Alternative Formation of Products of Direct or Cine Methoxydenitration of 1-Alkyl-3,4-dinitropyrroles

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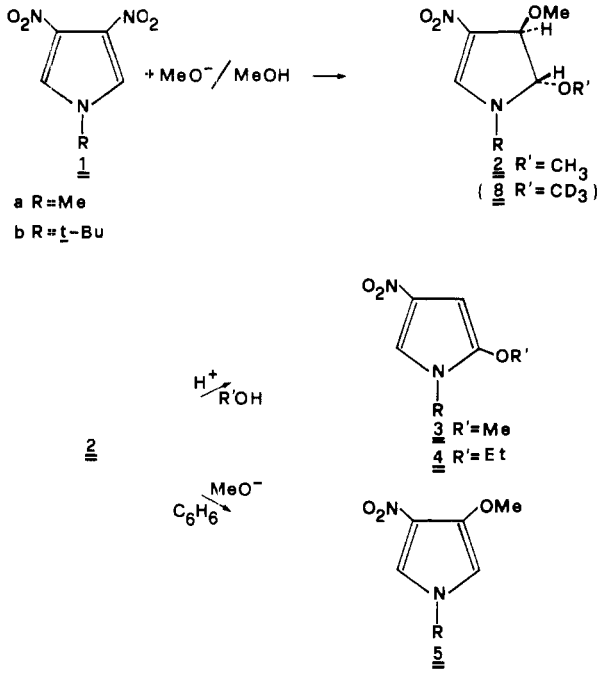
1-Alkyl-3,4-dinitropyrroles **1** with methoxide ion in refluxing methanol yield *trans*-1-alkyl-4,5-dimethoxy-3-nitro-2-pyrrolines **2**. The acid-promoted elimination of methanol from **2** is regioselective, yielding 1-alkyl-2-methoxy-4-nitropyrroles **3**, whereas the base-promoted elimination, under heterogeneous conditions, yields regiospecifically 1-alkyl-3-methoxy-4-nitropyrroles **5**. Acid-promoted reactions in ethanol or CD_3OD indicate the fast exchange of one alkoxy group of pyrrolines **2**, probably as a consequence of the ready formation of a cationic σ-adduct.

In a preliminary paper[1] the isolation of *trans*-4,5-dimethoxy-1-methyl-3-nitro-2-pyrroline (**2a**) in the reaction of 1-methyl-3,4-dinitropyrrole (**1a**) with sodium methoxide in methanol was described. The acid-promoted elimination of methanol from **2a** was found to yield 2-methoxy-1-methyl-4-nitropyrrole (**3a**), which is the formal product of cine substitution of **1a**.



In this work, besides the formation of another pyrroline (**2b**), we describe the elimination of methanol from pyrrolines **2** under different reaction conditions. The regioselectivity of the elimination is markedly affected so that base-promoted and acid-promoted reactions give isomeric products. Some indications about the mechanism of the acid-promoted reaction are also given by the results of the elimination carried out in different solvents.

Results

Formation of *trans*-1-Alkyl-4,5-dimethoxy-3-nitro-2-pyrrolines 2. 3,4-Dinitro-1-alkylpyrroles **1** react with 1 equiv of sodium methoxide in methanol to yield *trans*-4,5-dimethoxy-3-nitro-1-alkyl-2-pyrrolines **2**. The formation of pyrroline **2a** occurs more rapidly than that of **2b**.

Pyrrolines **2** are isolated after evaporation of the solvent and extraction with hexane. The evaporation has to be carried out at a temperature lower than 25 °C, in order to avoid decomposition reactions. The solid residue from the extraction has been identified as sodium nitrite. When the reaction is carried out with an excess of methoxide ion, this may induce a further reaction at the stage of extraction (see below). The pyrrolines, isolated after evaporation of hexane, are purified by chromatography and characterized by their mass and ^1H NMR spectra. A slight difference in the coupling constant between **2a** and **2b** is ascribed to the different steric requirement of the *N*-alkyl groups and to a different geometry of the ring. Since these products may be sensitive to the presence of acids and bases,[2] it had to be ascertained whether they were affected by this method of purification; indeed, ^1H NMR spectra were identical before and after chromatography.

Acid-Promoted Elimination of Methanol. At room temperature, in the presence of acids, pyrrolines **2** lose a molecule of methanol, yielding 2-methoxy-4-nitro-1-alkylpyrroles **3**. This reaction occurred easily in methanol, CCl_4, or chloroform. Products **3** were identified as methoxynitroalkylpyrroles from their ^1H NMR and mass spectra. Literature[3] values of pyrrole coupling constants do not help much to define their structure, probably because of the presence of a nitro group. The ^{13}C NMR spectrum of the methyl derivative **3a**, showing different C–H coupling constants for the ring carbon atoms bound to hydrogens, is consistent with a structure having an α and a β unsubstituted ring position. The conclusive proof of structure **3a** is given by the nuclear Overhauser effect.[1] Owing to the strong similarities of ^1H NMR and electronic spectra of **3a** and **3b** (Table I), similar structures are assigned to these compounds. The acid-promoted reaction of *tert*-butylpyrroline **2b** yields also minor amounts (5–10%, ^1H NMR analysis) of 1-*tert*-butyl-3-methoxy-4-nitropyrrole (**5b**), which is the only product of the base-promoted elimination (see below). It was verified that under these reaction conditions pyrroles **5** are not isomerized to pyrroles **3**.

When the acid-promoted reaction of pyrrolines **2** is carried out in ethanol, 2-ethoxy-4-nitro-1-alkylpyrroles **4** are obtained. The ^1H NMR and UV spectral analogies point out a strong similarity in structure of products **3** and **4**.

The acid-promoted reaction of **2** in CD_3OD yields 2-(trideuteriomethoxy)-4-nitro-1-alkylpyrroles. While the trideuteriomethoxy group is incorporated into the final product, very little H–D exchange occurs at the same time on the ring. It was verified that pyrroles **3** themselves can slowly undergo H–D exchange under the same reaction conditions.

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Table I. UV and ^{1}H NMR Data of 2- and 3-Alkoxy-1-alkyl-4-nitropyrroles

	λ_{max}[c] (log ϵ)	δ_{H-2}	δ_{H-3}	δ_{H-5}	$J_{2,5}$[a]	$J_{3,5}$[a]	δ_R	$\delta_{R'}$	solvent
3a	280 (3.84), 359 (3.62)		5.68	6.95		2.4	3.45	3.81	CCl_4
3b	277 (3.89), 360 (3.69)		5.72	7.15		2.3	1.60	3.80	CCl_4
4a	278, 358		5.76	7.14		2.3	3.50	4.06 (q),[b] 1.36 (t)[b]	$CDCl_3$
4b	275, 362		5.72	7.11		2.3	1.60	4.05 (q),[b] 1.46 (t)[b]	CCl_4
5a	297 (3.98)	6.16		7.32	3.0		3.67	3.82	$CDCl_3$
5b	300 (4.01)	6.40		7.45	3.0		1.57	3.77	CCl_4

[a] Hz. [b] J = 6.75 Hz. [c] In MeOH.

The course of the acid-promoted elimination of methanol from the unlabeled pyrroline **2b** in CD_3OD was followed by ^{1}H NMR spectroscopy. After nearly 50% reaction, the starting material is found to have undergone the methoxy–trideuteriomethoxy exchange of the methoxy group adjacent to the heteroatom without exchanging any hydrogen atom directly bound to the ring. Since under the same reaction conditions pyrroles **3** do not undergo exchange of the methoxy group, the formation of **3b** having the trideuteriomethoxy group should involve the formation of the appropriate deuterated pyrroline precursor **8**.

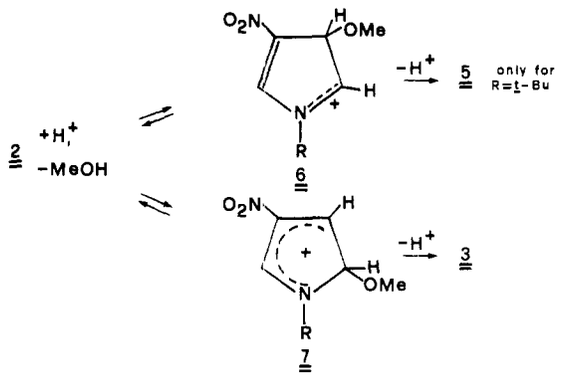
Base-Promoted Elimination of Methanol. While the prolonged treatment of pyrrolines **2** with an excess of methoxide in methanol yields no definite product, the reaction of each pyrroline with sodium methoxide in nonpolar aprotic solvents such as benzene or hexane, under heterogeneous conditions, yields the methoxynitroalkylpyrroles **5**. It may be excluded that these products are formed by a thermal elimination reaction, since only decomposition products are formed when pyrrolines **2** are heated in benzene in the absence of bases. However, the ^{1}H NMR and electronic spectra are different from those of pyrroles **3**. In particular, the coupling constants between the ring protons (J = 3 Hz) are larger than those in products **3** (J = 2.3 Hz). The chemical shift values are in agreement with the presence of two α hydrogen atoms. The mass spectrum is also characterized by the presence of an intense M − 47 peak that is displayed by nitro aromatic compounds bearing an ortho methoxy group[4] and is absent in the mass spectrum of 2-methoxy-4-nitro-1-alkylpyrroles. The conclusive evidence for structure **5** is given again by the nuclear Overhauser effect on the *tert*-butyl derivative, which shows that both hydrogen atoms are in the proximity of the *N*-alkyl group. Under these reaction conditions pyrroles **3** are not isomerized to pyrroles **5**.

Discussion

In the reaction of methylpyrroline **2a** the elimination of methanol occurs regiospecifically, yielding **3a** and **5a** in acid or basic conditions, respectively. The reaction of *tert*-butylpyrroline **2b** is regiospecific only under basic conditions, when only **5b** is formed, and is highly regioselective in the acid-promoted elimination, in CCl_4 (or MeOH), where the 2-methoxy derivative is formed together with a low amount of **5b** (5–10%).

The reactions leading from pyrrolines **2** to alkoxynitropyrroles are elimination processes involving the loss of a molecule of methanol. This kind of elimination is uncommon because of the low leaving group ability of alkoxy groups. Undoubtedly a strong driving force for the elimination is provided here by the formation of an aromatic system, as can also be observed in the elimination of methanol from 1-methoxyacenaphthene to acenaphthylene.[5]

Scheme I



Under basic conditions, elimination of alcohols is expected to occur with a stepwise E1cB mechanism. However, under our reaction conditions, it is not possible to define the mechanism because the reaction is carried out in a heterogeneous medium. Attempts to work in a homogeneous medium with the aid of crown ethers have not been satisfactory. The orientation in the regiospecific basic elimination from **2** to yield **5** is similar to that observed in the base-promoted dehydrochlorination from 2,3-dichloro-2,3-dihydrobenzofuran, yielding 3-chlorobenzofuran.[6] In our case the abstraction of a β hydrogen atom is also favored by the proximity of a nitro group, which increases its acidity.

The acid-promoted elimination of methanol should involve an E1-like reaction pathway[7] via protonation of **2**, departure of a molecule of methanol, and finally loss of H^+ (Scheme I). The cations formed after the departure of methanol should be relatively stable, because they are cationic σ adducts formed from pyrrole substrates.

The experiments in ethanol and CD_3OD show that there is a fast equilibrium reaction between pyrrolines **2** and σ complex **6**. However, the loss of H^+ from **6** seems to be a relatively slow process, since 3-methoxy-4-nitro-1-alkylpyrroles are formed, in very low yield, only in the case of the presence of a bulky group at position 1. On the other hand, the isomeric σ complexes **7**, which are the likely precursors of the main products, seem to have a low tendency to revert to the starting pyrrolines and prefer to lose a proton, yielding pyrroles **3**. As in the solvolysis of 2,3-dichloro-2,3-dihydrobenzofuran, no strict relationship is found between the orientation of elimination and the relative stabilities of the cationic σ adducts.[8]

Now it seems worth relating the course of the reaction between 1-alkyl-3,4-dinitropyrroles and methoxide ion to

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(8) A referee pointed out the fact that, if σ complexes are intermediates in both elimination from pyrrolines and electrophilic substitution, the different timing in the elimination process could mean that the rate-determining step in electrophilic substitution would be different for 2- and 3-substitution, the formation of the σ complex being rate-determining in the former case.

those of reactions of other aromatic or heteroaromatic substrates containing two adjacent nitro groups. In o-dinitrobenzene, only products of direct replacement of a nitro group are obtained. In this case the intermediate anionic σ adduct corresponding to the direct replacement can be satisfactorily stabilized by the adjacent nitro group. However, whenever this kind of stabilization cannot be attained, because of the low degree of conjugation between the reaction center and the nitro-group-bearing position, cine substitution may occur competitively with, or even more easily than, direct replacement. Examples of this behavior are known in reactions of nucleophiles with 2,3-dinitronaphthalene,[9,10] 3,4-dinitrothiophene,[11,12] and even some benzene substrates such as 1-alkoxy-4-amino-2,3-dinitrobenzene, where some bond fixation occurs because of the strong conjugation between the nitro groups and electron-releasing groups.[13] In these cine substitution reactions involving replacement of a nitro group, an elimination–addition mechanism has been ruled out, and a complex addition–elimination mechanism seems more likely.

Experimental Section

Melting points are uncorrected. UV spectra were recorded on a Perkin-Elmer 402 instrument. Mass spectra were obtained on an AEI MS12 spectrometer. Most ^{1}H NMR spectra were recorded on a JEOL C60-HL apparatus, except that of pyrroline **2b** which was recorded on a Bruker HX 90. Nuclear Overhauser effect measurements were carried out in a Bruker HX 90 apparatus, in Me_2SO-d_6. The solvent was first deoxygenated with an argon stream and then kept under vacuum. ^{13}C NMR spectra were recorded on a Bruker WH 90/DS instrument.

Elemental analyses were carried out by Professor A. Pietrogrande, Laboratorio di Microanalisi, Istituto di Chimica Farmaceutica, University of Padova.

For the sake of comparison, relevant UV and ^{1}H NMR data are collected in Table I.

3,4-Dinitro-1-alkylpyrroles 1 were prepared according to a described procedure.[14] **1a**: mp 160–162 °C (lit.[14] mp 162–166 °C); ^{1}H NMR δ (CD_3CN) 7.56 (s, 2 H), 3.70 (s, 3 H). **1b**: mp 150–151 °C; mass spectrum, m/e 213 (M^+); ^{1}H NMR δ (CD_3CN) 7.62 (s, 2 H), 1.55 (s, 9 H); yield 15%.

***trans*-1-Alkyl-4,5-dimethoxy-3-nitro-2-pyrrolines 2** were prepared as already described.[1] However, since **1b** is less reactive than **1a**, 2 equiv of sodium methoxide was used in the reaction of the former, and the reaction mixture was refluxed for a longer time (nearly 24 h). An excess of sodium methoxide accelerates (TLC analysis) the formation of the pyrrolines; however, a prolonged reaction of the pyrrolines in the presence of methoxide slowly leads to the appearance of tars, without giving a definite product.

2b: mp 98–100 °C; mass spectrum, m/e 230 (M^+); ^{1}H NMR δ (CCl_4) 1.40 (s, 9 H), 3.24 (s, 3 H), 3.44 (s, 3 H), 4.51 (s, 1 H), 4.72 (s, 1 H), 7.85 (s, 1 H); λ_{max} (MeOH) 370 nm; yield 35%.

At a sweep width of 1 Hz/cm, the spectrum shows coupling between the signals at δ 7.85 and 4.72 (J = 0.6 Hz), and between δ 4.51 and 4.72 (J = 0.8 Hz). At the usual sweep width of 20 Hz/cm the singlets of positions 4 and 5 of **2b**, at δ 4.51 and 4.72, are indeed slightly broadened. The corresponding positions of **2a** are also slightly coupled (J = 1.2 Hz).

Formation of 1-Alkyl-2-methoxy-4-nitropyrroles 3. Acid-promoted elimination of methanol from pyrrolines **2** was carried out at room temperature in methanol, as already described.[1] The reaction time was 4–5 h when the reaction was started from **2a** and 15–20 h from **2b**.

3a: mp 89-90 °C; ^{13}C NMR δ ($CDCl_3$) 32.2 (q, J = 141.4 Hz, NCH_3), 58.1 (q, J = 145.8 Hz, OCH_3), 80.0 (d, J = 181 Hz, C-3), 116.4 (d, J = 192.6 Hz, C-5), 133.9 (s, C-4), 147.8 (s, C-2); yield 90%. Anal. Calcd: C, 46.15; H, 5.17. Found: C, 46.05; H, 5.22.

3b: mp (from hexane) 46–47 °C; mass spectrum, m/e 198 (M^+); yield 90%. Anal. Calcd: C, 54.52; H, 7.13; N, 14.14. Found: C, 54.65; H, 7.19; N, 14.17.

Formation of 1-Alkyl-2-ethoxy-4-nitropyrroles 4. To a solution of pyrroline in ethanol ([**2a**] = 5×10^{-3} M or [**2b**] = 2×10^{-2} M) was added 10 equiv of CF_3CO_2H. After 15–20 h at room temperature the pyrroline had reacted completely (TLC analysis). The ethanol was evaporated, and the residue was taken up with ether and washed with a $NaHCO_3$ solution. After evaporation of the ether, the residue was worked up as described for the formation of **3**. The products were identified as 1-alkyl-2-ethoxy-4-nitropyrroles **4**. **4a**: mp (hexane) 68.5–69.5 °C; mass spectrum, m/e 170 (M^+); yield 74%. **4b**: mp (hexane) 40.5–41.5 °C; mass spectrum, m/e 212 (M^+); yield 30%.

Formation of 1-Alkyl-3-methoxy-4-nitropyrroles 5. To a 2×10^{-2} M solution of a pyrroline **2** in C_6H_6 the equivalent amount of concentrated (2–3 M) sodium methoxide in methanol was added. The suspension was refluxed. After 10 min TLC analysis showed that the pyrroline was converted into one product and tars. The benzene was removed, and the residue was extracted repeatedly with warm CCl_4. Evaporation of the CCl_4 left a residue that was purified from tars by chromatography (silica gel, benzene–ethyl acetate).

5a: mp 92.5–93.5 °C (CCl_4); mass spectrum, m/e 156 (M^+); yield 42%. Anal. Calcd: C, 46.15; H, 5.17. Found: C, 46.00; H, 5.28.

5b: mp 132.5–133 (hexane); mass spectrum, m/e 198 (M^+); the nuclear Overhauser effect gave, upon irradiation at δ 1.51 ($NC(CH_3)_3$), increases (19%) of δ 6.82 and 7.75; yield 46%. Anal. Calcd: C, 54.52; H, 7.13; N, 14.14. Found: C, 54.34; H, 7.12; N, 14.01.

Acid-Catalyzed Exchange of Pyrroline 2b in CD_3OD. Pyrroline **2b** (60 mg) was dissolved in 0.5 mL of CD_3OD. In this solvent, **2b** shows the following ^{1}H NMR spectrum: δ 1.41 (s, 9 H), 3.33 (s, 3 H), 3.48 (s, 3 H), 4.62 (s, 1 H), 5.00 (s, 1 H), 8.30 (s, 1 H). Upon addition of CF_3CO_2H (0.5 equiv), the slow appearance of signals of **3b** is observed. The intensity of the signals of **2b** decreases correspondingly. However, no indication can be given for the intensity of signals at δ 3–3.5, which are covered by methanol. The reaction was stopped at nearly 50% completion by neutralization with sodium methoxide. The solvent was evaporated. The ^{1}H NMR spectrum of the residue, taken up in CCl_4, showed the presence of 1-*tert*-butyl-2-(trideuteriomethoxy)-4-nitropyrrole and of pyrroline **2b**. In the spectrum of the latter compound, however, the signal at δ 3.24 was missing, whereas the other signals had the expected intensity.

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Registry No. **1a**, 68712-54-9; **1b**, 69726-50-7; **2a**, 68712-55-0; **2b**, 71426-12-5; **3a**, 68712-56-1; **3b**, 71426-13-6; **4a**, 71426-14-7; **4b**, 71426-15-8; **5a**, 71426-16-9; **5b**, 71426-17-0; 8, 71426-18-1.

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