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Organic and Bio-organic Chemistry

Polycondensed Nitrogen Heterocycles. Part 8.[1a] Pyrrolo[3,2-*b*]indole

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The reduction of the nitro-derivatives (4a—c) with iron–acetic acid leads to the pyrrolo[3,2-*b*]indoles (7a—c). This unusual indolization, in which displacement of the heterocycle amino-group occurs, is regarded as a nucleophilic attack by the 2-aminophenyl group on the pyrrole ring, and is an interesting example of intramolecular nucleophilic substitution in the pyrrole series.

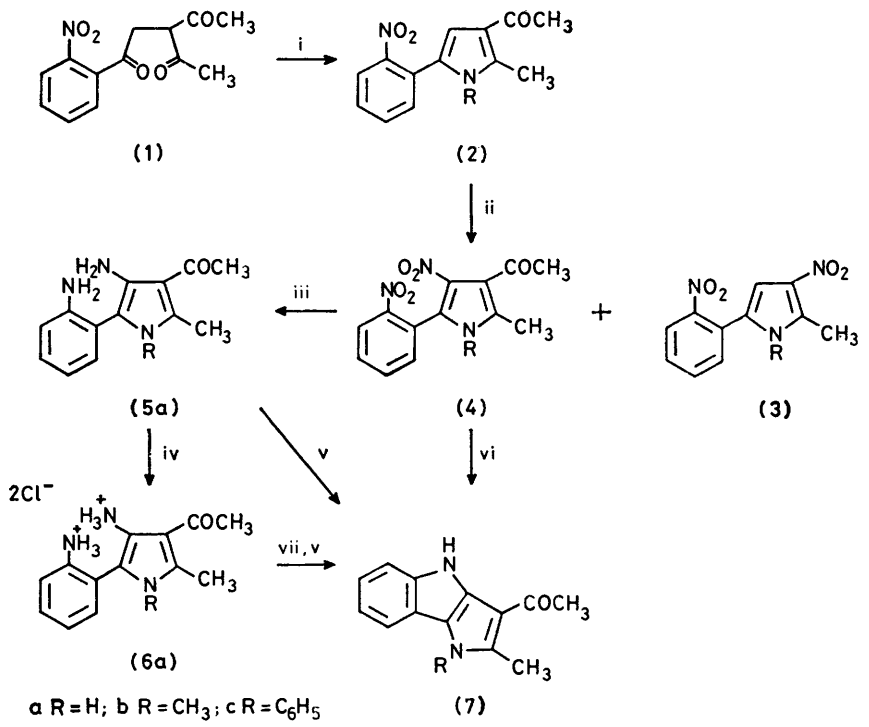
As part of our studies on polycondensed heterocycles as potentially active pharmaceutical agents,[1] we synthesized the diamino-derivatives of type (5) as intermediates in the formation of new polycondensed systems.

For this purpose, 2-nitrophenacyl bromide was treated with the sodium salt of acetylacetone to give the diketone (1). Treatment of (1) with the appropriate amines in refluxing acetic acid produced the corresponding substituted pyrroles (2a—c), which were nitrated by using nitric acid–acetic anhydride mixture in nitromethane at −15 °C according to the procedure described previously.[1b] This reaction gave the desired 4-nitro-derivatives (4a—c) in low yield (7—11%). In these experiments, products (3a—c) were also isolated. The identification of these compounds as 1-R-2-methyl-3-nitro-5-(2-nitrophenyl)pyrroles (R = H, Me, or Ph) is based on analytical results and i.r. (no carbonyl stretching vibration) and n.m.r. spectra (no coupling between pyrrole CH and CH_3 protons).[2] The nitration of (2a—c) with potassium nitrate in concentrated sulphuric acid at 0 °C was considered. This reaction was clean and gave the desired 4-nitro-derivatives (4a—c) in appreciable yield.

Catalytic reduction of the nitro-derivatives (4a—c) over 10% Pd–C in methanol gave the amino-derivatives (5) as intractable oils which generally decompose into resinous gums. The only amino-derivative which it was possible to isolate was (5a) in 30% yield. A different approach to amino-derivatives of type (5) was then undertaken using iron–acetic acid as the reducing agent. Surprisingly in this case the pyrrolo[3,2-*b*]indoles (7a—c) were obtained directly. The structures of the pyrrolo-[3,2-*b*]indoles were assigned on the basis of elemental analyses, molecular weights, and i.r. and n.m.r. data.

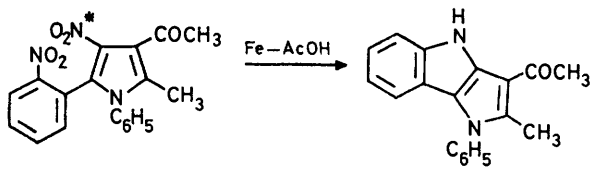
The pyrrole nucleus undergoes nucleophilic substitution by strong nucleophiles when it bears electron-withdrawing substituents and good leaving groups (*e.g.* the nitro-group).[3] Thus we thought that indolization could be achieved by preferential reduction of one of two nitro-groups followed by nucleophilic attack of the amino-group on the cationic substrate generated by the electron-withdrawing ability of the remaining nitro-group which is eventually displaced. However, under our conditions of reduction, it was unlikely that only one nitro-group should be reduced.

In order to clarify this unusual indolization, the diamino-derivative (5a) was heated at 70 °C in acetic acid; the pyrrolo[3,2-*b*]indole (7a) was again obtained in good yield. In contrast, when (5a) was refluxed in ethanolic hydrogen chloride, only the dihydrochloride (6a) was obtained. These facts suggested that the loss of one nitrogen atom, indispensable to closure of the indole ring, might take place by preferential protonation of one of the two amino-groups of (5a), followed by the nucleophilic attack by the remaining amino-group on the cationic substrate generated by the electron-withdrawing ability of the ammonium group which is displaced. Nevertheless there was no evidence to decide which of the two amino-groups in (5) is displaced and which contributes to the ring closure. As the electron density of aminopyrrole is higher than that of aniline, a weak acid such as acetic acid should protonate essentially the



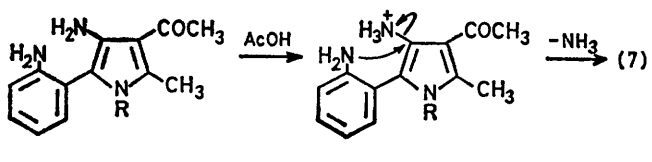
SCHEME *Reagents:* i, RNH_2; ii, HNO_3; iii, H_2-Pd; iv, HCl; v, AcOH; vi, Fe–AcOH; vii, pH *ca.* 7

pyrrole system and hence the aniline group should be responsible for the nucleophilic attack.



* = ^{15}N

To verify this supposition, (2c) was nitrated in concentrated sulphuric acid with isotopically labelled potassium nitrate. The labelled 4-nitro-derivative (4c) obtained on reduction with iron–acetic acid at 70 °C afforded (7c) and gave no trace of labelled pyrroloindole. This indicates that ring closure may occur by nucleophilic attack by the aniline amino-group on the 4-position of the



pyrrole ring, in which the amino-group was preferentially protonated and hence displaced.

This indolization represents the displacement of an amino group from a pyrrole substrate, and can be regarded as intramolecular nucleophilic substitution in the pyrrole series.

EXPERIMENTAL

All m.p.s were taken on a Buchi–Tottoli capillary apparatus and are uncorrected. I.r. spectra were determined for Nujol mulls with a Perkin-Elmer Infracord 137 spectrophotometer. N.m.r. spectra were obtained with a JEOL C-60 spectrometer (tetramethylsilane as internal reference). Mass spectra were run on a JEOL JMS-01 SG-2 double-focusing mass spectrometer operating with an electron-beam energy of 75 eV and 10 kW accelerating voltage. Exact measurements were performed at 20 000 resolving power and carried out to an accuracy of ±10 p.p.m.

General Method for the Preparation of Pyrroles (2a—c). According to the procedure described [1a] for (2a), to a solution of (1) (10 mmol) in acetic acid (40 ml), the appropriate amine [methylamine for (2b) and aniline for (2c)] (10 mmol) was added. The mixture was heated under reflux for 3 h. After cooling, the resultant solution was poured onto crushed ice. The solid precipitate was filtered off, air-dried, and recrystallized. *1,2-Dimethyl-3-acetyl-5-(2-nitrophenyl)-pyrrole* (2b) (75%) had m.p. 116—117 °C (orange needles from ethanol) (Found: C, 65.2; H, 5.5; N, 10.8%; M^+, 258.101 5. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.45; N, 10.85%; *M*, 258.100 4); $\nu_{max.}$ 1 650 (CO) 1 345 cm^{-1} (NO_2); δ ($CDCl_3$) 2.35, 2.60, and 3.25 (9 H, 3 s, CH_3), 6.37 (1 H, s, CH), and 7.25—8.15 (4 H, m, C_6H_4). *1-Phenyl-2-methyl-3-acetyl-5-(2-nitrophenyl)pyrrole* (2c) (80%) had m.p. 138 °C (yellow prisms from ethanol) (Found: C, 71.3; H, 5.0; N, 8.8%; M^+, 320.119 5. $C_{19}H_{16}N_2O_3$ requires C, 71.25;

H, 5.05; N, 8.75%; *M*, 320.116 0); $\nu_{max.}$ 1 660 (CO) and 1 350 cm^{-1} (NO_2); δ ($CDCl_3$) 2.35 and 2.38 (6 H, 2s, CH_3), 6.52 (1 H, s, CH), and 6.82—7.75 (9 H, m, C_6H_5 and C_6H_4).

Nitration of Pyrroles (2a—c).—(a) *With nitric acid–acetic anhydride in nitromethane.* The reaction was complex and several products could be detected by t.l.c. The oils obtained were essentially a mixture of compounds (3a—c) and (4a—c) which were separated by a dry column of silica gel (200 g) deactivated with water (15%). The first 800—1 000 ml of eluant gave compounds (3a—c). *2-Methyl-3-nitro-5-(2-nitrophenyl)pyrrole* (3a) was eluted with light petroleum (b.p. 50—70 °C)–ethyl acetate (7 : 3) (25%), m.p. 203 °C, orange needles from ethanol (Found: C, 53.5; H, 3.7; N, 17.1%; M^+, 247.060 6. $C_{11}H_9N_3O_4$ requires C, 53.45; H, 3.65; N, 17.0%; *M*, 247.059 3); $\nu_{max.}$ 3 350 cm^{-1} (NH); δ [$(CD_3)_2SO$] 2.55 (3 H, s, CH_3), 6.75 (1 H, d, CH, *J* 1.5 Hz, s on exchange with deuterium oxide), 7.40—8.20 (4 H, m, C_6H_4), and 11.30br (1 H, exchangeable NH). *1,2-Dimethyl-3-nitro-5-(2-nitrophenyl)pyrrole* (3b) was eluted with light petroleum (b.p. 50—70 °C)–ethyl acetate (8 : 2) (20%), m.p. 145 °C, yellow prisms from ethanol (Found: C, 55.2; H, 4.25; N, 16.0%; M^+, 261.077 3. $C_{12}H_{11}N_3O_4$ requires C, 55.15; H, 4.25; N, 16.1%; *M*, 261.074 9), δ ($CDCl_3$) 2.70 and 3.23 (6 H, 2 s, CH_3), 6.70 (1 H, s, CH), and 7.20—8.20 (4 H, m, C_6H_4). *1-Phenyl-2-methyl-3-nitro-5-(2-nitrophenyl)-pyrrole* (3c) was eluted with light petroleum (b.p. 50—70 °C)–ethyl acetate (8 : 2) (25%), m.p. 184 °C, yellow prisms from ethanol (Found: C, 63.1; H, 4.05; N, 13.05%; M^+, 323.088 7. $C_{17}H_{13}N_3O_4$ requires C, 63.15; H, 4.05; N, 13.0%; *M*, 323.090 6); δ ($CDCl_3$) 2.49 (3 H, s, CH_3), 6.89 (1 H, s, CH), and 7.05—8.00 (9 H, m, C_6H_5 and C_6H_4).

Further elution (1 200—1 400 ml) gave compounds (4a—c). *2-Methyl-3-acetyl-4-nitro-5-(2-nitrophenyl)pyrrole* (4a) was eluted with light petroleum (b.p. 50—70 °C)–ethyl acetate (7 : 3) (7%), m.p. 190 °C, yellow prisms from benzene (Found: C, 54.0; H, 3.9; N, 14.45%; M^+, 289.070 3. $C_{13}H_{11}N_3O_5$ requires C, 54.0; H, 3.85; N, 14.55; *M*, 289.069 9); $\nu_{max.}$ 3 250 (NH) and 1 645 cm^{-1} (CO); δ [$(CD_3)_2SO$] 2.24 and 2.30 (6 H, 2 s, CH_3), 7.20—8.50 (4 H, m, C_6H_4), and 11.90br (1 H, exchangeable, NH). *1,2-Dimethyl-3-acetyl-4-nitro-5-(2-nitrophenyl)pyrrole* (4b) was eluted with light petroleum (b.p. 50—70 °C)–ethyl acetate (8 : 2) (10%), m.p. 155 °C, yellow prisms from ethanol (Found: C, 55.5; H, 4.3; N, 13.9%; M^+, 303.087 8. $C_{14}H_{13}N_3O_5$ requires C, 55.45; H, 4.3; N, 13.85%; *M*, 303.085 5); $\nu_{max.}$ 1 670 cm^{-1} (CO); δ ($CDCl_3$) 2.35, 2.45, and 3.30 (9 H, 3 s, CH_3) and 7.30—8.30 (4 H, m, C_6H_4). *1-Phenyl-2-methyl-3-acetyl-4-nitro-5-(2-nitrophenyl)pyrrole* (4c) was eluted with light petroleum (b.p. 50—70 °C)–ethyl acetate (8 : 2) (11%), m.p. 177 °C, yellow prisms from ethanol (Found: C, 62.5; H, 4.1; N, 11.55%; M^+, 365.106 3. $C_{19}H_{15}N_3O_5$ requires C, 62.45; H, 4.15; N, 11.5%; *M*, 365.101 2); $\nu_{max.}$ 1 675 cm^{-1} (CO); δ ($CDCl_3$) 2.15 and 2.50 (6 H, 2 s, CH_3) and 7.00—8.20 (9 H, m, C_6H_5 and C_6H_4).

(b) *With potassium nitrate in sulphuric acid.* A solution of KNO_3 (16 mmol) in concentrated sulphuric acid (5 ml) was added dropwise to a cooled (−5 to 0 °C) and stirred solution of (2a—c) (15 mmol) in concentrated sulphuric acid (8 ml). The resulting mixture was stirred at 0 °C for 0.5 h and then set aside to warm to room temperature over 3 h. The mixture was poured onto crushed ice and the precipitate filtered off, dried, and purified by elution through a dry column of silica gel (200 g) deactivated with water (15%). The yield of (4a) was 40%, of (4b) 40%, and of (4c) 45%. According to this procedure, labelled (4c) was obtained using labelled (99.1% ^{15}N) potassium nitrate.

2-Methyl-3-acetyl-4-amino-5-(2-aminophenyl)pyrrole (5a). —Compound (4a) was reduced on 10% Pd–C in methanol in a Parr apparatus at 45 lb in^{-2} for 8 h at room temperature. The catalyst was filtered off and the solvent evaporated under reduced pressure. The brown oil obtained was crystallized (30%), m.p. 252—254 °C, brown *needles* from ethanol (Found: C, 68.2; H, 6.6; N, 18.4%; M^+, 229.122 1. $C_{13}H_{15}N_3O$ requires C, 68.1; H, 6.6; N, 18.35%; *M*, 229.121 5); $\nu_{max.}$ 3 400—3 060 (2 × NH_2 and NH) and 1 620 cm^{-1} (CO); δ [$(CD_3)_2SO$] 2.27 and 2.42 (6 H, 2 s, CH_3), 4.77 and 4.90 (4 H, 2 s, exchangeable NH_2), 6.50—7.17 (4 H, m, C_6H_4), and 10.45 (1 H, s, exchangeable NH).

2-Methyl-3-acetyl-4-amino-5-(2-aminophenyl)pyrrole dihydrochloride (6a) had m.p. 320 °C (from absolute ethanol–diethyl ether) (Found: C, 51.7; H, 5.6; N, 13.8%. $C_{13}H_{17}Cl_2N_3O$ requires C, 51.65; H, 5.65; N, 13.9%).

General Method for the Preparation of 1-R-2-Methyl-3-acetylpyrrolo[3,2-b]*indoles* (7a—c).—A solution of (4a—c) (4 mmol) in acetic acid (50 ml) was heated at 70 °C, when iron powder (1.2 g) was added over 1 h. After the addition was complete, the mixture was kept at 70 °C for 12 h, then poured onto crushed ice. The precipitate was recrystallised. *2-Methyl-3-acetylpyrrolo*[3,2-b]*indole* (7a) (55%) was purified on a dry column of silica gel (100 g) deactivated with water (15%) by elution with light petroleum (b.p. 50—70 °C)–ethyl acetate (1 : 1), m.p. 249 °C, needles from benzene (Found: C, 73.6; H, 5.75; N, 13.25%; M^+, 212.093 1. $C_{13}H_{12}N_2O$ requires C, 73.55; H, 5.7; N, 13.2%; *M*, 212.095 0); $\nu_{max.}$ 3 410 and 3 300 (each NH) and 1 625 cm^{-1} (CO); $\lambda_{max.}$ (ethanol) 205 (ε 9 310), 246 (42 400), and 286 (24 300) nm; δ [$(CD_3)_2SO$] 2.41 and 2.56 (6 H, 2 s, CH_3), 6.76—7.47 (4 H, m, C_6H_4), and 10.30 and 11.30 (2 H, 2 s, exchangeable NH). Compound (7a) was also obtained by heating overnight at 70 °C a solution of (5a) or a neutralized (Na_2CO_3), aqueous solution of (6a) in acetic acid. The mixture was poured onto crushed ice and the precipitate purified as described above. *1,2-Dimethyl-3-acetylpyrrolo*-[3,2-b]*indole* (7b) (65%) had m.p. 250 °C, brown plates from ethanol (Found: C, 74.3; H, 6.3; N, 12.4%; M^+, 226.110 0. $C_{14}H_{14}N_2O$ requires C, 74.3; H, 6.25; N, 12.4; *M*, 226.110 6); $\nu_{max.}$ 3 300 (NH) and 1 600 cm^{-1} (CO); $\lambda_{max.}$ (ethanol) 204 (ε 11 280), 247 (44 200), and 287 (27 440) nm; δ [$(CD_3)_2SO$], 2.45, 2.60, and 3.80 (9 H, 3 s, CH_3), 6.80—7.80 (4 H, m, C_6H_4), and 10.65 (1 H, s, exchangeable NH). *1-Phenyl-2-methyl-3-acetylpyrrolo*[3,2-b]*indole* (7c) (51%) had m.p. 213 °C, needles from ethanol (Found: C, 79.2; H 5.6; N, 9.7%; M^+, 288.127 0. $C_{19}H_{16}N_2O$ requires C, 79.15; H, 5.6; N, 9.7%; *M*, 288.126 3); $\nu_{max.}$ 3 280 (NH) and 1 630 cm^{-1} (CO); $\lambda_{max.}$ (ethanol) 204 (ε 21 380), 247 (41 780), and 290 (25 750) nm; δ [$(CD_3)_2SO$] 2.50 and 2.52 (6 H, 2 s, CH_3), 6.72—7.60 (9 H, m, C_6H_5 and C_6H_4), and 10.78 (1 H, s, exchangeable NH).

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