

Nitration of 2-Methylpyrrole

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The present work was undertaken to prepare and characterize *C*-methyl nitropyrroles. Such compounds should prove useful in the construction of fused heterocyclic ring systems since one could exploit the expected acidity of the methyl hydrogens.

The nitration of pyrrole obtained by using fuming nitric acid in acetic anhydride at low temperatures produces 2- and 3-nitropyrroles in a ratio of 9:1 (1). When the same procedure was used with 2-methylpyrrole, a mixture of two mononitration products resulted. Variations in temperature had no discernible effect on the yield (12-15%) and relative amount (85% I, 15% II by glc) of the products. Separation of the mixture was accomplished by column chromatography and by recrystallization from water of mixtures rich in II (I was more soluble).

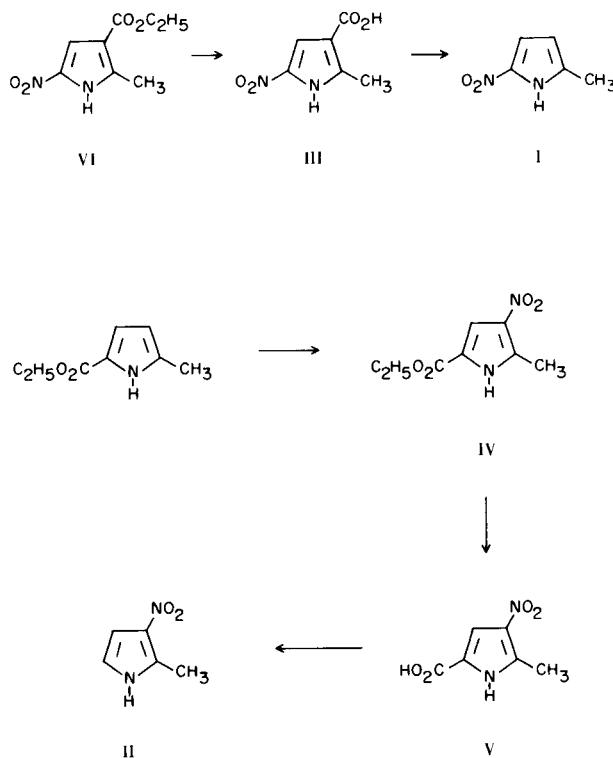
Component I, moved more rapidly than II by glc and the which suggests that compound I has a 2-nitro group. Also, the ir spectrum of I (10^{-4} M in carbon tetrachloride) showed a strong NH band at 3440 cm^{-1} , while II displayed this band at 3458 cm^{-1} . This difference in NH stretching frequencies between I and II parallels the differences observed in these frequencies for 2- and 3-carbethoxypyrroles (2) and for 2- and 3-nitropyrroles (1). The uv data (methanol) also paralleled those reported for these nitropyrroles (1) (I: λ_{max} 230 $\text{m}\mu$, ϵ 4800; 355 $\text{m}\mu$, ϵ 15800; II: λ_{max} 270 $\text{m}\mu$, ϵ 6660; 328 $\text{m}\mu$, ϵ 5760).

Because electrophilic substitution of 2-methylpyrrole would be expected to occur at position 3 rather than at 4, the structure II was assigned to the minor component. The aryl protons of II are coupled by 3.2 Hz which lends support to the assignment (3) (see Table I).

Alternate syntheses aided in verification of these structures and afforded a route to the pure isomers. Compound I was obtained from ethyl 2-methyl-5-nitropyrrole-3-carboxylate (4) by hydrolysis to the acid III, and then by decarboxylation with quinoline and copper chromite at 180° . The nitration of ethyl 2-methylpyrrole-5-carboxylate (5) with cold concentrated nitric acid produced IV. The starting material for the nitration is known to undergo both formylation and acylations at C3 (6). Conversion to the acid V was followed by decarboxylation as before, producing 2-methyl-3-nitropyrrole which was identical with the minor nitration product, II.

The NH frequencies of the nitropyrroles prepared in

this work were examined in dilute (10^{-4} M) carbon tetrachloride solution and substituent constants for α - and β -nitro groups determined (see Table II). The effects of substituents such as methyl and carbethoxy on the NH frequency have been discussed and the additivity of these effects noted (7). No compound bearing both an α -nitro and an α -carbethoxyl or more than one nitro substituent has been examined. Modified substituent constants might be required for such compounds as is the case for di- α -carbethoxypyrroles (7).



EXPERIMENTAL

Infrared spectra were measured with a Perkin-Elmer Model 521 infrared spectrophotometer, and chemical analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Company and trade names are given for identification purposes only and do not constitute endorsement by the U. S. Department of Agriculture.

TABLE I
NMR Data for the Nitropyrroles (a).

	CH ₃	H3	H4	H5	
I	2.26	6.04	7.03	--	J=4.1 Hz (c)
II	2.51	--	6.71	6.61	J=3.2 Hz (c)
III	2.52	--	7.30	--	
IV (b)	2.57	--	7.22	--	
V	2.57	--	7.20	--	
VI (d)	2.50	--	7.28	--	

(a) Spectra were measured in DMSO-d₆ with a 100 Mc instrument. Shifts are in ppm from TMS. (b) Ethyl CH₃ at 1.32(t), CH₂ at 4.32(q). (c) Trace of piperidine in sample to remove NH-CH coupling. (d) Ethyl CH₃ at 1.30(t), at CH₂ at 4.23(q).

TABLE II
NH Frequencies of the Nitropyrroles.

	Observed	Calculated (a)
2-Nitropyrrole	3446	3447
I	3440	3438
VI	3423	3425
3-Nitropyrrole	3466	3467
II	3458	3458
IV	3418	3417

(a) Substituent constants (7) used were: α -CH₃ = -9 cm⁻¹, α -CO₂Et = -41, and β -CO₂Et = -13. The values determined for NO₂ were: α -NO₂ = -49, and β -NO₂ = -29.

Nitration of 2-Methylpyrrole.

A solution of 4.76 g. of 90% nitric acid in 30 ml. of acetic anhydride was added dropwise to a stirred solution of 5.00 g. of 2-methylpyrrole in 30 ml. of acetic anhydride. The reaction mixture was kept at -50° during addition (1 hour) and 1 hour longer. It was then brought to room temperature, poured into 1 liter of ice-water, neutralized with solid sodium carbonate, and extracted with ether. The extract was dried (magnesium sulfate) and concentrated. The residue was filtered through alumina with ether to give 1.09 g. (14%) of a red solid which was a mixture of the two mononitration products, I and II. Column chromatography of 3.2 g. of this material on 60 g. of alumina (Brockmann, neutral, activity I) provided pure I on elution with benzene-ether. Recrystallization from benzene-cyclohexane gave pale yellow needles, m.p. 66.5-67.5°.

Anal. Calcd. for C₅H₆N₂O₂: C, 47.61; H, 4.80; N, 22.22. Found: C, 47.44; H, 4.77; N, 22.10.

Later fractions became increasingly rich in II. One recrystallization of these from water provided virtually pure II as yellow needles. An analytical sample obtained by recrystallization from benzene showed m.p. 170-172°.

Anal. Calcd. for C₅H₆N₂O₂: C, 47.61; H, 4.80; N, 22.22. Found: C, 47.66; H, 4.80; N, 22.02.

2-Methyl-5-nitropyrrole (I).

A solution of 1.17 g. of potassium hydroxide and 1.28 g. of ethyl 2-methyl-5-nitropyrrole-3-carboxylate (4) in 10 ml. of water was heated under reflux for 90 minutes, then cooled, acidified with hydrochloric acid, and extracted with ether. The extract was dried and concentrated, to give a quantitative yield of the acid III, m.p. 220.5-221° (toluene).

Anal. Calcd. for C₆H₆N₂O₄: C, 42.36; H, 3.56; N, 16.47. Found: C, 42.58; H, 3.53; N, 16.45

This acid could be used directly for the next step. Compound III (200 mg.) was added to a suspension of 100 mg. of copper chromite in 2 ml. of quinoline and the mixture was heated under nitrogen at 170-190° for 3 hours. The reaction mixture was cooled, diluted with ether, and filtered. The filtrate was washed with dilute hydrochloric acid to remove all of the quinoline and was then dried and concentrated, providing 105 mg. (71%) of I.

Ethyl 2-Methyl-3-nitropyrrole-5-carboxylate (IV).

Ethyl 2-methylpyrrole-5-carboxylate (5) (2.3 g.) was added portionwise to 20 ml. of 72% nitric acid while the reaction mixture was stirred vigorously and maintained at 0°. After 1 hour, the mixture was kept in a freezer at -20° for 16 hours and then poured over cracked ice, whereupon the product precipitated. It was collected by filtration (0.87 g., 30%) and showed m.p. 182-183° (benzene). Variation of the nitrating reagent and reaction conditions did not improve the yield; infrared (chloroform), ν (C=O) 1685.

Anal. Calcd. for C₈H₁₀N₂O₄: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.48; H, 5.12; N, 14.06.

2-Methyl-3-nitropyrrole (II).

The hydrolysis of IV and decarboxylation of the resulting acid, V, were conducted essentially as described above. The decarboxylation of V was very rapid, being essentially complete after 75 minutes. The yields from saponification and decarboxylation were 100% and 69%, respectively. The acid, V, melted above 260°.

Anal. Calcd. for C₆H₆N₂O₄: C, 42.36; H, 3.56; N, 16.47. Found: C, 42.52; H, 3.59; N, 16.29.

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