Alkyl Nitrate Nitration of Active Methylene Compounds. Nitration of 1-Methyl-4-piperidone, 1-Methyl-2-pyrrolidinone and 1,3-Dimethyl-2-pyrrolidinone (1)

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Received October 6, 1978

The reaction of 1-methyl-4-piperidone (**1**) with amyl nitrate in the potassium *tert*-butoxide-tetrahydrofuran system gave dipotassium 5-methyl-2-oxo-1,3-piperidinedinitronate (**4**) in 78% yield. Similar treatment of 1-methyl-2-pyrrolidinone (**2**) afforded potassium 3-methyl-2-oxo-pyrrolidinenitronate (**7**) in 85% yield. In contrast, the nitration of 1,3-dimethyl-2-pyrrolidinone (**3**) led to opening of the lactam ring with the formation of amyl 2-aza-2-methyl-5-nitrohexanoate (**10**) in 40% yield.

Acidification of disalt **4** did not cause ring opening but gave the dipolar ion of 1-methyl-3-nitro 4-hydroxy-5-*aci*-nitro-Δ^3-tetrahydropyridinium (**6**).

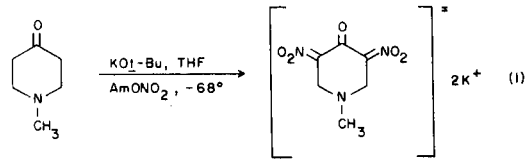
J. Heterocyclic Chem., **16**, 481 (1979).

In continuation of our studies of the alkyl nitrate nitration (**2**), we are now reporting on its application to the nitration of 1-methyl-4-piperidone (**1**), 1-methyl-2-pyrrolidinone (**2**) and 1,3-dimethyl-2-pyrrolidinone (**3**).

Nitration of 1-Methyl-4-piperidone (**1**).

Dipotassium 5-methyl-2-oxo-1,3-piperidinedinitronate (**4**) was obtained in 78% yield (95.8% purity) when **1** was treated with amyl nitrate in tetrahydrofuran (THF) in the presence of sublimed potassium *t*-butoxide (**3**) (Equation 1). Compound **4** was also prepared in the presence of potassium *t*-butoxide which was formed *in situ* from *t*-butyl alcohol and potassium amide in THF. Nitration of **1** in the sodium amide-liquid ammonia system afforded a 54% yield of the disodium salt of 5-methyl-2-oxo-1,3-piperidinedinitronate.

The structure of **4** was ascertained by its spectral data. As in the case of the disalts of α,α'-dinitrocyclanones (**3**), bromination of **4** with potassium hypobromite resulted in



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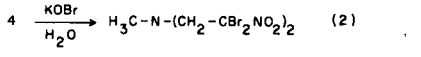
ring opening (Equation 2). Thus, 3-aza-3-methyl-1,1,5,5-tetrabromo-1,5-dinitropentane (**5**) was obtained in 62% yield.



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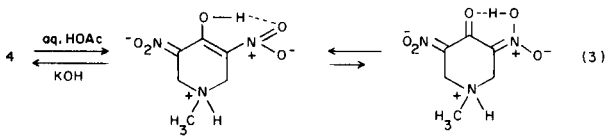
It was anticipated that acidification of **4** would result in ring cleavage as was the case with the disalts of α,α'-dinitrocyclanones (**4**). However, treatment of **4** with dilute acetic acid or hydrogen chloride in ether gave a yellow-orange, water insoluble solid **6**. It still contained the piperidine ring, for **6** was reconverted into **4** in 86% yield on treatment with potassium hydroxide (Equation 3).



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Based primarily on its nmr spectrum, **6** is believed to be largely the dipolar ion of 1-methyl-3-nitro-4-hydroxy-5-*aci*-nitro-Δ^3-tetrahydropyridinium. Compound **6** (0.046 g. in 1 ml. of dry DMSO-d_6) showed peaks at 17.5 (s, 1, enolic OH), 10.1 (s, 1, $^+$NH), 4.3 (s, 4CH_2), and 2.9 ppm (s, 3, CH_3). The presence of the enolic, intramolecularly bonded hydroxyl group was indicated by the broad downfield absorption at 17.5 ppm (5,6).

In the ir spectrum of **6**, the carbonyl band at 1600 cm^{-1}, present in salt **4**, was absent. Moreover **6** exhibited a broad band near 2750 cm^{-1} characteristic of an intramolecularly bonded hydroxyl group (**7**). Also, in the uv spectrum, a band at 364 nm which was absent in the spectrum of compound **4**, points to the presence of a carbon-carbon double bond (**8**). Although the spectral data confirm structure **6** the existence of the tautomeric form **6a** cannot be ruled out.

Chemical evidence for the presence of two acidic hydrogens in **6** was obtained by the fact that addition of diborane caused immediate evolution of two equivalents of hydrogen. In a control test with potassium 2-keto-3-nitrocyclopentanenitronate, which has been established to exist in the keto-form (**4**), no initial hydrogen evolution occurred on adding diborane. It is also well known that nitroalkanes are not affected by diborane (**9**).

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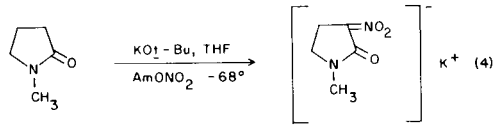
Nitration of 1-Methyl-2-pyrrolidinone (**2**) and 1,3-Dimethyl-2-pyrrolidinone (**3**).

The successful introduction of a nitro group into *N*-disubstituted alkylamides (**10**) prompted us to apply the alkyl nitrate nitration to lactams.

When 1-methyl-2-pyrrolidinone (**2**) was dissolved in THF and treated with amyl nitrate in the presence of sublimed potassium *t*-butoxide, potassium 1-methyl-2-oxo-3-pyrrolidinenitronate (**7**) was obtained in 85% yield. When ether was employed as the solvent, **7** was obtained in a yield of only 56% (Equation 4). It is of interest to note that **7** was stable to the atmosphere after thorough



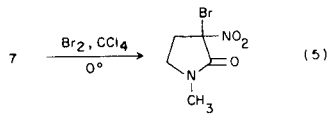
(4)

2 7

washings with THF. However, washing with anhydrous ether resulted in charring and decomposition of **7** upon exposure to air. Very likely this was due to absorbed potassium *t*-butoxide which was not completely removed by the ether wash. The heat of hydration generated by the reaction of the base with moisture then initiated the decomposition of salt **7**.

Attempts to convert **7** into the free nitro compound on acidification with hydrogen chloride in THF or with glacial acetic acid in ether afforded a dark colored liquid which evolved oxides of nitrogen after removal of solvent. Similar results were obtained with the nitro salts of *N,N*-disubstituted α-nitroalkylamides (**10**).

Anhydrous bromination of **7** gave a stable compound in 56% yield which was identified as 1-methyl-3-bromo-3-nitro-2-pyrrolidinone (**8**) (Equation 5).



(5)

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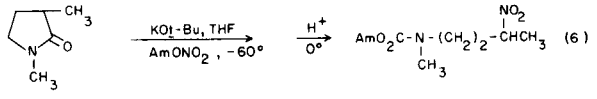
Aqueous bromination of **7** did not result in ring opening but again afforded **8**. In contrast, these reaction conditions have always resulted in ring opening and formation of aliphatic bromonitro compounds with disalt **4** (*vide supra*) as well as with the disalts of 2-oxo-1,3-cycloalkyldinitronates (**3,11**).

The alkyl nitration of 1,3-dimethyl-2-pyrrolidinone (**3**) led to ring cleavage. The carbamic ester amyl 2-aza-2-methyl-5-nitrohexanoate (**9**) was obtained in 40% yield



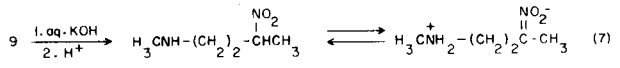
(6)

3 9

and 40% of **3** was recovered (Equation 6). The results of this experiment are in agreement with our previous observations that in nitrations of active methylene compounds which would afford tertiary nitro compounds, cleavage is the prevalent reaction (2b). An exception was noted in the nitration of neopentyl 2-butanesulfonate in which no cleavage of the carbon-sulfur bonding occurred. The tertiary nitro compound, neopentyl 2-nitro-2-butanesulfonate, was obtained (12).

The mechanism shown in Scheme I explains the formation of **9** and the recovery of appreciable amounts of **3**. Carbanion A generated in step 1 undergoes a nucleophilic attack on the nitrate ester to give intermediate B in step 2. Collapse of B in step 3 leads to the tertiary nitro compound C and amylate ion. Compound C which cannot be stabilized by salt formation can react with amylate (or any other base present) to regenerate carbanion A *via* intermediate B. Alternatively, electrophilic attack of amylate ion on the carbonyl carbon of C, as shown in step 4, leads to intermediate D. The latter, in step 5, is converted to the salt of **9** by irreversible ring opening. Suitable acidification of the salt then affords **9**.

The carbamic ester structure of **9** was indicated by its decarboxylation to 2-aza-5-nitrohexane (**10**) on treatment with base and subsequent acidification (Equation 7) (13).



(7)

10 10a

EXPERIMENTAL

Equipment.

All infrared spectra were taken with a Perkin Elmer recording spectrophotometer, Models 21 and 421. Nuclear magnetic resonance spectra were determined on a Varian Model A-60 analytical nmr spectrometer or on a 90 MHz Model R-32 Perkin Elmer spectrometer using tetramethylsilane as an internal standard.

Apparatus.

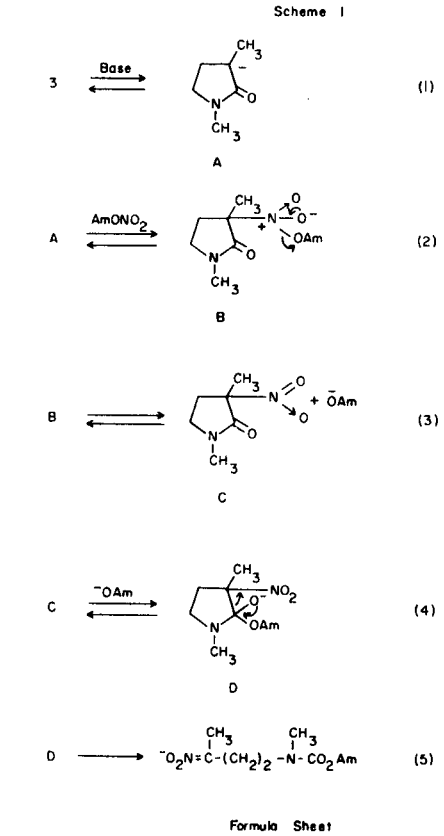
Nitrations were performed in a thoroughly dried 500 ml. three-necked flask equipped with a mechanical stirrer, thermometer and pressure equalizing dropping funnel. A positive nitrogen pressure was maintained during the reaction.

Materials.

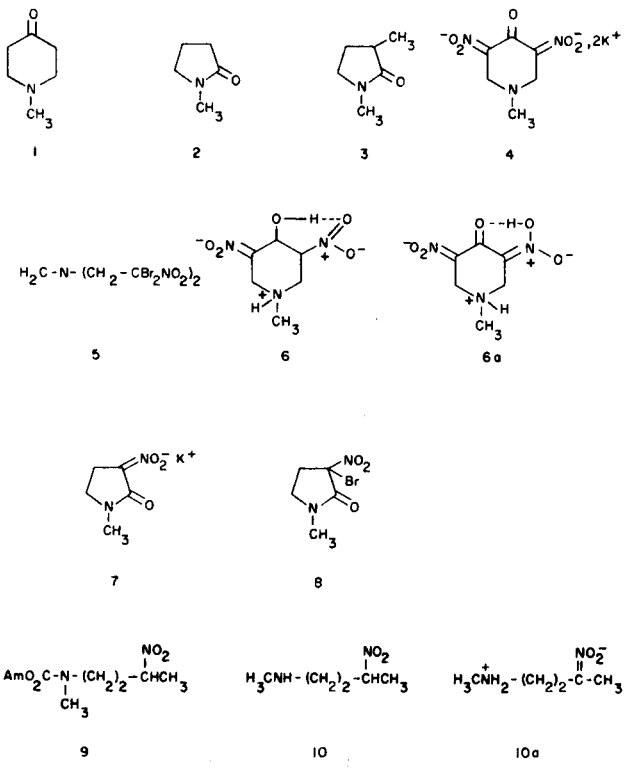
Amyl nitrate, a mixture of the *n*-amyl and *iso*-amyl isomers was a generous gift of the Ethyl Corperation and was distilled at 45° and 5 mm before use. Sublimed potassium *t*-butoxide was prepared as described by Feuer, *et al.* (3). 1-Methyl-2-pyrrolidinone and 1-methyl-4-piperidone were obtained from the Aldrich Chemical Co. The latter was purified by distilling at 30° and 1 mm. Propyl nitrate was of Eastman White Label grade.

Dipotassium 5-Methyl-2-oxo-1,3-piperidinedinitronate (**4**).

Scheme I



Formula Sheet



A. Using Sublimed Potassium *tert*-Butoxide.

A solution of potassium *t*-butoxide (37 g., 0.33 mole) in 180 ml. of purified THF was cooled with stirring to -40° and 1-methyl-4-piperidone (**1**) (11.3 g., 0.1 mole) dissolved in 120 ml. of THF was added dropwise over 30 minutes. A solution of amyl nitrate (29.2 g., 0.22 mole) in 60 ml. of THF was then added dropwise over 30 minutes with the temperature maintained at -60°. As the reaction mixture was allowed to warm to 25° a yellow gel formed. It was dispersed by adding 200 ml. of anhydrous ethyl ether and vigorous stirring. After filtration and addition of 60 ml. water the ether layer was removed. Addition of 1000 ml. of ethanol to the aqueous layer and drying of the precipitated yellow solid at ambient temperature and 0.1 mm gave 21.9 g. (78% yield) of dipotassium 5-methyl-2-oxo-1,3-piperidinedinitronate (**4**) of 95.8% purity as determined by titration (14). Redissolving crude **4** in a solution of 21 g. potassium hydroxide in 60 ml. of water reprecipitating with 750 ml. of ethanol and washing with methanol gave after drying, 16.1 g. (57.7%) of pure **4** m.p. 227° dec.; ir: (Nujol) 1600 (C=O), 1228 and 1155 cm^{-1} (NO_2^-); uv (50% ethanol): λ max 234 nm (log 3.70), 308 (3.61) and 390 (4.01); nmr (deuterium oxide): δ 2.4 (s, 3, CH_3) and 3.7 (s, 4, CH_2).

Anal. Calcd. for $C_6H_7N_3O_5K_2 \cdot \frac{1}{2}H_2O$: C, 25.00; H, 2.78; N, 14.58; K, 27.08; neut. equiv. 96. Found: C, 24.94; H, 2.97; N, 14.87; K, 27.02; neut. equiv. 97.

B. Using Potassium *t*Butoxide Prepared *in Situ*.

To 300 ml. of liquid ammonia was added at -33° a catalytic amount of ferric nitrate and freshly cut potassium metal (12.9 g., 0.33 g. atom). After the potassium amide had formed, the ammonia was replaced with 180 ml. of THF. Then, 24.4 g. (0.33 mole) of *t*-butyl alcohol was added and the reaction mixture refluxed one hour. Compound **1** (11.3 g., 0.1 mole) dissolved in 120 ml. of THF was added to the reaction mixture at ambient temperature during 30 minutes. After lowering the temperature to -40°, *n*-propyl nitrate (32.6 g., 0.31 mole) dissolved in 60 ml. of THF was added during 30 minutes. Then, the reaction mixture was worked up as described in Part A to give 18.1 g. of pure **4** (64.9%), m.p. 227° dec.

C. From Dipolar Ion of 1-Methyl-3-nitro-4-hydroxy-5-*aci*-nitro-Δ^3-tetrahydropyridinium (**6**).

To a solution of 0.97 g. (15 mmoles, 85% assay) potassium hydroxide in 20 ml. of water, was added compound **6** (1.50 g., 7.4 mmoles). Addition of 500 ml. ethanol precipitated 2.03 g. of yellow **4** (86.5%), the spectral data of which were identical with **4** obtained in Part A.

Disodium 5-Methyl-2-oxo-1,3-piperidinedinitronate.

To 300 ml. of liquid ammonia at -33° was added a small amount of ferric nitrate and freshly cut sodium metal (5.75 g., 0.25 g. atom). After the sodium amide had formed, compound **1** (11.3 g., 0.1 mole) was added. The reaction mixture was stirred at -33° for 30 minutes and then cooled to -60°, and *n*-propyl nitrate (32.6 g., 0.31 mole) was added rapidly, while maintaining the temperature below -40° (*Caution:* cooling must be maintained during the addition of the nitrating agent, as long as the exotherm persists). After stirring for 30 minutes at -40°, the reaction mixture was allowed to warm as the ammonia was gradually replaced by ether. Then 60 ml. of water was added, the aqueous layer separated and 1000 ml. of ethanol added to precipitate the crude disodium salt (16.76 g., 67.8%). The salt was further purified by dissolving it in 15 g. of sodium hydroxide dissolved in 60 ml. of water. Addition of 1000 ml. ethanol to the solution

gave 13.3 g. (53.8% yield) of pure disodium salt m.p., 195° (*Explosion*); ir (potassium bromide): 1600 (C=O), 1228 and 1155 cm^{-1} (NO_2); nmr (deuterium oxide): δ 2.5 (s, 3, CH_3) and 3.7 (s, 4, CH_2).

Anal. Calcd. for $C_6H_7N_3O_5Na_2 \cdot 2H_2O$: C, 25.44; H, 3.89; N, 14.84; Na, 16.25. Found: C, 25.54; H, 3.74; N, 14.71; Na, 16.53.

Dipolar Ion of 1-Methyl-3-nitro-4-hydroxy-5-*aci*-nitro-Δ^3-tetrahydropyridinium (**6**).

To compound **4** (4.65 g., 0.016 mole) dissolved in 50 ml. of water was added glacial acetic acid (1.96 g., 0.033 mole) at -5°. The reaction mixture was stirred for 30 minutes, the orange solid filtered off and washed with methanol and water. Drying at room temperature and 0.2 mm gave 1.90 g. (60% yield) of dipolar ion **6**, m.p. 119° dec.; ir (potassium bromide): 3050 (CH), 2750 (OH) and 1270 cm^{-1} (NO_2^-); uv (50% ethanol): λ max 304 nm (log 3.35), 364 (3.54) and 410 (3.62); nmr (DMSO-d_6): δ 17.5 (s, 1, enolic OH), 10.1 (s, 1, NH), 4.3 (s, 4, CH_2) and 2.9 (s, 3, CH_3).

Anal. Calcd. for $C_6H_9N_3O_5$: C, 35.46; H, 4.48; N, 20.69. Found: C, 35.47; H, 4.47; N, 20.67.

3-Aza-3-methyl-1,1,5,5-tetrabromo-1,5-dinitropentane (**5**).

To 8.8 g. (0.12 mole, 85% assay) of potassium hydroxide dissolved in 20 ml. of water was added 8.8 g. (0.056 mole) of bromine at -5° over a 30 minute period. Then dipotassium 5-methyl-2-oxo-1,3-piperidinedinitronate (2.79 g., 0.01 mole) dissolved in 10 ml. of water was added rapidly at -5°. The solid was taken up in ether, the resulting solution dried (magnesium sulfate), filtered and then concentrated. Addition of hexane to the cloud point followed by filtering and drying gave 3.04 g. (62% yield) of **5**, m.p. 74-75° (hexane); ir (chloroform): 1560 and 1320 (NO_2) cm^{-1}; nmr (carbon tetrachloride): δ 2.7 (s, 3, CH_3) and 4.3 (s, 4, CH_2).

Anal. Calcd. for $C_5H_7Br_4N_3O_4$: C, 12.18; H, 1.42; Br, 64.91; N, 8.52. Found: C, 12.55; H, 1.40; Br, 65.01; N, 8.49.

Potassium 1-Methyl-2-oxo-3-pyrrolidinenitronate (**7**).

A solution of sublimed potassium *t*-butoxide (18.5 g., 0.165 mole) in 70 ml. of purified THF was cooled to -60° and 1-methyl-2-pyrrolidinone (**2**) (10 g., 0.1 mole) was added dropwise in one hour. Then, a solution of amyl nitrate (14.6 g., 0.11 mole) in 50 ml. of THF was added in 30 minutes while the temperature was kept at -60°. After room temperature was reached (one hour), the reaction mixture was filtered under nitrogen pressure and the residue washed first with 2 x 50 ml. portions of ether and then with THF until the washings were only weakly basic (*p*H 8).

Dissolving the salt in a minimum of methanol and then reprecipitating it by addition of ether gave after drying at room temperature (0.2 mm) 15.2 g. (85% yield) of **7**, m.p. 200-209° dec.; ir (potassium bromide): 1680 (C=O), 1198 and 1133 cm^{-1} (NO_2^-); uv (water): λ max 210 nm (log ε 3.71) and 290 (3.90); nmr (deuterium oxide): δ 3.45 (t, 2, C_5H_2) and 2.85 (singlet superimposed on triplet, 5, NCH_3 and C_4H_2).

Anal. Calcd. for $C_5H_7N_2O_3K$: C, 32.96; H, 3.85; N, 15.38; K, 21.43; neut. equiv. 182. Found: C, 32.72; H, 4.00; N, 15.00; K, 21.67; neut. (14) equiv. 181.

1-Methyl-3-bromo-3-nitro-2-pyrrolidinone (**8**).

To a slurry of **7** (0.225 g., 1.4 millimoles) in 30 ml. of absolute ether was added at 0° a solution of bromine (0.40 g., 2.5 millimoles) in 50 ml. of carbon tetrachloride. The precipitate was filtered and washed with 2 x 25 ml. portions of ether. The filtrate and washings were combined and dried (magnesium sulfate). The solvent was removed *in vacuo* and the remaining oil distilled in a sublimator at 85° (0.5 mm) to give 0.175 g. (56% yield) of **8**, m.p. 58.5-60°; ir (potassium bromide): 1713 (C=O), 1571 and 1342 cm^{-1} (NO_2); nmr (deuteriochloroform): δ 3.58 (m, 2, C_5H_2), 2.98 (s, 3, NCH_3) and 2.94 (m, 2, C_4H_2).

Anal. Calcd. for $C_5H_7BrN_2O_3$: C, 26.90; H, 3.14; Br, 35.87; N, 12.56. Found: C, 27.20; H, 3.43; Br, 35.55; N, 12.39.

Amyl 2-Aza-2-methyl-5-nitrohexanoate (**9**).

The experimental procedure was similar to that described for the preparation of **7** except that 9.3 g. (0.083 mole) of sublimed potassium *t*-butoxide, 5.7 g. (0.05 mole) of 1,3-dimethyl-2-pyrrolidinone (15) (**3**) and 7.3 g. (0.06 mole) of amyl nitrate were used. The reaction mixture was acidified with glacial acetic acid at -55°, the precipitate filtered off and washed with 3 x 50 ml. portions of ether. The filtrate and washings were combined, dried (magnesium sulfate) and the solvents removed *in vacuo*. Distillation afforded 5 g. (41% yield) of **9**, b.p. 150-164° (0.6 mm), n_D^{20} 1.4526; ir (neat) 1713 (CO), and 1556 and 1363 cm^{-1} (NO_2); nmr (neat): δ 4.66 (m, 1, CH), 3.37 (t, 2, -N-CH_2), 2.88 (s, 3, NCH_3), 2.16 (m, 2, CH_2CH) and 1.56 (d, 3, CH_3).

Anal. Calcd. for $C_{11}H_{22}N_2O_4$: C, 53.65; H, 8.94; N, 11.38. Found: C, 53.74; H, 9.04; N, 11.47.

Collection of a lower boiling fraction gave 1.3 g. (41% recovery) of **3**, b.p. 94-98° (20 mm).

2-Aza-5-nitrohexane (**10**).

To a refluxing solution of potassium hydroxide (2.80 g., 0.05 mole) in 40 ml. of water was added **9** (2.46 g., 0.01 mole) over a 90 minute period. Refluxing was continued for 11 hours and then the reaction mixture was acidified at room temperature with acetic acid to *p*H 6. Extracting with 2 x 50 ml. portions of ether, drying the extract (sodium sulfate) and removing the ether *in vacuo* afforded 0.9 g. (37% recovery) of **9**, the identity of which was established by glpc.

The aqueous filtrate was basified (*p*H 9) and extracted with ether for 24 hours. Drying the extract (sodium sulfate) and removing the ether *in vacuo* left a red oil, the glpc of which gave an additional 5% of unreacted **9**, (retention time 12 minutes) and a material of lower retention time (6 minutes) which was further purified on a SF-96 on chromosorb w column at 135° to give 0.11 g. (8% yield) of **10**; ir (neat): 3370 and 1597 (NH), 1558 and 1365 cm^{-1} (NO_2); nmr (deuterium oxide): δ 3.20 (t, 2, NCH_2), 2.68 (s, 3, $H_3C\overset{+}{N}H_2$-), 2.63 (m, 2, CH_2-CH) and 1.90

$$\begin{matrix} NO_2^- \\ | \\ \end{matrix}$$

1.90 (s, 3, -CCH_3) (13).

Anal. Calcd. for $C_5H_{12}N_2O_2$: C, 45.45; H, 9.09; N, 21.21. Found: C, 45.19; H, 9.27; N, 21.44.

REFERENCES AND NOTES

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(13) The nmr spectrum indicates that the dipolar structure **10a** is an important contributor. This is based on the observation that the absorption of the methyne hydrogen is absent and that the hydrogens in the one and six positions appear as singlets. Moreover, the ammonium hydrogens are not observed because of exchange with the solvent deuterium oxide.

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