The Nitration of some 1-Aryl(or benzyl)pyrroles

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Dedicated in memory of Professor N. E. Alexandrou of the University of Thessaloniki, Greece

Nitration of 1-arylpyrroles **1a-c** with acetyl nitrate, and 1-arylpyrroles, **1a-e** and 1-(2-ethoxycarbonylbenzyl)pyrrole **4** with trifluoroacetyl nitrate gave the corresponding 2-nitro isomers **2a-e** and **5**, and 3-nitro isomers **3a-e** and **6**. 3-Nitropyrroles **3d** and **3e** were further nitrated with a mixture of nitric and sulfuric acids to give compounds **10**, **11** and **12**, respectively. Under the same conditions 1-(2-ethoxycarbonylbenzyl)-3-nitropyrrole **6** gave derivative **13**.

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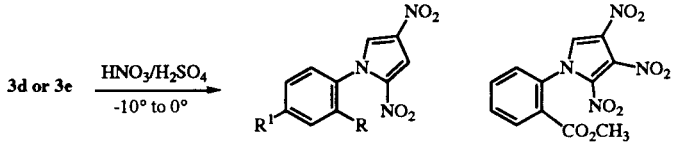
Nitropyrroles have been synthesized both as potential chemotherapeutic agents and as intermediates for further syntheses [1-5]. The nitration of 1-alkyl(or aryl)pyrroles requires the use of acetyl nitrate at temperatures below or near 0°. Under these conditions a mixture of 2- and 3-nitro isomers is obtained in ratios which depend on the size of the 1-substituent.

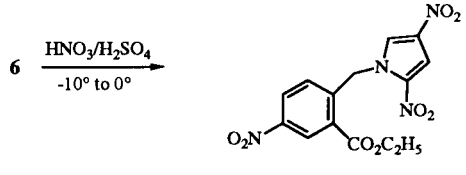
We have shown interest in the nitration of 1-aryl(or benzyl)pyrroles as a means of obtaining the 2-nitro derivatives for use as intermediates in the synthesis of novel tricycles. To this end we have reported the synthesis of tricycles **7**, **8**, and **9** by catalytic hydrogenation of 2-nitropyrroles **2d** and **5**, respectively. These reactions show that a consequence of reducing 2-nitropyrroles is concomitant saturation of the pyrrole ring [6]. Grehn observed a similar effect, but reported also that catalytic hydrogenation of a 2,4-dinitropyrrole resulted in reduction of only one nitro group [7].

In connection with these results we required 3-nitropyrroles **3d**, **3e** and **6**, in order to introduce a second nitro group in the pyrrole ring, and then study the behavior of the resulting 2,4-dinitro derivatives upon reduction. Our previous experience of nitrating pyrroles **1d**, **1e** and **4** with acetyl nitrate at -40 to -30° gave us good yields of the corresponding 2- and 3-nitro pyrroles **2d**, **3d**, **2c** and **3e**, **5** and **6** in ratios of approximately 1:2 [6].



10, R = CO_2CH_3, R^1 = NO_2
11, R = $NHCH_2CO_2C_2H_5$, R^1 = H

12



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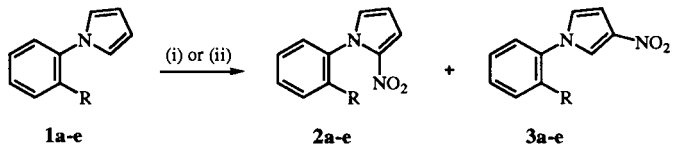
We now report the nitration of pyrroles **1a**, **1b** and **1c** with acetyl nitrate at -40 to -30° and pyrroles **1a-e** and **4** with trifluoroacetyl nitrate at -10 to 0°. Trifluoroacetyl nitrate is the reactive species in tetrabutylammonium nitrate-trifluoroacetic anhydride mixtures. This reagent has been known to effect some of the most selective nitrations of aromatic systems [8] but has not been used on pyrroles. In the above reactions, all 2- and 3-nitro derivatives were easily separated by flash chromatography. In Tables 1 and 2 the yields and ratios of the 2- and 3-nitro isomers resulting from nitrating pyrroles **1a-e** and **4** by the two methods are compared.

Although the nitrations of pyrroles **1a-e** and **4** with trifluoroacetyl nitrate occurred with practically no polymerization, the difference in the total yield between the two methods differs marginally (5-7%). The percentage of the 3-nitro isomer in the reactions with trifluoroacetyl nitrate has increased by 6-27%.

Dinitration has been carried out on 1-alkylpyrroles using acetyl nitrtate at 20° [9] and on 1-alkyl(or aryl)-3-nitropyrroles using a mixture of nitric and sulfuric acids at 0° [10]. By the first method 1-alkylpyrroles gave four dinitro isomers whereas 1-alkyl-3-nitropyrroles gave a mixture of two dinitro and two trinitro isomers. 1-(2-Nitrophenyl)-3-nitropyrrole upon nitration with sulfuric acid and nitric acid gave a mixture of 1-(2-nitrophenyl)-2,4-dinitropyrrole and 1-(2-nitro-phenyl)-3,4-dinitropyrrole in a ratio of 72:28 [10].

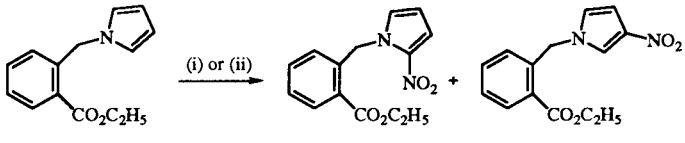
We now report the nitration of 3-nitropyrroles **3d**, **3e** and **6** with fuming nitric acid in concentrated sulfuric acid at -10 to 0°. Compound **3d** gave a mixture of 2,4-dinitropyrrole **10** and 2,3,4-trinitropyrrole **12** in a ratio of 4:1. On the other hand, compound **3e** afforded 2,4- dinitropyrrole **11**, were hydrolysis of the tosyl group had occurred, and compound **6** yielded 2,4-dinitropyrrole **13**. In compounds **10** and **13** nitration had also occurred in the phenyl ring. Nitration of the phenyl ring using similar reaction conditions has been reported for 1-phenylpyrrole which gave 1-(4-nitrophenyl)pyrrole in 25% yield as the only product [11].

Catalytic hydrogenation of compounds **10**, **11** and **13**



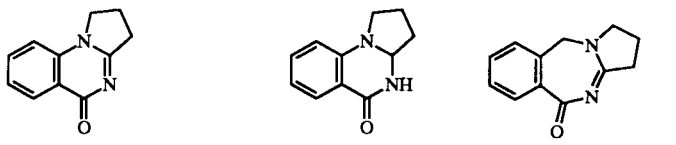
1a-e **2a-e** **3a-e**

a, R = H, **b**, R = NO_2, **c**, R = CN, **d**, R = CO_2CH_3, **e**, R = $NTsCH_2CO_2C_2H_5$



4 **5** **6**

(i) fuming HNO_3, $(CH_3CO)_2O$, -30° to 40°, (ii) *t*-Bu_4NNO_3, $(CF_3CO)_2O$, -10° to 0°



7 **8** **9**

gave intractable oils which appeared as several polar spots on thin layer chromatography. A gc-ms study of these mixtures did not help in identifying any products.

Table 1

Nitration of 1-Substituted Pyrroles **1a-e** and **4** with Acetyl Nitrate: Overall Yields and 2-Nitro/3- Nitro Ratios

Starting material	2-nitro isomer	3-nitro isomer	Total yield (%)	2-nitro/3-nitro ratio
1a	**2a**	**3a**	65	2:1
1b	**2b**	**3b**	57	1.5:1
1c	**2c**	**3c**	61	1.5:1
1d	**2d**	**3d**	89	1:2
1e	**2e**	**3e**	65	1:2
4	**5**	**6**	62	1:2

Table 2

Nitration of 1-Substituted Pyrroles **1a-e** and **4** with Trifluoroacetyl Nitrate: Overall Yields and 2-Nitro/3-Nitro Ratios

Starting material	2-nitro isomer	3-nitro isomer	Total yield (%)	2-nitro/3-nitro ratio
1a	**2a**	**3a**	71	1:2
1b	**2b**	**3b**	63	1:3
1c	**2c**	**3c**	68	1:3
1d	**2d**	**3d**	87	1:3
1e	**2e**	**3e**	70	1:4.5
4	**5**	**6**	67	1:2.5

EXPERIMENTAL

Melting points were measured with a Büchi 510 apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 257 spectrometer. Solids were taken as Nujol mulls and liquids as thin films between sodium chloride discs. The nmr spectra were measured at 360.1 MHz on a Brüker AM 360 spectrometer or at 400.1 MHz on a Brüker AMX 400 spectrometer using tetramethylsilane as the internal standard. Mass spectra were obtained with a JEOL JMS-AX 505W machine. Elemental analyses were performed by the School of Pharmacy, University of London, on a Carlo Erba 1106 elemental analyser. Solvents and reagents were used as received from the manufacturers except for acetic anhydride, which was freshly distilled, and, ethyl acetate and petroleum ether (bp 40-60°), which were purified according to methods described by Perrin *et al.* [12]. Silica gel Merck (230-400 mesh) was used throughout for purification by flash chromatography, and Fluka silica gel 60 F_{254} was used for thin layer chromatography.

1-Phenylpyrrole **1a**, 1-(2-nitrophenyl)pyrrole **1b**, 1-(2-cyanophenyl)pyrrole **1c**, 1-(2-methoxycarbonylphenyl)pyrrole **1d** and, ethyl *N*-[2'-[1'-(pyrrolyl)]phenyl]-*N*-toluene-4-sulfonylglycinate **1e** and 1-(2-ethoxycarbonylbenzyl)pyrrole **4** were prepared according to the literature methods [11], [13], [14], [15], [16] and [17], respectively.

General Procedure for the Nitration of Pyrroles **1a-c** with Fuming Nitric Acid in Acetic Anhydride (Acetyl Nitrate).

Fuming nitric acid (0.32 ml, 8 mmoles) was added dropwise to acetic anhydride (30 ml) at -10° while stirring. The resulting mixture was added dropwise to a stirred solution of appropriate pyrrole **1a, b** or **c** (5 mmoles) in acetic anhydride (30 ml) at -30 to -40°. The temperature was maintained at -30 to -40° for 1 hour, allowed to rise to 0° and then stirred at that temperature for a further 2 hours. The mixture was poured onto ice (180 g) and extracted with chloroform (3 x 50 ml). The combined organic layers were washed with brine (3 x 20 ml), dried over anhydrous sodium sulfate, and filtered. Chloroform was evaporated and the remaining acetic acid in the mixture removed by codistillation with toluene. The crude solid was purified by flash chromatography with ethyl acetate:petroleum ether (bp 40-60°) (1:4) as eluents. Evaporation of the solvents afforded 2-nitro-1-arylpyrroles **2a-c** and 3-nitro-1-arylpyrroles **3a-c**.

Pyrroles **2a-b** and **3a-b** were in all respects identical to authentic samples.

1-(2-Cyanophenyl)-2-nitropyrrole **2c**.

This compound crystallized from ethanol as pale yellow needles (28%), mp 123-124°; ir: ν 2220 cm^{-1} (CN), 1520 asym (NO_2) and 1350 sym (NO_2); pmr (deuteriochloroform): δ 6.10 (dd, J = 3.7 and 2.8 Hz, 4-H), 6.58 (dd, J = 2.8 and 1.9 Hz, 5-H), 7.03 (dd, J = 3.7 and 1.9 Hz, 3-H), 7.14 (dd, J = 7.35 and 1.9 Hz, 6'-H), 7.33 (td, J = 7.71 and 1.7 Hz, 5'-H), 7.41 (td, J = 7.68 and 1.7 Hz, 4'-H), 7.68 (dd, J = 7.68 and 1.8 Hz, 3'-H); ms: m/z 213 (M^+, 44), 167 (100), 140 (48), 102 (40), 75 (38).

Anal. Calcd. for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 61.95; H, 3.08; N, 20.00.

1-(2-Cyanophenyl)-3-nitropyrrole **3c**.

This compound crystallized from propan-2-ol as pale yellow needles (63%), mp 97-98°; ir: ν 2220 cm^{-1} (CN), 1525 asym (NO_2) and 1355 sym (NO_2); pmr (deuteriochloroform + drops of dimethyl sulphoxide-d_6): δ 6.71 (dd, J = 3.2 and 1.8 Hz, 4-H), 7.08 (dd, J = 3.2 and 2.5 Hz, 5-H), 7.21 (dd, J = 7.7 and 1.5 and Hz, 6'-H), 7.30 (td, J = 7.4 and 1.4 Hz, 4'-H), 7.45 (td, J = 7.4 and 1.7 Hz, 5'-H), 7.58 (dd, J = 7.3 and 1.4 Hz, 3'-H), 7.66 (dd, J = 2.5 and 1.8 Hz, 2-H); ms: m/z 213 (M^+, 45), 167 (100), 140

(30), 102 (38), 75 (25).

Anal. Calcd. for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 61.91; H, 3.04; N, 19.95.

General Procedure for the Nitration of Pyrroles **1a-e** and **4** with Tetrabutylammonium Nitrate in Trifluoroacetic Anhydride (Trifluoroacetyl Nitrate).

To a mixture of trifluoroacetic anhydride (1.4 ml, 10 mmoles) and tetrabutylammonium nitrate (3 g, 10 mmoles) in dichloromethane (20 ml) at -10°, was added dropwise a solution of the appropriate pyrrole **1a-e** or **4** (5 mmoles) in dichloromethane (20 ml). The reaction mixture was stirred at 0° for 8 hours and then at room temperature for 4 hours. The solvent was evaporated off and the products purified by flash chromatography. For products **2a-e** and **3a-e** ethyl acetate:petroleum ether (40-60°) (1:4) was used as eluent, whereas for **5** and **6** ethyl acetate:petroleum ether (40-60°) (1:8) was used as eluent.

Pyrroles **2a** and **3a**, **2b** and **3b**, **2d-e**, **3d-e**, **5** and **6**, were in all respects identical to authentic samples [11], [10] and [6], respectively. Pyrroles **2c** and **3c** were identical to the corresponding samples from the above experiments.

General Procedure for the Nitration of Pyrroles **3d**, **3e** and **6** with Nitric Acid and Sulfuric Acid.

To stirred mixture of the appropriate 3-nitropyrrole **3d**, **3e** or **6** (5 mmoles) in 95-98% sulfuric acid (5 ml) at -10° was added dropwise fuming nitric acid (0.4 ml, 10 mmoles). The reaction mixture was stirred at 0° for 5 hours and at room temperature for 3 hours before pouring into ice-water (50 ml). The resulting mixture was extracted with chloroform (3 x 20 ml), washed with saturated aqueous sodium bicarbonate (3 x 20 ml), dried over anhydrous sodium sulfate, filtered, and the solvent evaporated to afford a residue. The products **10** and **12**, **11** or **13** were purified by flash chromatography. Compounds **10** and **12** were separated using ethyl acetate:petroleum ether (40-60°) (1:3) as eluent. For **11**, ethyl acetate:petroleum ether (40-60°) (1:4) was used as eluent, whereas for **13**, ethyl acetate:petroleum ether (40-60°) (1:8) was used as eluent.

1-(2-Methoxycarbonyl-4-nitrophenyl)-2,4-dinitropyrrole **10**.

This compound was obtained as pale yellow needles (propan-2-ol), (53%), mp 151-152°; ir: ν (1735 cm^{-1} (C=O), 1525 (br) (unsym NO_2) and 1360 (br) (sym NO_2); pmr (deuteriochloroform): δ 3.92 (s, 3H, Me), 7.26 (d, J = 2.3 Hz, 3-H), 7.61 (d, J = 2.3 Hz, 5-H), 7.75 (dd, J = 8.7 and 0.9 Hz, 6'-H), 8.66 (dd, J = 8.7 and 2.5 Hz, 5'-H), 9.07 (dd, J = 2.5 and 0.8 Hz, 3'-H); cmr: δ 53.9 (CH_3), 122.8 (C-3), 127.4 (C-6'), 128.2 (C-5), 128.5 (C-4), 128.8 (C-2), 129.9 (C-5'), 131.6 (C-3'), 134.1 (C-2'), 140.2 (C-1'), 149.0 (C-4'), 161.9 (C=O); ms: m/z 335 (M^+-1, 5.3), 290 (100), 259 (4), 157 (4.4), 77 (6).

Anal. Calcd. for $C_{12}H_8N_4O_8$: C, 42.87; H, 2.40; N, 16.67. Found: C, 42.91; H, 2.53; N, 16.53.

Ethyl *N*-[2'-[1'-(2,4-Dinitropyrrolyl)]phenyl]glycinate **11**.

This compound was obtained as yellow amorphous solid, (75%), mp 18-20°; ir: ν 3210 cm^{-1} (NH), 1750 (C=O), 1520 (br) (unsym NO_2) and 1355 (br) (sym NO_2); pmr (deuteriochloroform): δ 1.27 (t, 3H, Me), 3.89 (t, 2H, NCH_2), 4.01 (s, br, 1H, NH, Deuterium oxide-exchangeable), 4.20 (q, 2H, CH_2), 6.72 (dd, J = 8.3 and 1.0 Hz, 3'-H), 6.86 (td, J = 7.4 and 1.2 Hz, 5'-H), 7.12 (dd, J = 7.8 and 1.5 Hz, 6'-H), 7.41 (td, J = 7.4 and 1.5 Hz, 4'-H), 7.68 (d, J = 2.3 Hz, 3-H), 7.81 (d, J = 2.2 Hz, 5-H); cmr δ 14.1 (CH_3), 45.2 (NCH_2), 61.8 (OCH_2), 107.4 (C-3), 112.6 (C-5), 118.3 (C-4), 123.6 (C-2), 126.8 (C-5'), 127.3 (C-6'), 131.7 (C-3'), 135.7 (C-4'), 136.8 (C-1'), 142.8 (C-2'), 170.3 (C=O); ms: m/z 334 (M^+, 38), 288 (47), 214 (100), 168 (36).

Anal. Calcd. for $C_{14}H_{14}N_4O_6$: C, 50.30; H, 4.22; N, 16.76. Found: C, 50.40; H, 4.33; N, 16.58.

1-(2-Methoxycarbonylphenyl)-2,3,4-trinitropyrrole **12**.

This compound was obtained as pale yellow microcrystals (propan-2-ol), (13%), mp 149-150°; ir: ν 1730 cm^{-1} (C=O), 1520 (br) (unsym NO_2) and 1355 (br) (sym NO_2); pmr (deuteriochloroform): δ 3.83 (s, 3H, Me), 7.58 (dd, J = 6.6 and 0.7 Hz, 6'-H), 7.76 (td, J = 7.6 and 1.2 Hz, 4'-H), 7.83 (td, J = 7.8 and 1.5 Hz, 5'-H), 7.95 (s, 1H, 5'-H), 8.25 (dd, J = 7.7 and 1.5 Hz, 3'-H); cmr: δ 52.4 (CH_3), 123.7 (C-4), 123.8 (C-3), 125.8 (C-2), 126.1 (C-5'), 126.1 (C-6'), 127.9 (C-4'), 130.9 (C-3'), 131.5 (C-2'), 133.8 (C-5), 135.0 (C-1'), 163.3 (C=O); ms: m/z 336 (M^+, 6.2), 290 (100).

Anal. Calcd. for $C_{12}H_8N_4O_8$: C, 42.87; H, 2.40; N, 16.67. Found: C, 42.94; H, 2.48; N, 16.59.

1-(2-Ethoxycarbonyl-4-nitrobenzyl)-2,4-dinitropyrrole **13**.

This compound was obtained as colorless needles (ethanol), (58%), mp 172-173°; ir: ν 1725 cm^{-1} (C=O), 1540 (br) (unsym NO_2) and 1350 (br) (sym NO_2); pmr (dimethyl sulfoxide-d_6): δ 1.42 (t, 3H, Me), 4.45 (q, 2H, CH_2), 6.15 (s, 2H, CH_2), 7.05 (d, J = 8.7 Hz, 6'-H), 7.93 (d, J = 2.3 Hz, 3-H), 8.33 (dd, J = 8.7 and 2.5 Hz, 5'-H), 8.58 (d, J = 2.3 Hz, 5-H), 8.72 (d, J = 2.5 Hz, 3'-H); cmr δ 13.9 (CH_3), 52.5 (OCH_2), 62.0 (CH_2), 108.6 (C-3), 125.1 (C-5), 127.3 (C-4), 127.9 (C-2), 128.8 (C-1'), 129.2 (C-6'), 133.9 (C-5'), 136.5 (C-3'), 144.5 (C-2'), 146.6 (C-4'), 164.4 (C=O); ms: m/z 365 (M^++1, 4), 347 (100), 318 (17), 77 (6).

Anal. Calcd. for $C_{14}H_{12}N_4O_8$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.04; H, 3.41; N, 15.59.

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