products. The solid was separated and was identified as piperidine hydrochloride (0.08 g). The reaction mixture, after the removal of the solvent, was subjected to column chromatography (silica gel, 1:1 benzene/ethyl acetate), and two products were obtained: the first one (0.06 g) [mp (petroleum ether) 90–91.5 °C; ^{1}H NMR (CD_3COCD_3) δ 1.65 (m, 6 H, $NCH_2CH_2CH_2$), 3.15 (m, 2 H, $NHCH_2CH_2CH_2$), 3.80 (m, 2 H, $NCH_2CH_2CH_2$), 7.50–8.00 (m, 4 H, H5–H8), 9.20 (s, 1 H, H-2); mass spectrum calcd for $C_{14}H_{15}N_3O$ (M^+) m/e 241.121 503, found 241.12104] was identified as 4-(1-piperidylcarbonyl)quinazoline (**5**) (yield 25%), and the second one (0.06 g) was identified as 4-hydroxyquinazoline[14] (**6**) (yield 41%).

Reaction of 2 with Propylamine. To a stirred solution of 0.26 g of **2** (0.68 mmol) in 50 mL of MeCN, was added 0.60 mL of propylamine (7.25 mmol) dropwise at room temperature. Within about 18 h, the reaction was complete. A TLC analysis (silica gel, 1:1 benzene/ethyl acetate) showed the presence of two products. The solvent was removed, and the residue was taken up with ethyl acetate. A white crystalline solid separated and was identified as propylamine hydrobromide (0.17 g). The residue was subjected to column chromatography (silica gel, 3:2 and 3:7 benzene/ethyl acetate), and two products were obtained: the first one (0.06 g) was identified as 4-(dibromomethyl)quinazoline[5] (**9**) (yield 30%), and the second one (0.1 g) [mp 54–56 °C; ^{1}H NMR (CD_3COCD_3) δ 1.00 (pseudotriplet, 3 H, $CONHCH_2CH_2CH_3$), 1.72 (pseudosextet, 2 H, $CONHCH_2CH_2CH_3$), 2.95 (s, 1 H, NH), 3.43 (pseudoquartet, 2 H, $CONHCH_2CH_2CH_3$), 7.50–8.00 (m, 3 H, H6–H8), 9.10–9.30 (m, 2 H, H2–H5); mass spectrum calcd for $C_{12}H_{13}N_3O$ (M^+) m/e 215.105 854, found 215.1053] was identified as *N*-propyl-4-quinazolinecarboxamide (**7**) (yield 68%).

Reaction of 2 with Pyrrolidine. To a stirred solution of 0.25 g of **2** (0.66 mmol) in 50 mL of MeCN was added 0.60 mL of pyrrolidine (7.22 mmol) dropwise at room temperature. Within 18 h, the reaction was complete. A TLC analysis (silica gel, 1:1 benzene/ethyl acetate) showed the presence of a main product together with a minor one. The latter was identified by comparison (TLC) as compound **9**. The reaction mixture, after the removal of the solvent, was subjected to column chromatography (silica gel, 1:1 benzene/ethyl acetate), and a white solid was obtained (0.08 g) [mp 95–97 °C; ^{1}H NMR (CD_3COCD_3) δ 1.85 (m, 4 H, $CONCH_2CH_2$), 3.20 (m, 2 H, $CONCH_2CH_2$), 3.60 (m, 2 H, $CONCH_2CH_2$), 7.50–8.10 (m, 4 H, H5–H8), 9.20 (s, 1 H, H-2); mass spectrum calcd for $C_{13}H_{13}N_3O$ (M^+) m/e 227.105 854, found 227.105 25], identified as 4-(1-pyrrolidinylcarbonyl)quinazoline (**8**) (yield 53%).

Reaction of 2 with Piperidine. To a stirred solution of 0.25 g of **2** (0.66 mmol) in 50 mL of MeCN was added 0.65 mL of piperidine (6.6 mmol) dropwise at room temperature. Within 24 h, the reaction was complete. A TLC analysis (silica gel, 1:1 benzene/ethyl acetate) showed the presence, together with a major product, of a very small amount of compound **9**. The solvent was removed, and the residue was taken up with ethyl acetate. A crystalline white solid separated (0.3 g) and was identified as piperidine hydrobromide. The residue was purified by column chromatography (silica gel, 1:1 benzene/ethyl acetate), and a white solid (0.13 g), identified as compound **5** (yield 82%), was obtained.

Kinetic Measurements. The kinetic measurements for the reaction of **1** with propylamine and pyrrolidine were carried out spectrophotometrically, at 42 °C, in the thermostated cell compartment of a Cary 219 instrument. The solvent (MeCN) was purified by distillation over P_2O_5, and the amines were purified by distillation over Na. A large excess of the amine was present so that the reactions occurred under pseudo-first-order conditions. The reactions were followed at 290 and 297 nm, wavelengths corresponding to absorbance maxima for compounds **3** and **4**, respectively.

Least-squares treatment of the data reported in Table I for the reaction of **1** with propylamine yields the following: slope = 1.02×10^{-3} M^{-2} s^{-1} (standard deviation = 1.2×10^{-5}), intercept = 6.60×10^{-6} M^{-1} s^{-1} (standard deviation = 3.8×10^{-6}), correlation coefficient = 0.9997. The same treatment of the data reported in Table II yields the following: slope = 2.58×10^{-4} M^{-2} s^{-1} (standard deviation = 7.7×10^{-6}), intercept = -2.96×10^{-5} M^{-1} s^{-1} (standard deviation = 7.7×10^{-6}), correlation coefficient = 0.9941.

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Registry No. 1, 99356-81-7; **2**, 112762-96-6; **3**, 22754-05-8; **4**, 81870-89-5; **5**, 124286-51-7; **6**, 491-36-1; **7**, 124286-52-8; **8**, 124286-53-9; **9**, 112762-97-7; propylamine, 107-10-8; propylamine hydrochloride, 4905-83-3; pyrrolidine, 123-75-1; piperidine, 110-89-4; piperidine hydrochloride, 6091-44-7.

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Nitromethylenation of *N*-Methylpyridinium Salts[1]

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Extensive NMR investigations on the ammonia adducts of quaternized azaheteroaromatics (pyridinium, isoquinolinium, pyrimidinium, and pyrazinium salts[2-6]) have shown that the addition occurs quantitatively at the position adjacent to the quaternary nitrogen, yielding 2-aminodihydroazines. For steric reasons *N*-*tert*-butylpyridinium salts also gave addition at the 4-position in quaternary salts.[7] The σ-adducts are easily oxidized by potassium permanganate to the corresponding *N*-alkyl-2-(4)-imino derivatives,[8] and therefore this amination–oxidation reaction forms an interesting new synthetic tool for the preparation of *N*-alkyl-2-iminoazines. The facile replacement of the ring hydrogen in azinium salts (S_NH reactions[8]) by the imino group prompted us to look into the possibility of S_NH replacement reactions by other nucleophilic species. It has been reported[9] that the nitromethide ion, formed from nitromethane and liquid ammonia at −10 °C or lower, can successfully compete with the liquid ammonia in the addition reaction, as evidenced by ^{1}H NMR spectroscopy. Thus we decided to study the addition/oxidation reaction of nitromethide with pyridinium salts in liquid ammonia.

The behavior of the disubstituted pyridinium salts 1,2-dimethyl- (**1a**), 1,3-dimethyl- (**1b**), 1-methyl-3-phenyl- (**1c**), 1,4-dimethyl- (**4a**), and 3-methoxy-1-methylpyridinium chlorides (**4b**) was investigated first. Treatment of solutions of **1a–c** in liquid ammonia, containing nitromethide, with potassium permanganate afforded the

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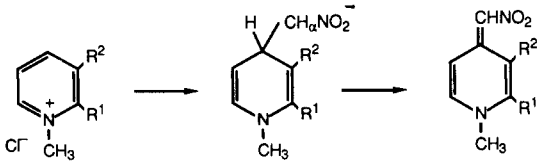
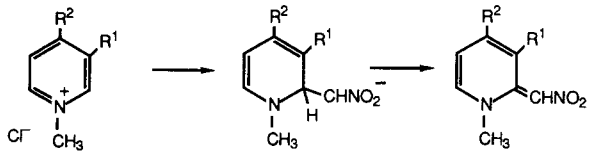
Scheme I



1 2 3

a) $R_1 = CH_3$, $R^2 = H$
b) $R^1 = H$, $R^2 = CH_3$
c) $R^1 = H$, $R^2 = C_6H_5$

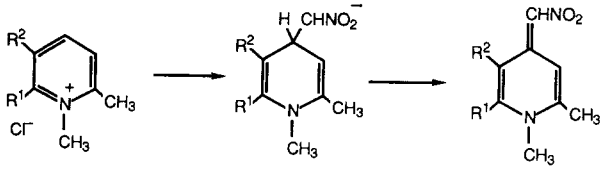
Scheme II



4 5 6

a) $R^1 = H$, $R^2 = CH_3$
b) $R^1 = OCH_3$, $R^2 = H$

Scheme III



7 8 9

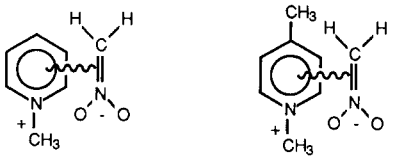
a) $R^1 = H$, $R^2 = CH_3$
b) $R^1 = H$, $R^2 = C_2H_5$
c) $R^1 = CH_3$, $R^2 = H$

4-nitromethylene derivatives **3a**, **3b**, and **3c** in more than 80% yield (Scheme I). However, when the compounds **4a** and **4b** were treated in a similar manner, the isomeric 2-(nitromethylene)pyridines **6a** and **6b** were formed (80–90%) (Scheme II).

Similar behavior to that of **1a–c** was observed with the trialkylpyridinium salts 1,2,5-trimethyl- (**7a**), 1,2-dimethyl-5-ethyl- (**7b**), and 1,2,6-trimethylpyridinium chlorides (**7c**). These compounds gave 4-nitromethylene derivatives **9a–c** on treatment with nitromethide in liquid ammonia and subsequent oxidation by potassium permanganate (Scheme III).

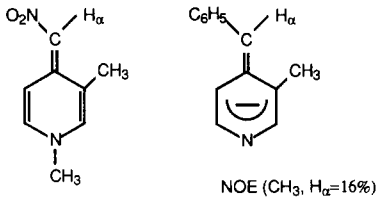
From these results it is evident that the dialkyl- and trialkylpyridinium salts, in which position 4 is free, undergo nitromethylenation at position 4 but that the reaction takes place at the alternative position 2 if position 4 is blocked (see **4a**). There is sound NMR spectral evidence that 3-X-substituted (X = CH_3, Cl, COR, CF_3, CN, NO_2) 1-methylpyridinium salts when subjected to attack by nitroalkane anions undergo addition at position 4.[10,11] However, one exception is the case of X = OCH_3 in which the nitromethide anion attacks position 2.[11] We have confirmed these results. These intermediates are present as conjugate bases, based on the appearance of a doublet in their ^1H NMR spectra for hydrogen at C-α (see structure **2**) with a coupling of $J_{\alpha,4} = 7$ Hz. It seems reasonable to assume that the σ-adducts **2a–c**, **5a,b**, and **8a–c** are also intermediates in the formation of compounds **3a–c**, **6a,b**, and **9a–c**.

It can be suggested[10] that before adduct formation a complex **10** or **11** is formed between the pyridinium ring and the nitromethide. Some evidence for π-complex formation can be taken from the fact that on mixing the pyridinium salt, nitromethane and liquid ammonia a bright yellow color appears.



10 11

On the *E*/*Z* Configuration of the (Nitromethylene)pyridines 3a–c, 6a,b, and 9a–c. Two geometrical *E* and *Z* forms are possible owing to show rotation around the bond linking the C-4 (C-2) of the pyridine ring and the methylene carbon. For some of the 4-nitromethylene derivatives obtained in this study, this had indeed been observed experimentally. For example, the ^1H NMR spectrum of compound **3a** shows two singlets for H-3 (8.42 and 6.35), two doublets for H-5 (6.38 and 8.39), and two doublets for H-6 (7.37 and 7.24). To establish unambiguously which protons belong to the *E* isomer and which to the *Z* isomer, we applied the NOE technique. The geometry of compound **3b** was investigated first since its NMR spectrum is less complex; it does not show the presence of two geometrical forms, so apparently only one geometrical isomer is present. For steric reasons, it can be anticipated that the **3b(*E*)** structure would be preferred. This has been confirmed by an NOE experiment. Irradiation of the methyl group at position 3 causes a positive increase of intensities from H-2 (15%) and H-α (30%). This result indicates that **3b** has the *E* configuration, in which the methyl and nitro groups are in the trans orientation. A similar positive increase was observed in the anion of 3-methyl-4-benzylpyridine (**12**).[12]



3b (E) NOE (CH_3, H_α=16%)

12

That compound **3b** is only present in the *E* form (no indication is found for the presence of the **3b(*Z*)** form) indicates that the *Z* form is considerably less stable, evidently owing to steric interference between the methyl and the nitro groups in the latter. In the **3b(*E*)** isomer H-5 is found at 8.65 ppm, a chemical shift value considered to be typical for a hydrogen being cis-oriented to the nitro group. When considering the *E*/*Z* geometry in compound **3a**, the chemical shift value of the singlet at 8.42 is assigned to H-3, the hydrogen being in the cis orientation to the nitro group, i.e., **3a(*Z*)**. The singlet at 6.35 has to be the hydrogen trans-oriented to the nitro group, i.e., **3a(*E*)**. That the hydrogen cis-oriented to the nitro group resonates at a lower field compared to the hydrogen in the trans

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Table I. ^{1}H NMR Spectral Data for (Nitromethylene)pyridines

compd	H-2	H-3	H-4	H-5	H-6	N-CH_3	C-CH_3	H-CNO_2	$J_{2,6}$ (Hz)	$J_{5,6}$ (Hz)	$J_{4,6}$ (Hz)
3a(Z)		8.42 s		6.38 d	7.37 d	3.71 s	2.46 s	6.81 s		6.7	
3a(E)		6.35 s		8.39 d	7.24 d	3.71 s	2.40 s	6.81 s		6.6	
3b(E)	7.17 d			8.65 d	7.32 dd	3.75 s	2.04 s	6.87 s	1.6	7.3	
3c(E)[a]	7.16 d			8.73 d	7.36 dd	3.80 s		6.76 s	1.8	7.3	
6a(E)		8.92 br s		6.48 d	7.39 d	3.60 s	2.37 s	6.94 s		6.8	
6b[b]			6.99 dd	6.93 dd	7.44 dd	3.91 s		7.28 s		7.7	1.3
9a(E)		8.57 s			7.21 s	3.70 s	2.44[d] s 2.00[e] s	6.79 s			
9b(E)[c]		8.63 s			7.29 s	3.74 s	2.41 s	6.87 s			
9c		8.41 br s		6.32 br s		3.63 s	2.49[d] s 2.43[f] s	6.81 s			

[a] C_6H_5: 7.25 (m), 7.40 (m). [b] OCH_3: 3.98 (s). [c] CH_2CH_3: 2.40 (q), 1.20 (t). [d] C-2. [e] C-5. [f] C-6. All spectra were measured in $CDCl_3$ as solvent.

orientation is in agreement with the expectation. The doublets observed for H-5 at 6.38 and 8.39 are in full agreement with the **3a**/*Z*–**3a**/*E* geometry.

The anticipated *E* structure is assigned on the basis of the chemical shifts of H-3 for compounds **9a,b** (around 8.6). In **9c** hydrogens cis and trans to the nitro group are observed. The signals are broad, indicating a slow rotation around the C=C bound. In the 2-(nitromethylene)-pyridine derivative **6a** the chemical shift value for H-3 is 8.92 (s), indicating that H-3 is cis-oriented to the nitro group; consequently **6a** has the *E* structure. For the 3-methoxy-2-nitromethylene derivative **6b**, the *E*/*Z* geometry could not be established.

Experimental Section

Melting points are uncorrected. Mass spectra were determined on an AEI MS 902 mass spectrometer equipped with a VG ZAB console. The ^{1}H NMR spectra were recorded on a Bruker CXP-300 spectrometer and the data are summarized in Table I.

Preparation of Starting Materials. All the pyridinium chlorides were prepared from the corresponding iodides by passing these compounds, dissolved in water, over a Dowex 1-X 2 column column. The compounds 1,2-dimethyl-,[13] 1,3-dimethyl-,[14] 1,4-dimethyl-,[13] 1-methyl-3-phenyl-,[15] 1,2,6-trimethyl-,[13] 1,2-dimethyl-5-ethyl-,[16] and 1-methyl-3-methoxypyridinium[9] iodides were synthesized by reacting the appropriate pyridines with methyl iodide. 1,2,5-Trimethylpyridinium iodide was prepared in the same way (mp 206–207 °C).

Procedure of the Reaction of Pyridinium Chlorides with Nitromethane/Liquid Ammonia/Potassium Permanganate. To a mixture of 4 mmol of the starting material and 8 mmol of nitromethane in 25–30 mL of liquid ammonia was added 4 mmol of solid potassium permanganate. The mixture was stirred for 4 h at −40 °C. The ammonia was evaporated and the residue was extracted with chloroform. The solvent was evaporated and the residue purified by column chromatography using Kieselgel 60 (70–230-mesh ASTM) with chloroform/methanol (4:1) as eluent. Crystallization from benzene gave the product, which was identified by its melting point, ^{1}H NMR (for data, see Table I), exact mass data, and microanalysis.

1,4-Dihydro-1,2-dimethyl-4-(nitromethylene)pyridine (3a): yield 75–80%; mp with decomposition at about 150 °C; exact mass 166.0746 (calcd 166.0742).

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.58; H, 6.01; N, 16.92.

1,4-Dihydro-1,3-dimethyl-4-(nitromethylene)pyridine (3b): yield 80%; mp 229–230 °C; exact mass 166.0743 (calcd 166.0742).

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.64; H, 6.06; N, 17.03.

1,4-Dihydro-1-methyl-3-phenyl-4-(nitromethylene)pyridine (3c): yield 80%; mp 207–208 °C; exact mass 228.0899 (calcd 228.0899).

Anal. Calcd for $C_{13}H_{12}N_2C_2$: C, 68.40; H, 5.29; N, 12.27. Found: C, 68.66; H, 5.28; N, 12.19.

1,2-Dihydro-1,4-dimethyl-2-(nitromethylene)pyridine (6a): yield 85–90%; mp 195–196 °C; exact mass 166.0749 (calcd 166.0742).

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.90; H, 6.08; N, 17.07.

1,4-Dihydro-4-(nitromethylene)-1,2,5-trimethylpyridine (9a): yield 80–85%; mp 240–241 °C; exact mass 180.0900 (calcd 180.0899).

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.66; N, 15.59. Found: C, 59.33; H, 6.61; N, 15.41.

1,4-Dihydro-1,2-dimethyl-5-ethyl-4-(nitromethylene)-pyridine (9b): yield 80%; mp 218–220 °C; exact mass 194.1060 (calcd 194.1055).

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26; N, 14.42. Found: C, 61.95; H, 7.27; N, 14.55.

1,4-Dihydro-4-(nitromethylene)-1,2,6-trimethylpyridine (9c): yield 75–80%; decomposition at about 90 °C; exact mass 180.0899 (calcd for $C_9H_{12}N_2O_2$ 180.0883).

1,2-Dihydro-3-methoxy-1-methyl-2-(nitromethylene)-pyridine (6b): yield 75–80%; mp 175–176 °C; exact mass 182.0714 (calcd 182.0691).

Anal. Calcd for $C_8H_{10}N_2O_3 \cdot {}^1/_3H_2O$: C, 51.06; H, 5.71; N, 14.88. Found: C, 50.91; H, 5.35; N, 14.67.

Acknowledgment. We are indebted to Drs. C. A. Landheer and Mr. C. J. Teunis for providing us with exact mass data and to Mr. H. Jongejan for carrying out the microanalyses.

Registry No. **1a**, 1121-26-2; **1b**, 38078-46-5; **1c**, 123934-18-9; (*Z*)-**3a**, 123934-22-5; (*E*)-**3a**, 123934-23-6; (*E*)-**3b**, 123934-24-7; (*E*)-**3c**, 123934-25-8; **4a**, 38078-47-6; **4b**, 123934-19-0; (*E*)-**6a**, 123934-26-9; **6b**, 123934-27-0; **7a**, 123934-20-3; **7b**, 69259-94-5; **7c**, 123934-21-4; (*E*)-**9a**, 123934-28-1; (*E*)-**9b**, 123934-29-2; **9c**, 123934-30-5; H_3CNO_2, 75-52-5.

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