drop of $D_2O$ to the solution caused the two proton signal due to $NH_2$ to disappear. IR: intense absorption at 1750 $cm^{-1}$ (C=O) and weak absorption at 2900 $cm^{-1}$ ($NH_2$).

**Denitrosation of *N*-Nitrosamines. General Procedure.** Dry hydrogen chloride gas was bubbled through a solution of *N*-nitrosamine (2.0 g) in dry methanol (25 mL) for about 30 min. The solution was evaporated to dryness under vacuum and the residue was washed with cold acetone (3 × 20 mL). The residue was the hydrochloride of the corresponding amine. Recrystallization from ethyl acetate, diethyl ether, or petroleum ether yielded the analytically pure salt identified by analysis and/or NMR.

Denitrosation of dimethyl-, diethyl-, dipropyl-, and dibutylnitrosamines yielded salts of the corresponding secondary amines. If the effluent gases were passed through an ether solution of 2,3-dimethyl-2-butene, a royal blue color developed within 10 min. I and IV also underwent denitrosation to yield VI and VIII, respectively, as already described.

**Acknowledgment.** This investigation was supported by Grants CA-18618, 12227, and 05280 from the National Cancer Institute, DHEW, and the Samuel S. Fels Fund.

**Registry No.**—I, 3684-91-7; IV, 60153-49-3; VI, 65103-49-3; VIII, 65103-50-6; IX, 25808-30-4; X, 13515-93-0.

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(8) Nitrosamines were prepared as described in ref 3 or purchased from Aldrich or Eastman. NMR spectra were recorded with a Varian XL-100 spectrometer using $Me_4Si$, HOD, or $Me_2SO$ as internal standards. UV spectra were obtained using a Cary Model 14 spectrophotometer. IR spectra were obtained on a Perkin-Elmer 225 or Pye Unicam AP 1000 spectrophotometer. Differential pulse polarography was conducted as described in ref 3. All solvents and reagents were the finest obtainable. All work with nitrosamines was conducted on the smallest scale necessary to obtain the requisite information utilizing efficient hoods and maximum protection of personnel.

# Nuclear Magnetic Resonance Studies on σ Adducts of Heterocyclic Systems with Nucleophiles. 18.[1] Proton and Carbon-13 Nuclear Magnetic Resonance Investigations on σ-Adduct Formation between 1,*X*-Naphthyridines and Some Methyl-1,8-naphthyridines with Potassium Amide in Liquid Ammonia

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1,5-, 1,6- and 1,8-naphthyridines dissolved in liquid ammonia containing potassium amide showed the H-2 and C-2 resonances at about 4 and 90 ppm higher field, respectively, than the H-2 and C-2 resonances observed in solutions of these naphthyridines in $CDCl_3$. It indicated that all three naphthyridines underwent addition of the amide ion to position 2, yielding a 2-amino-1,2-dihydro-1,*X*-naphthyridinide ion. The 1,7-naphthyridine showed a more complex reactivity pattern toward amide ions. Besides addition at C-2, addition at C-6 and at C-8 has been found. The relation of this study with that of the Chichibabin amination of the 1,*X*-naphthyridines is discussed. It was further proven that under the influence of the amide ion 2-methyl- and 4-methyl-1,8-naphthyridine only gave deprotonation of the methyl group and that 3-methyl-1,8-naphthyridine gave formation of the 2-amino-1,2-dihydro-3-methyl-1,8-naphthyridinide ion.

Recently there has been great interest in the study of the formation of the 1:1 σ adducts between azines and amide ions[2] and between azinium salts and liquid ammonia.[3,4] This is due to the fact that the many often surprising rearrangements which can take place in these systems[5-7] occur via the intermediacy of these σ adducts. NMR spectroscopy has been found to be a valuable tool for the detection of these adducts, since the newly formed tetrahedral center causes a consider-

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