

NITROPYRROLES—I

THE PREPARATION AND PROPERTIES OF 2- AND 3-NITROPYRROLE

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Abstract—Re-examination of the nitropyrroles has shown that the 2-isomer has m.p. 65° and the 3-isomer m.p. 101°. The low m.p. usually reported for the 2-nitro compound is due to the presence of small amounts of 3-nitropyrrole. The substance formed by the action of amyl nitrate on sodio pyrrole is identified as 2-nitropyrrole. There is no evidence for the existence of the 3-nitro compound as a dimer. These structural assignments are confirmed by the spin-spin coupling constants derived from the NMR spectra.

AS PART of a series of studies of the chemical and physical characteristics of heterocyclic systems, it was decided to examine the properties of the nitropyrroles. Both the C-nitro derivatives of pyrrole are known and are relatively easily accessible. The 2-nitro compound (I) is formed in satisfactory yield by the direct nitration of pyrrole; 3-nitropyrrole (II) is obtained by the decarboxylation of 4-nitropyrrole-2-carboxylic acid (IV). Despite this considerable obscurity surrounds the properties of these compounds, particularly those of 3-nitropyrrole. In an attempt to remove this obscurity the nature of these compounds has been investigated by a wide variety of physical methods.

2-Nitropyrrole. The nitration of pyrrole using a cold solution of nitric acid in acetic anhydride,¹ gives a brown resinous material from which 2-nitropyrrole can be extracted. When prepared by this conventional method the product has been reported¹⁻³ as showing a m.p. within the range 52–58°. It was found that the extraction procedure could be simplified by subjecting the crude product to chromatography on alumina. The product obtained in this way had m.p. 63° which rose after crystallization from light petroleum to 65–66.5°. Comparison of the IR spectra of material m.p. 53–56° and of m.p. 65° showed small but significant differences and GLC revealed the presence of a second, minor component in the material of lower m.p.—the main component showed an identical retention volume to that of the single component of the higher melting material.

Anderson² and Fournari and Tirouflet³ have reported that the direct nitration of pyrrole gives in addition to the 2-nitro derivative a small amount of 3-nitropyrrole. Comparison of GLC showed that the minor component of the low melting material had the same retention volume as authentic 3-nitropyrrole. Further a synthetic mixture of pure 2-nitro- (m.p. 65°) and 3-nitropyrrole in the appropriate proportions could be crystallized from light petroleum giving a material, m.p. 48–52°, whose IR

¹ I. J. Rinkes, *Rec. Trav. Chim.* **53**, 1167 (1934).

² H. J. Anderson, *Canad. J. Chem.* **35**, 21 (1957).

³ P. Fournari and J. Tirouflet, *Bull. Soc. Chim. Fr.* 484 (1963).

spectrum and gas-liquid chromatogram were similar to those obtained from the low melting nitration product. The gas-liquid chromatograms, IR spectra, and X-ray powder photographs of samples of 2-nitro-pyrrole, m.p. 53–56° prepared in other laboratories revealed similarly that they too were contaminated by a small amount of 3-nitropyrrole.

The X-ray powder photograph, the UV and IR spectra of the pure substance, m.p. 65°, were recorded (Experimental); the NMR spectrum (see below) is entirely consistent with the structure of 2-nitropyrrole.

3-Nitropyrrole. The most convenient route to 3-nitropyrrole is provided⁴ by the condensation of nitromalondialdehyde (III) and glycine ester. Hydrolysis of the product gives 4-nitropyrrole-2-carboxylic acid (IV). It was found that the acid could be smoothly decarboxylated to 3-nitropyrrole, m.p. 101°, by the use of a copper-chromite catalyst in quinoline. The properties of the product are largely in agreement with those reported by other workers^{3,4} for 3-nitropyrrole prepared by this method. However, from the reaction of isoamyl nitrate on sodio pyrrole, it has been reported⁵ that a 3-nitropyrrole, m.p. 64° can be obtained. In view of this and on the basis of a mol. wt. determination the substance m.p. 101° has been regarded as dimeric and the structure (V) has been suggested.⁴

The direct nitration of pyrrole in the 3-position by the action of alkali and isoamyl nitrate is widely listed⁶ as a useful method for the preparation of 3-nitropyrrole. The evidence on which the orientation of the substituent was assigned is however, slender, being based on analogy with the formation of 3-nitroindole under similar conditions;⁵ and the yield of nitropyrrole available from this route appears to be small. From the black reaction mixture obtained by the action of isoamyl nitrate on sodio pyrrole, nitropyrrole was isolated in very small yield (ca. 1%) by means of its silver salt. The product melted at 64°. As was expected, the X-ray powder photograph of this substance differed from that of the "dimer"; that the differences were not due merely to polymorphism was confirmed by the non-identity of the UV and IR spectra of solutions of the two compounds. A gas-liquid chromatogram of the lower melting substance showed a retention volume which indicated that the similarity of the m.p. to that of 2-nitropyrrole might extend further. Comparison of spectra and of X-ray powder photographs supported this and confirmed the identity of the substance formed by the action of isoamyl nitrate as 2-nitropyrrole.

The failure previously to recognise this identity can be ascribed in part to the greater selectivity of alkaline nitration. The product shows no contamination with 3-nitropyrrole such as is present in the product from acidic nitration: in the absence of chromatographic purification the m.p. of the latter material remains significantly below that of pure 2-nitropyrrole. The confusion must also be ascribed to the mistaken claims⁴ that a reversible equilibrium exists between the substances m.p. 64° and 101°. Hale and Hoyt⁴ reported that heating the lower melting substance in water gave the higher melting compound whereas the reverse change resulted from the slow evaporation of an aqueous solution of the higher melting compound. Attempts to reproduce

⁴ W. J. Hale and W. Hoyt, *J. Amer. Chem. Soc.* 37, 2551 (1915).

⁵ A. Angeli and L. Alessandri, *Atti Acad. Real. Lincei* (5) 20, 311 (1910).

⁶ R. M. Acheson, *Chemistry of Heterocyclic Compounds* p. 59. Interscience (1960); A. R. Katritzky and J. M. Lagowski, *Heterocyclic Chemistry* p. 175. Methuen (1960); T. S. Stevens, *Chemistry of Carbon Compounds* (Edited by E. H. Rodd) Vol. IVA; p. 47, Elsevier (1957).

these results were not successful. It is possible that the reported changes reflect, in the former case the purification of crude material by recrystallization from water; in the latter case contamination of the pure substance m.p. 101° may well have occurred during slow evaporation of the solution. A similar explanation may well account for the recent report² that the lower melting substance, isolated chromatographically as a minor product of acidic nitration could be converted (in low yield) by the action of hot water to the higher melting substance: the different solubilities of 2- and 3-nitropyrrole suggests that water is a useful solvent for their separation.

The unusual directive effect which has hitherto been thought to be operative in the reaction of isoamyl nitrate with pyrrole is clearly no longer necessary to explain the product. With the demonstration⁷ that thiocyanation⁸ also takes place at the 2-position this leaves nitrosation by alkyl nitrite⁹ as the only substitution reaction of pyrrole reported to occur preferentially at the 3-position. However, as with the related nitration the evidence for the orientation of the nitrosopyrrole is merely analogy with the nitrosation of indole and it appears probable that this reaction too leads to the 2-substituted pyrrole.

The nature of the material, m.p. 101° can now be clarified. The molecular skeleton is established by the mode of synthesis. Redetermination of the mol. wt. showed that the material had the same mol. wt. as 2-nitropyrrole and was monomeric. The UV spectrum was similar to that of 2-nitropyrrole and typical of a molecule containing an aromatic chromophore. The IR spectrum contained bands characteristic of a pyrrole N—H group and a C—NO₂ group: no aliphatic C—H groups could be detected. In the light of this evidence, the substance, m.p. 101° can be assigned the structure of 3-nitropyrrole. This assignment is confirmed by the formation of small amount of this substance as a minor product of the acidic nitration of pyrrole. The NMR spectrum is in agreement with this structure.

NMR spectra. Because of the previous confusion concerning the nitropyrroles, it was considered desirable to confirm independently the orientation of the substituent in the two compounds. For this purpose NMR spectroscopy provides a convenient method. The NMR spectra of mono-substituted pyrroles are complex: coupling occurs between the four residual protons giving an ABXY system. By the addition of piperidine to the solution of the pyrrole Gronowitz *et al.*¹⁰ was able to remove the coupling with the imino proton; a similar result is achieved by measuring the spectra of water soluble compounds in D₂O or more elegantly for substances less soluble in water by the use of spin-decoupling. The resultant spectra have the ABX or AXY form and are relatively simple. Using this method it has been possible to resolve the spectra of many pyrroles and from the analysis of the spectrum of thiocyanopyrrole it was possible to show⁷ that it corresponded to a 2-substituted pyrrole.

Chemical shift values and coupling constants for nitro- and acetyl-pyrroles are shown in the Table; the values for the chemical shifts of the nitro compounds are in good agreement with those obtained by Anderson.¹¹

⁷ S. Gronowitz, A.-B. Hörnfeldt, B. Gestblom and R. A. Hoffman, *Arkiv för Kemi* **18**, 151 (1961).

⁸ D. S. Matteson and H. J. Synder, *J. Org. Chem.* **22**, 1500 (1957); *J. Amer. Chem. Soc.* **79**, 3610 (1957).

⁹ M. Spica and F. Angelico, *Gazzetta* **29** (2), 49 (1899).

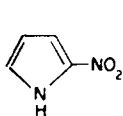
¹⁰ S. Gronowitz, A.-B. Hörnfeldt, B. Gestblom and R. A. Hoffman, *Arkiv för Kemi* **18**, 133 (1961).

¹¹ H. J. Anderson, private communication.

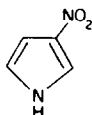
The spectra of 2-nitro- and 2-acetyl-pyrrole are similar. Bands due to H_3 in 2-nitropyrrole appear at lower field strength than those due to H_5 : this order differs from that of the 2-acetyl derivative and the change can be ascribed to the influence of the nitro group. Both spectra show similar coupling constants.

The spectrum of 3-nitropyrrole is relatively simple. It contains a quintet at 766 c/s and a quartet of double intensity at 675 c/s. The spin decoupled spectrum shows these groups of bands as a triplet and a doublet respectively. Although the positions of these bands correspond to those expected for a 3-substituted pyrrole the form of the spectrum may be contrasted with that of 3-acetylpyrrole which contains a triplet (743 c/s) and two quartets (678, 664 c/s). The differences in the spectra are reconciled if the chemical shifts of H_4 and H_5 in the nitropyrrole are assigned the same value and if their coupling constants to H_1 and H_2 are similar. Inspection of the spectrum confirms that J_{24} and J_{25} must be similar and comparison with the values for 3-acetylpyrrole supports this. Similar chemical shift values for protons on heterocyclic rings are not uncommon and occur frequently in thiophene derivatives.¹²

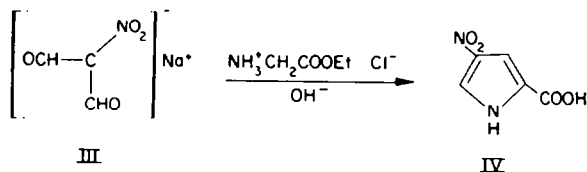
These spectral comparisons leave no doubt that 2- and 3- nitropyrroles are correctly described by the conventional formulae, (I, II).



I

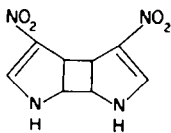


II



III

IV



V

EXPERIMENTAL

A cold solution of HNO_3 (5.8 g) in acetic anhydride (30 ml) was added dropwise over a period of $1\frac{1}{2}$ hr to a solution of pyrrole (5 g) in acetic anhydride (30 ml) cooled to -50° . The mixture was stirred at this temp for a further $1\frac{1}{2}$ hr and then allowed to stand without cooling for 1 hr. The mixture was poured over ice and the product extracted into ether (4×100 ml). The ethereal extract

¹² S. Gronowitz and R. A. Hoffman, *Arkiv för Kemi* 13, 279 (1958).

was washed with water and 10% Na_2CO_3 aq and dried. Evaporation of the ether left a black residue which was dissolved in dry ether and chromatographed on an alumina column. Elution with ether gave 2-nitropyrrole (4.63 g; 55%), m.p. 65–66.5° as pale yellow coloured needles from light petroleum (b.p. 100–120°). (Mol. wt. for 0.024 molar solution in benzene: Found: 121.0 Calc. for $\text{C}_4\text{H}_4\text{N}_2\text{O}_2$; 112). The gas liquid chromatogram contained only one band. The UV spectrum of 2-nitropyrrole showed bands λ_{max} 232 $\text{m}\mu$ ($\log \epsilon$ 3.46), 320 $\text{m}\mu$ (412) (hexane) and λ_{max} 231 $\text{m}\mu$ (3.61), 335 (4.23) (MeOH); the IR spectrum showed ν_{NH} 3430 cm^{-1} (CH_2Cl_2), ν_{NO_2} 1350, 1510 cm^{-1} (CH_2Cl_2). The solubility in water at 25° of 2-nitropyrrole is 19.5 gpl.

TABLE 1. NMR SPECTRA OF SOME MONO-SUBSTITUTED PYRROLES

Substituent	Chemical Shift ^a (ppm)								
	H ²	H ₃	H ₄	H ₅					
2-Nitro	—	713	629	705					
3-Nitro ^b	766	—	675	675					
2-Acetyl	—	689	625	709					
3-Acetyl	743	—	678	664					
Coupling Constants (c/s)									
	J ₂₄	J ₃₅	J ₃₄	J ₃₅	J ₄₅	J ₁₂	J ₁₃	J ₁₄	J ₁₅
2-Nitro	—	—	4.2	1.7	2.8	—	2.5	2.75	3.1
3-Nitro ^b	1.9	1.9	—	—	—	3.5	—	2.65	2.65
2-Acetyl	—	—	3.75	1.35	2.4	—	2.5	2.4	3.0
3-Acetyl	1.9	1.7	—	—	3.0	3.0	—	2.6	3.3

^a Spectra measured for CDCl_3 solutions at 100 Mcs using tetramethylsilane as reference.

^b Acetone added to solution in CDCl_3 .

When the nitration was carried out at 0° a less pure material, m.p. 52–55°, was obtained which after rechromatography showed m.p. 65–66° and was identical with that obtained previously. A mixture (10:1) of 2- and 3-nitropyrrole had m.p. 48–52° after crystallization from light petroleum.

Action of isoamyl nitrate on pyrrole. A mixture of pyrrole (10 g), isoamyl nitrate (28 g) and Na (4.8 g) in ether (80 ml) was kept at 25–30° for 3 days. The resultant dark coloured solution was treated with ice and unreacted pyrrole extracted into ether (100 ml). The addition of 20% AgNO_3 (100 ml) to the residual aqueous phase precipitated a Ag-salt which was collected, and washed until the washings were free of Ag. A suspension of the Ag-salt in water (200 ml) was treated with NaCl (100 g) giving a precipitate of AgCl and a red solution of the Na-salt. The free nitro compound was obtained by saturating the filtered solution with CO_2 and extraction into ether (150 ml). Evaporation of the ether left an oil which was dissolved in a 1:1 mixture of benzene and light petroleum and treated with charcoal. Removal of the solvents and recrystallization of the residue from light petroleum (b.p. 100–120°) gave nitropyrrole, (0.17 g, 1%), m.p. 63–64°, m.p. mixed with authentic 2-nitropyrrole, 63–64.5°; the compound was identical in all respects with 2-nitropyrrole.

Ethyl 4-nitropyrrole-2-carboxylate. A solution of glycine ethyl ester hydrochloride (4.4 g) and sodio-nitromalondialdehyde (5 g) in 65% MeOH (25 ml) was treated with 20% NaOH aq (75 ml). The solution was allowed to stand at 45° for 30 min when the ester (66%) m.p. 172.5–174° which separated as a crystalline solid was collected and crystallized from MeOH.

4-Nitropyrrole-2-carboxylic acid. A suspension of the ester (3 g) in 20% KOH aq (45 ml) was heated on a water bath for 5 hr. The resultant solution was cooled and neutralized with conc. HCl. Evaporation of an ether (215 ml) extract gave acid (2.3 g, 90%) m.p. 217–219° from water.

3-Nitropyrrole. A mixture of acid (1 g) and copper chromite (0.5 g) in quinoline (5 ml) was heated at 210–222° for 1 hr. Ether (50 ml) was added to the cooled mixture and the filtered solution was washed with 1:1 HCl (20 ml). Evaporation of the dried ethereal layer gave 3-nitropyrrole (0.376 g; 41%) m.p. 99–101° from light petroleum (b.p. 100–120°). (Mol. wt. for 0.025 molar solution in benzene: Found: 121.0 Calc. for $\text{C}_4\text{H}_4\text{N}_2\text{O}_2$; 112).

The gas liquid chromatogram contained only one band. The UV spectrum of 3-nitropyrrole showed bands λ_{max} 247 $\text{m}\mu$ (3.18), 289 $\text{m}\mu$ (2.99) (hexane), λ_{max} 268 $\text{m}\mu$ (3.86), 315 $\text{m}\mu$ (3.73); the IR spectrum showed ν_{NH} 3450 cm^{-1} , ν_{NO_2} 1500, 1360 cm^{-1} , (CH_2Cl_2).

The solubility of 3-nitropyrrole in water at 25° is 4.7 gpl. A solution of 3-nitropyrrole (50 mg) in water (250 ml) was allowed to stand at 0° for 3 days. Removal of the water on a rotary evaporator ($t < 20^\circ$) gave 3-nitropyrrole, m.p. 101–102°. Removal of the water from a similar hot solution gave similarly unchanged starting material m.p. 101–102°.

Gas-liquid chromatograms were obtained on a Perkin-Elmer F11 using a silicone column at 215° UV spectra were obtained with Unicam SP800 and IR spectra with a Perkin-Elmer 237 spectrometer. NMR spectra were measured on a Varian HA100 spectrometer.

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