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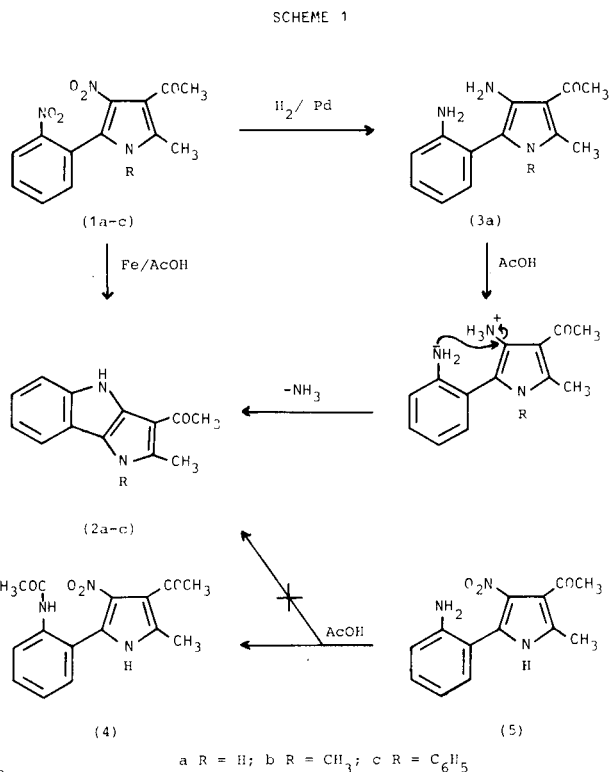
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An intramolecular nucleophilic substitution in the pyrrole series has been generalized. The behaviour of nitro, chlorine, bromine and iodine as leaving groups towards the nucleophilic amino group was observed. An acid catalyzed mechanism has been proposed.

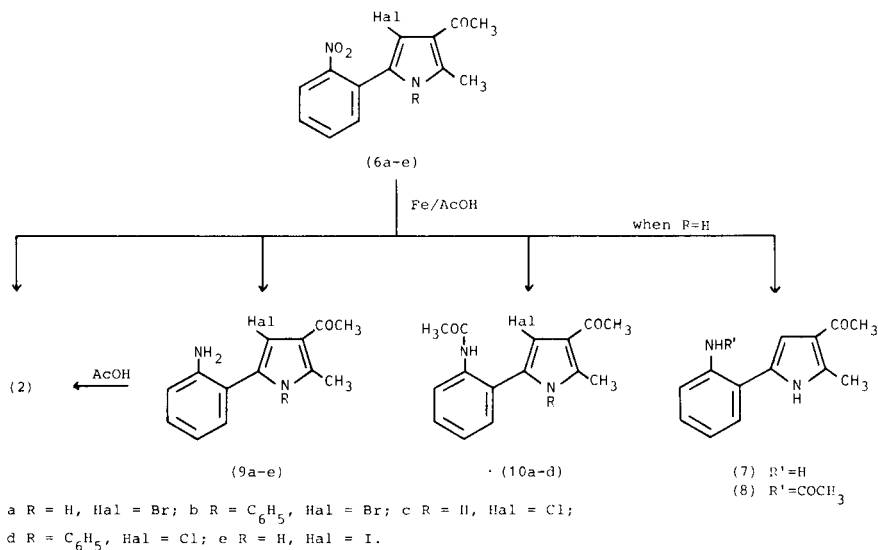
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We have recently described the formation of pyrrolo[3,2-*b*]indoles **2a-c** by reduction, with iron-acetic acid at 70°, of the nitro derivatives **1a-c** [2]. This unusual indolization was considered to involve the amino groups formed during the reaction. Protonation preferentially takes place on the pyrrolyl amino group and the cationic substrate, generated by the electron withdrawing ability of the ammonium cation, undergoes nucleophilic attack by the non-protonated anilino group. Subsequent displacement of the ammonium group affords the pyrroloindoles **2** (Scheme 1).

This indolization could therefore be regarded as an intramolecular nucleophilic substitution in the pyrrole series and to represent the first example of displacement of an amino group from the pyrrole substrate. In fact most nucleophilic substitutions in the pyrrole series have involved the displacement of a nitro group in activated pyrroles [3], and our novel results prompted us to investigate further this pattern of nucleophilic substitution in the pyrrole series. Hence, we have attempted to generalize this kind of indolization by varying the leaving group and/or the nucleophile. In this paper the behaviour of nitro, bromine,



SCHEME 2



chlorine and iodine as leaving groups towards the nucleophilic anilino group is reported. For this purpose the nitropyrrole **5** was prepared as described in the experimental and was kept in acetic acid at 70° overnight, as described by us previously [2]. The reaction did not afford the pyrroloindole **2**, but unreacted starting material was found together with traces of compound **4**.

The indolization was not observed even when the nitro derivative **5** was refluxed for eight hours in the same medium. In this case only the compound **4** was isolated in high yield (70%).

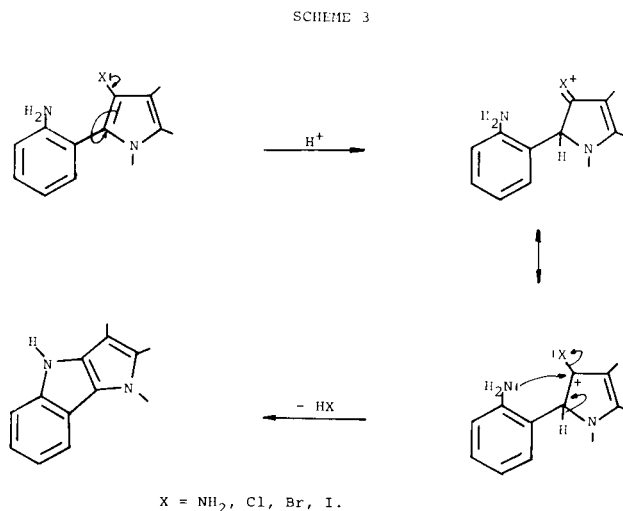
The halo compounds **6a-e** were prepared using *N*-halo-succinimide in dimethylformamide, according to the procedure described previously [4], and their reduction with iron-acetic acid at 70° afforded a mixture of several products (Scheme 2).

In the case of *N*-unsubstituted halopyrroles, the reduction did not give any prevalent product, but the indole **2a** and the compounds **7**, **8**, **9** and **10** were isolated in comparable yields. The reduction of *N*-substituted halopyrroles chiefly afforded the amino derivatives **9** (65% yield) and compounds **10** (15-20% yield), while the pyrroloindole **2c** was obtained in only 6-12% yield.

Therefore, the reduction of halo derivatives produced indolization in lower yields than those (*ca.* 60%) observed in the case of the displacement of the amino group. Only when the amino derivatives **9** were refluxed in acetic acid for 90 minutes were compounds **2** obtained in higher yield (60-78%).

Because of the low yields of pyrroloindole **2** by displacement of halogen at 70°, and the failure of the indolization in the case of the nitro derivatives **5**, the earlier mechanism proposed for the nucleophilic displacement of the amino group must be revised. In fact, if the factor determining the nucleophilic attack was the partial positive charge generated on the reaction site, it is to be expected that the yields of pyrroloindoles would have been proportional to the electron-withdrawing power of the leaving groups. We actually found that when the ammonium group was displaced the indole was obtained in higher yield than that observed when the leaving group was halogen, whereas the presence of the nitro group did not permit nucleophilic attack by the anilino group in spite of its considerable electron-withdrawing power. These experimental data suggest that the reaction goes through initial protonation of the 2-position of the pyrrole, assisted by the electronic effects of substituents in the 3-position. The reactivity order observed is thus justified by the electronic effects that the substituents, which in a second step become leaving groups, exert on the 2-position of the heterocycle (Scheme 3). We recognize that doubts can arise when protonation at the 2-position of the ring of the 3-aminopyrroles is considered. Nevertheless, such protonation seems reasonable by analogy with protonation of

2-aminopyrroles, which occurs at the 5-position of the ring [5].



Even if the behaviour of 3-aminopyrroles were different from that of 2-amino derivatives and their protonation at nitrogen were preferred, electrophilic attack at the ring could always take place and, even if to a small extent, produce the species which undergoes the nucleophilic displacement reaction.

The ¹³C nmr studies indicate a change in the electron density on the ring carbon atoms which is compatible with a change in the basicity of the pyrrole ring resulting from the influence of the substituent in the 3-position [6].

The necessity of acid catalysis was confirmed by the observation that compounds **9b,d** gave only unreacted starting material when refluxed for a long time in 2-propanol or in a dipolar aprotic solvent like DMF.

In conclusion, our findings seem to demonstrate that the indolization can be regarded as an acid-catalyzed nucleophilic substitution reaction in which the protonation of the pyrrole ring is the key step in the reaction pathway.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary apparatus and are uncorrected. The ir spectra were determined for Nujol mulls with a Perkin-Elmer Infracord 299 spectrophotometer. The nmr spectra were obtained with a Varian FT 80 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 kV accelerating voltage. Exact mass measurement were performed at 20,000 resolving power and carried out to an accuracy of ± 10 ppm. The glc analyses were carried out using a Varian 3700 gas chromatograph equipped with a hydrogen flame ionization detector and fitted with a 2m stainless steel column (1/8" o.d.) packed with 5% OV-101 on Chromosorb G-HP (100-120 mesh). The column was maintained at approximately 220°, the flow of the carrier gas (nitrogen) was 30 ml min⁻¹. The components of the analyzed mixture were identified by comparing their retention time with those of authentic samples. The chromatography was performed on dry column of silica gel deactivated with water (15%).

Preparation of 3-Acetyl-5-(2-aminophenyl)-2-methyl-4-nitropyrrole (5).

3-Acetyl-5-(2-aminophenyl)-2-methylpyrrole (7) [7] (10 mmoles) in acetic anhydride was stirred at room temperature for 3 hours. The solution was poured onto crushed ice and the solid was collected, air dried and recrystallized to give 3-acetyl-5-(2-*N*-acetylaminophenyl)-2-methylpyrrole (8), (yield 95%), mp 202° (white needles from ethanol); ir: 3250 and 3170 (NH), 1670 and 1620 (CO) cm^{-1} ; nmr (DMSO- d_6): δ 2.05, 2.35 and 2.51 (9H, 3s, CH_3), 6.76 (1H, d, CH, s on exchange with deuterium oxide), 7.18-7.61 (4H, m, C_6H_4), 9.26 and 11.49 (2H, 2 broad, exchangeable NH); ms: $M^+ = 256.097$, $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_2$ requires $M^+ = 256.121$.

Anal. Calcd. for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.10; H, 6.40; N, 11.02.

The nitration of 8 was carried out using a nitric acid-acetic anhydride mixture in nitromethane at -15° according to the procedure described previously [8].

3-Acetyl-5-(2-*N*-acetylaminophenyl)-2-methyl-4-nitropyrrole (4).

This compound was obtained in a yield of 50%, mp 232° (yellow prisms from ethanol); ir: 3240 and 3140 (NH), 1670 and 1640 (CO) cm^{-1} ; nmr (DMSO- d_6): δ 1.90, 2.32 and 2.35 (9H, 3s, CH_3), 7.36-7.63 (4H, m, C_6H_4), 9.37 and 12.30 (2H, 2 broad, exchangeable NH); ms: $M^+ = 301.121$, $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_4$ requires $M^+ = 301.106$.

Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_4$: C, 59.79; H, 5.02; N, 13.95. Found: C, 59.61; H, 5.23; N, 13.81.

To a solution of compound 4 (10 mmoles) in the minimum volume of ethanol, was added aqueous potassium hydroxide (10%, 100 ml) and the solution was refluxed for 2 hours. The solution was diluted with water, neutralized with hydrochloric acid (1*N*) and extracted with diethyl ether (3 \times 100 ml).

The extracts were dried over sodium sulphate and evaporated under reduced pressure. Chromatography of the product using light petroleum (bp 50-70°)-ethyl acetate (1:1) as eluent gave 3-acetyl-5-(2-aminophenyl)-2-methyl-4-nitropyrrole (5), (yield 70%), mp 167° (yellow needles from benzene); ir: 3470 and 3380 (NH_2), 3200 (NH), 1640 (CO) cm^{-1} ; nmr (deuteriochloroform): δ 2.35 and 2.45 (6H, 2s, CH_3), 3.95 (2H, s, exchangeable NH_2), 6.65-7.50 (4H, m, C_6H_4), 9.35 (1H, broad, exchangeable NH); ms: $M^+ = 259.122$, $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_3$ requires $M^+ = 259.096$.

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.51; H, 5.17; N, 16.01.

Action of Acetic Acid on 3-Acetyl-5-(2-aminophenyl)-2-methyl-4-nitropyrrole (5).

a) Ten mmoles of compound 5 was kept in acetic acid overnight. The tlc showed unreacted starting material with traces of 3-acetyl-5-(2-*N*-acetylaminophenyl)-2-methyl-4-nitropyrrole (4). b) The acetic solution was refluxed for 8 hours and then poured onto crushed ice. The solid precipitate was collected air dried and recrystallized from ethanol to give 3-acetyl-5-(2-*N*-acetylaminophenyl)-2-methyl-4-nitropyrrole (4) (yield 70%).

General Method for the Reduction of Pyrroles 6a-e with Iron in Acetic Acid.

A solution of halopyrroles 6a-e [4] (3 mmoles) in acetic acid (50 ml) was heated at 70° whilst iron powder (1 g) was added over 1 hour. After the addition was complete, the mixture was kept at 70° for 12 hours and then poured onto crushed ice. In the case of the pyrroles 6a,c,e, the solution was extracted with ethyl acetate or dichloromethane (3 \times 100 ml). The extracts, dried over sodium sulphate, were evaporated under reduced pressure and chromatographed using light petroleum (bp 50-70°)-ethyl acetate (6:4) as eluant. In the case of *N*-substituted pyrroles 6b,d, the crude solid was collected, air dried and chromatographed using light petroleum (bp 50-70°)-ethyl acetate (4:1) as eluant. In the case of the compound 6a the first 450 ml of eluant gave 3-acetyl-5-(2-aminophenyl)-4-bromo-2-methylpyrrole (9a), (yield 11%), mp 161° (white needles from ethanol); ir: 3440 and 3360 (NH_2), 3260 (NH), 1635 (CO) cm^{-1} ; nmr (deuteriochloroform): δ 2.50 and 2.60 (6H, 2s, CH_3), 3.80 (2H, broad, exchangeable NH_2), 6.65-7.50 (4H, m, C_6H_4), 9.10 (1H, broad, exchangeable

NH); ms: $M^+ = 292.099$, $\text{C}_{13}\text{H}_{13}\text{BrN}_2\text{O}$ requires $M^+ = 292.021$.

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{BrN}_2\text{O}$: C, 53.26; H, 4.47; N, 9.56. Found: C, 53.12; H, 4.54; N, 9.69.

Further elution (400 ml) gave a mixture of 3-acetyl-5-(2-aminophenyl)-2-methylpyrrole (7) and pyrrolo[3,2-*b*]indole 2a (yield 35%) which were identified by glc (ratio 3:1).

Further elution (600 ml) gave 3-acetyl-5-(2-*N*-acetylaminophenyl)-4-bromo-2-methylpyrrole (10a), (yield 15%), mp 213° (white needles from ethanol); ir: 3290 and 3170 (NH), 1665 and 1635 (CO) cm^{-1} ; nmr (DMSO- d_6): δ 2.00, 2.47 and 2.50 (9H, 3s, CH_3), 7.19-7.82 (4H, m, C_6H_4), 9.01 and 11.84 (2H, 2 broad, exchangeable NH); ms: $M^+ = 334.083$, $\text{C}_{15}\text{H}_{15}\text{BrN}_2\text{O}_2$ requires $M^+ = 334.032$.

Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{BrN}_2\text{O}_2$: C, 53.75; H, 4.51; N, 8.36. Found: C, 53.58; H, 4.71; N, 8.57.

Further elution (500 ml) gave 3-acetyl-5-(2-acetylaminophenyl)-2-methylpyrrole (8) (yield 15%).

In the case of the compound 6b, the first 700 ml of eluant gave 3-acetyl-5-(2-aminophenyl)-4-bromo-2-methyl-1-phenylpyrrole (9b), (yield 65%), mp 200° (white needles from ethanol); ir: 3460 and 3350 (NH_2), 1640 (CO) cm^{-1} ; nmr (deuteriochloroform): δ 2.37 and 2.68 (6H, 2s, CH_3), 3.68 (2H, broad, exchangeable NH_2), 6.35-7.65 (9H, m, C_6H_5 and C_6H_4); ms: $M^+ = 368.093$, $\text{C}_{19}\text{H}_{17}\text{BrN}_2\text{O}$ requires $M^+ = 368.053$.

Anal. Calcd. for $\text{C}_{19}\text{H}_{17}\text{BrN}_2\text{O}$: C, 61.80; H, 4.64; N, 7.59. Found: C, 62.03; H, 4.49; N, 7.72.

Further elution (500 ml) gave pyrrolo[3,2-*b*]indole 2c (yield 12%) and then further elution (1000 ml) gave 3-acetyl-5-(2-*N*-acetylaminophenyl)-4-bromo-2-methyl-1-phenylpyrrole (10b), (yield 20%), mp 220° (white needles from ethanol); ir: 3340 (NH), 1695 and 1640 (CO) cm^{-1} ; nmr (deuteriochloroform): δ 2.10, 2.35 and 2.70 (9H, 3s, CH_3), 6.80-8.50 (10H, m, C_6H_5 , C_6H_4 and exchangeable NH); ms: $M^+ = 410.021$, $\text{C}_{21}\text{H}_{19}\text{BrN}_2\text{O}_2$ requires $M^+ = 410.063$.

Anal. Calcd. for $\text{C}_{21}\text{H}_{19}\text{BrN}_2\text{O}_2$: C, 61.32; H, 4.66; N, 6.81. Found: C, 61.56; H, 4.51; N, 7.02.

In the case of the compound 6c, the first 600 ml of eluant gave 3-acetyl-5-(2-aminophenyl)-4-chloro-2-methylpyrrole (9c), (yield 45%), mp 144° (white needles from benzene); ir: 3400 and 3330 (NH_2), 3210 (NH), 1620 (CO) cm^{-1} ; nmr (deuteriochloroform): δ 2.50 and 2.57 (6H, 2s, CH_3), 3.67 (2H, broad, exchangeable NH_2), 6.70-7.45 (4H, m, C_6H_4), 8.87 (1H, broad, exchangeable NH); ms: $M^+ = 248.098$, $\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{O}$ requires $M^+ = 248.072$.

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{O}$: C, 62.78; H, 5.27; N, 11.27. Found: C, 63.01; H, 5.41; N, 11.33.

Further elution (360 ml) gave a mixture of 3-acetyl-5-(2-aminophenyl)-2-methylpyrrole (7) and pyrrolo[3,2-*b*]indole 2a (yield 16%) which were identified by glc (ratio 3:1).

Further elution (1000 ml) gave 3-acetyl-5-(2-*N*-acetylaminophenyl)-4-chloro-2-methylpyrrole (10c), (yield 20%), mp 235° (white needles from benzene-ethanol); ir: 3250 and 3100 (NH), 1670 and 1630 (CO) cm^{-1} ; nmr (DMSO- d_6): δ 2.00 (3H, s, CH_3), 2.45 (6H, s, 2 \times CH_3), 7.00-8.05 (4H, m, C_6H_4), 9.15 and 11.80 (2H, 2 broad, exchangeable NH); ms: $M^+ = 290.121$, $\text{C}_{15}\text{H}_{15}\text{ClN}_2\text{O}_2$ requires $M^+ = 290.082$.

Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{ClN}_2\text{O}_2$: C, 61.96; H, 5.10; N, 9.64. Found: C, 61.63; H, 4.91; N, 9.73.

Further elution (600 ml) gave 3-acetyl-5-(2-*N*-acetylaminophenyl)-2-methylpyrrole (8) (yield 10%).

In the case of the compound 6d the first 700 ml of eluant gave 3-acetyl-5-(2-aminophenyl)-4-chloro-2-methyl-1-phenylpyrrole (9d), (yield 65%), mp 203° (white needles from ethanol); ir: 3470 and 3350 (NH_2), 1640 (CO) cm^{-1} ; nmr (deuteriochloroform): δ 2.35 and 2.66 (6H, 2s, CH_3), 3.50 (2H, s, exchangeable NH_2), 6.40-7.50 (9H, m, C_6H_5 and C_6H_4); ms: $M^+ = 324.181$, $\text{C}_{19}\text{H}_{17}\text{ClN}_2\text{O}$ requires $M^+ = 324.103$.

Anal. Calcd. for $\text{C}_{19}\text{H}_{17}\text{ClN}_2\text{O}$: C, 70.26; H, 5.28; N, 8.63. Found: C, 70.40; H, 5.39; N, 8.41.

Further elution (400 ml) gave pyrrolo[3,2-*b*]indole 2c (yield 6%). Further elution (700 ml) gave 3-acetyl-5-(2-*N*-acetylaminophenyl)-4-chloro-2-methyl-1-phenylpyrrole (10d), (yield 15%), mp 213° (white needles from ethanol); ir: 3360 (NH), 1700 and 1640 (CO) cm^{-1} ; nmr (deuteriochloro-

form): δ 2.10, 2.35 and 2.65 (9H, 3s, CH₃), 6.80-8.45 (10H, m, C₆H₅, C₆H₄ and exchangeable NH); ms: M⁺ = 366.181, C₂₁H₁₉ClN₂O₂ requires M⁺ = 366.113.

Anal. Calcd. for C₂₁H₁₉ClN₂O₂: C, 68.75; H, 5.22; N, 7.64. Found: C, 68.46; H, 5.38; N, 7.29.

In the case of the compound **6e**, the first 450 ml of eluant gave 3-acetyl-5-(2-aminophenyl)-4-iodo-2-methylpyrrole (**9e**), (yield 25%), mp 166° (white needles from benzene); ir: 3400 and 3320 (NH₂), 3215 (NH), 1630 (CO) cm⁻¹; nmr (deuteriochloroform): δ 2.48 and 2.57 (6H, 2s, CH₃), 3.70 (2H, broad, exchangeable NH₂), 6.72-7.55 (4H, m, C₆H₄), 8.91 (1H, broad, exchangeable NH); ms: M⁺ = 340.210, C₁₃H₁₃IN₂O requires M⁺ = 340.170.

Anal. Calcd. for C₁₃H₁₃IN₂O: C, 45.90; H, 3.85; N, 8.29. Found: C, 46.08; H, 4.01; N, 8.13.

Further elution (500 ml) gave a mixture of 3-acetyl-5-(2-aminophenyl)-2-methylpyrrole (**7**) and pyrrole[3,2-*b*]indole **2a** (yield 40%) which were identified by glc (ratio 3:1). Further elution (1000 ml) gave 3-acetyl-5-(2-*N*-acetylaminophenyl)-2-methylpyrrole (**8**) (yield 20%).

Action of Acetic Acid on 3-Acetyl-5-(2-aminophenyl)-4-halo-2-methyl-1-phenylpyrroles (**9**).

Two mmoles of compound **9b,d** was refluxed in acetic acid for 90 minutes. The solution was poured onto crushed ice. The solid was collected, air dried and recrystallized from ethanol to give pyrrolo[3,2-*b*]indole **2c** in 78% yield when the halogen was bromine and 60% yield when the halogen was chlorine. In the latter case traces of compound **10d** were also detected *tfc*.

Attempted Indolization of **9b,d** in 2-Propanol and in DMF.

Two mmoles of 3-acetyl-5-(2-aminophenyl)-4-halo-2-methyl-1-phenylpyrrole (**9b,d**) were refluxed for 30 hours. When DMF was used, the solution was poured onto crushed ice and the solid was collected and recrystallized. When 2-propanol was used, the cooled mixture was filtered and the solid recrystallized. In both cases only unreacted starting

material was isolated.

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REFERENCES AND NOTES

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[1] Part **12**: G. Dattolo, G. Cirrincione, A. M. Almerico, I. D'Asdia and E. Aiello, *J. Heterocyclic Chem.*, **19**, 1237 (1982).

[2] E. Aiello, G. Dattolo and G. Cirrincione, *J. Chem. Soc., Perkin Trans. I*, 1 (1981).

[3a] J. R. Beck, *Tetrahedron*, **34**, 2057 (1978); [b] P. Mencarelli and F. Stegel, *J. Chem. Soc., Chem. Commun.*, 123 (1980) and references cited therein; [c] R. A. Jones and G. P. Bean, "The Chemistry of Pyrroles", Academic Press, London, 1977, p 116, and references cited therein.

[4] E. Aiello, G. Dattolo, G. Cirrincione, A. M. Almerico and I. D'Asdia, *J. Heterocyclic Chem.*, **19**, 977 (1982).

[5] C. T. Wie, S. Sunder and C. D. Blanton, *Tetrahedron Letters*, 4605 (1968).

[6] E. Aiello, G. Dattolo, G. Cirrincione, A. M. Almerico, R. A. Jones and W. Hinz, unpublished work.

[7] E. Aiello, G. Dattolo, G. Cirrincione, S. Plescia and G. Daidone, *J. Heterocyclic Chem.*, **16**, 209 (1979).

[8] E. Aiello, G. Dattolo, G. Cirrincione, S. Plescia and G. Daidone, *ibid.*, **15**, 537 (1978).