Reactivity of Aminopyrroles: Protonation [a]

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The behaviour of 2- and 3-aminopyrroles towards protonation is similar. In dimethyl sulphoxide/trifluoroacetic acid they are protonated at the exocyclic nitrogen, whereas in pure trifluoroacetic acid, protonation at the 5- and/or 3-position of the ring takes place.

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Recently we have utilized 3-aminopyrroles as synthons for the synthesis of new pharmacologically interesting ring systems such as pyrrolo[3,4-*c*]pyridazine [1], pyrrolo-[3,2-*c*]cinnoline [2], pyrrolo[3,4-*d*][1,2,3]triazine [3] and the synthesis of 3-triazenopyrroles, a new class of pyrrole derivatives [4] that have shown remarkable *in vitro* antileukemic activity [5].

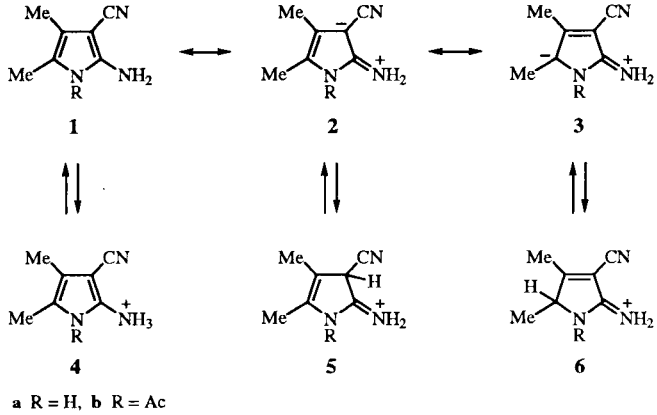
3-Aminopyrroles behave as aromatic amines. In fact they undergo diazotization, to give isolable pyrrole 3-diazonium salts or the 3-diazopyrroles upon neutralization [6], and protonation at the amino nitrogen in dimethyl sulphoxide/trifluoroacetic acid [7].

Additionally 2-aminopyrroles can be precursors of pharmacologically active compounds such as 2-diazopyrroles and 2-triazenopyrroles, deaza-analogue of dacarbazine [8]. 2-Aminopyrroles can also be useful synthons for the preparation of the new ring system pyrrolo[2,1-*d*][1,2,3,5]tetrazine, deaza-analogue of the antineoplastic mitozolomide and temozolomide [9]. But 2-aminopyrroles are considerably less stable than the corresponding 3-isomers, which are already difficult to handle and sometimes difficult to isolate as pure samples. The presence of an electron donating group on an already electron rich nucleus makes these classes of compounds rather unstable, unless strong electron withdrawing substituents are also present on the ring.

Reactivity studies on 2-aminopyrroles are thus limited to those compounds that have a high degree of stability and the data are limited to a few, often unclear and sometimes contradictory reports. It was, however, reported that 2-aminopyrroles do not behave as aromatic amines based on the reactivity towards electrophiles shown by 2-aminopyrrole derivatives **1**. In fact they are not protonated like typical aromatic amines to give the ammonium salts **4**, but their behaviour is characteristic of the zwitterionic form **2** or **3** to give the *C*-protonated salts **5** or **6** [10].

Moreover upon diazotization and neutralization 2-aminopyrroles do not give the corresponding 2-diazopyrroles [11]. Thus, so far, only two derivatives of this class of compounds have been obtained, in very low yield (2-6%), by direct introduction of the diazo group into the pyrrole nucleus [12]. However, in our opinion, the failure in the diazotization and the very low yield of the direct introduction of the diazo group might be ascribed to the instability of the reagents or of the reaction products rather than to a lack of reactivity.

Scheme 1



a R = H, b R = Ac

Since diazotization is generally achieved under acidic conditions, we prepared, by standard procedures [13], a series of 2-aminopyrroles **7a-g** to study their tautomerism and behavior towards protonation, by nmr techniques.

The ^1H and ^{13}C nmr spectra of the free bases were measured in deuterated dimethyl sulphoxide and the protonated species were generated by addition of a two-fold excess of trifluoroacetic acid to the dimethyl sulphoxide solution. Using these conditions we have already studied the protonation of the isomeric 3-aminopyrroles and have demonstrated that the protonation occurs at the amino group [7].

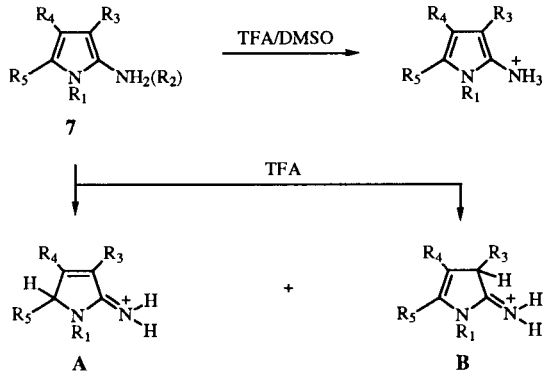
The ^1H nmr spectral data of the free bases and their protonated forms were strongly indicative of protonation of the amino group (Tables 1, 2). All of the ^1H resonance signals showed downfield shifts with no change in multiplicity and, significantly, there was no evidence for upfield signals expected for the ring protonated species. The broadened signals attributable to the 2-amino group showed a downfield shift of about 4-6 ppm upon protonation and the integration of the signals increased from two to three protons. The resonance signal for the pyrrole NH showed 0.1-0.4 ppm downfield shift.

Table 1

^{1}H NMR Data for 2-Aminopyrroles (DMSO)

Substituent Compound	R_1	R_2	R_3	R_4	R_5
R_1 = H R_3 = CN R_4 = Me R_5 = Me	9.78 (1H, s)	5.29 (2H, s)		1.84 (3H, s)	1.92 (3H, s)
R_1 = H R_3 = CN R_4 = Me R_5 = CH_2Ph	9.86 (1H, s)	5.39 (2H, s)		1.92 (3H, s)	3.66 (2H, s) 7.15 (1H, t) 7.16 (2H, t) 7.26 (2H, d)
R_1 = H R_3 = CN R_4 = Me R_5 = Ph	10.47 (1H, s)	5.63 (2H, s)		2.13 (3H,s)	7.12-7.19 (1H, m) 7.35-7.40 (4H, m)
R_1 = H R_3 = CN R_4 = Ph R_5 = H	10.38 (1H, s)	5.75 (2H, s)		7.19 (1H, t) 7.34 (2H, t) 7.59 (2H, d)	6.56 (1H, s)
R_1 = H R_3 = Ph R_4 = Ac R_5 = Me	10.56 (1H, bs)	4.06 (2H, bs)	7.15 (3H, m) 7.29 (2H, t)	2.29 (3H, s)	1.84 (3H, s)
R_1 = C_6H_{11} R_3 = H R_4 = CN R_5 = H	1.33-1.87 (10H, m) 3.90 (1H, m)	4.73 (2H, s)	5.36 (1H, d)		7.15 (1H, d)
R_1 = CH_2Ph R_3 = H R_4 = CN R_5 = H	4.83 (2H, s) 7.16 (2H, d) 7.29 (1H, t) 7.34 (2H, t)	5.02 (2H, s)	5.23 (1H, d)		7.14 (1H, d)

Scheme 2



a R_1 = H, R_3 = CN, R_4 = R_5 = Me (**1a**)
b R_1 = H, R_3 = CN, R_4 = Me, R_5 = CH_2Ph
c R_1 = H, R_3 = CN, R_4 = Me, R_5 = Ph
d R_1 = R_5 = H, R_3 = CN, R_4 = Ph
e R_1 = CH_2Ph, R_3 = R_4 = H, R_5 = CN
f R_1 = c-C_6H_{11}, R_3 = R_5 = H, R_4 = CN
g R_1 = H, R_3 = Ph, R_4 = Ac, R_5 = Me

In the ^{13}C nmr spectra it was expected that the protonation of either the amino group, or of the pyrrole ring would lead to distinct changes in the ^{13}C chemical shifts of the "*ipso*" carbon and the "*ortho*" carbon resonances, respectively. Thus protonation on the amino group produces a non-stabilized cation but does not disrupt the aromatic character of the pyrrole ring. Such a situation involves upfield shift of the "*ipso*" carbon and downfield shift of the "*ortho*" carbon resonances. Such a behaviour was already shown by aniline, 3-aminothiophenes, 4-aminopyrazoles, and the isomeric 3-aminopyrroles [7,14]. In contrast, protonation on the ring produces resonance stabilized cations which involves a downfield shift of the "*ipso*" carbon, an upfield shift of the protonated carbon, C-3 or C-5, accompanied by a downfield shift of the C-5 or C-3 carbons, respectively.

Examination of the ^{13}C nmr spectra confirms the site of protonation assigned by ^{1}H nmr data (Tables 3, 4). In fact, the ^{13}C spectra of the protonated species show that the pyrrole ring retains aromaticity and the C-2 resonances shift upfield of 3-5 ppm and those of C-3 shift downfield of 1.5-2.5 ppm in the case of the 1*H*-pyrrole derivatives **7a-e**. 1-Substituted derivatives **7f,g** showed C-2 upfield and C-3 downfield shifts of 7-11 and 5-9 ppm, respectively. The directions of these shifts are as expected for the protonation of the amino group but the magnitudes are smaller than those observed in the case of the aniline, 3-aminothiophenes, and 3-aminopyrroles [7,14]. No ready explanation of these data is available, but probably the influence of the adjacent ring nitrogen is relevant.

Thus 2- and 3-aminopyrroles, in dimethyl sulphoxide/trifluoroacetic acid behave similarly, undergoing protonation at the amino group. Therefore we wanted to verify whether also in pure trifluoroacetic acid 2- and 3-amino-

Table 2

^{1}H NMR Data for Protonated 2-Aminopyrroles (DMSO/TFA)

Substituent Compound	R_1	R_2	R_3	R_4	R_5
R_1 = H R_3 = CN R_4 = Me R_5 = Me	10.17 (1H, s)	9.32 (3H, bs)		1.88 (3H, s)	1.96 (3H, s)
R_1 = H R_3 = CN R_4 = Me R_5 = CH_2Ph	10.08 (1H, s)	11.48 (3H, bs)		1.94 (3H, s)	3.69 (2H, s) 7.17 (3H, t) 7.26 (2H, d)
R_1 = H R_3 = CN R_4 = Me R_5 = Ph	10.64 (1H, s)	10.73 (3H, s)		2.19 (3H, s)	7.14-7.20 (1H, m) 7.29-7.54 (4H, m)
R_1 = H R_3 = CN R_4 = Ph R_5 = H	10.50 (1H, s)	10.61 (3H, bs)		7.19 (1H, t) 7.35 (2H, t) 7.58 (2H, d)	6.56 (1H, s)
R_1 = H R_3 = Ph R_4 = Ac R_5 = Me	10.98 (1H, bs)	8.65 (3H, bs)	7.24 (3H, m) 7.36 (2H, t)	2.33 (3H, s)	1.83 (3H, s)
R_1 = C_6H_{11} R_3 = H R_4 = CN R_5 = H	1.15-1.98 (10H, m) 4.00 (1H, m)	9.74 (3H, bs)	6.13 (1H, s)		7.64 (1H, s)
R_1 = CH_2Ph R_3 = H R_4 = CN R_5 = H	5.12 (2H, s) 7.20 (2H, d) 7.31 (1H, t) 7.34 (2H, t)	11.19 (3H, bs)	5.88 (1H, s)		7.29 (1H, s)

Table 3

^{13}C NMR Data for 2-Aminopyrroles (DMSO)

Substituent Compound	C-2	C-3	C-4	C-5	R_1	R_3	R_4	R_5
R_1 = H R_3 = CN R_4 = Me R_5 = Me	146.3 (s)	71.3 (s)	111.1 (s)	115.2 (s)		118.7 (s)	9.5 (q)	10.1 (q)
R_1 = H R_3 = CN R_4 = Me R_5 = CH_2Ph	146.7 (s)	71.1 (s)	112.0 (s)	118.4 (s)		118.4 (s)	9.5 (q)	30.5 (t) 125.8 (d) 128.0 (d) 128.2 (d) 140.3 (s)
R_1 = H R_3 = CN R_4 = Me R_5 = Ph	147.8 (s)	74.0 (s)	114.6 (s)	119.3 (s)		117.8 (s)	11.2 (q)	125.0 (d) 125.0 (d) 128.5 (d) 132.4 (s)
R_1 = H R_3 = CN R_4 = Ph R_5 = H	149.7 (s)	68.4 (s)	121.7 (s)	108.7 (d)		118.8 (s)	125.0 (d) 125.8 (d) 128.6 (d) 134.3 (s)	
R_1 = H R_3 = Ph R_4 = Ac R_5 = Me	133.6 (s)	103.4 (s)	119.5 (s)	127.5 (s)		124.9 (d) 128.0 (d) 130.0 (d) 136.6 (s)	30.2 (q) 194.1 (s)	13.3 (q)
R_1 = C_6H_{11} R_3 = H R_4 = CN R_5 = H	138.8 (s)	90.6 (d)	88.4 (s)	119.3 (d)	24.8 (t) 25.2 (t) 32.9 (t) 53.0 (d)		118.2 (s)	

Table 3 (continued)

Substituent Compound	C-2	C-3	C-4	C-5	R_1	R_3	R_4	R_5
$R_1 = CH_2Ph$ $R_3 = H$ $R_4 = CN$ $R_5 = H$	139.7 (s)	90.5 (d)	88.9 (s)	122.8 (d)	48.1 (t) 127.2 (d) 127.4 (d) 128.6 (d) 137.5 (s)		117.9 (s)	

Table 4

^{13}C NMR Data for Protonated 2-Aminopyrroles (DMSO/TFA)

Substituent Compound	C-2	C-3	C-4	C-5	R_1	R_3	R_4	R_5
$R_1 = H$ $R_3 = CN$ $R_4 = Me$ $R_5 = Me$	141.2 (s)	73.8 (s)	112.1 (s)	116.7 (s)		118.3 (s)	9.6 (q)	10.1 (q)
$R_1 = H$ $R_3 = CN$ $R_4 = Me$ $R_5 = CH_2Ph$	143.2 (s)	72.6 (s)	112.7 (s)	119.4 (s)		118.4 (s)	9.6 (q)	30.8 (t) 126.1 (d) 128.3 (d) 128.5 (d) 140.5 (s)
$R_1 = H$ $R_3 = CN$ $R_4 = Me$ $R_5 = Ph$	144.6 (s)	75.3 (s)	115.0 (s)	120.1 (s)		117.8 (s)	11.1 (q)	125.2 (d) 125.3 (d) 128.6 (d) 132.5 (s)
$R_1 = H$ $R_3 = CN$ $R_4 = Ph$ $R_5 = H$	146.4 (s)	70.1 (s)	121.9 (s)	108.9 (d)		118.9 (s)	125.2 (d) 126.0 (d) 128.7 (d) 134.5 (s)	
$R_1 = H$ $R_3 = Ph$ $R_4 = Ac$ $R_5 = Me$	130.2 (s)	105.7 (s)	119.6 (s)	128.4 (s)		125.3 (d) 128.0 (d) 130.0 (d) 135.9(s)	30.2 (q) 194.0 (s)	13.3 (q)
$R_1 = C_6H_{11}$ $R_3 = H$ $R_4 = CN$ $R_5 = H$	127.6 (s)	99.9 (d)	90.5 (s)	124.2 (d)	25.0 (t) 25.6 (t) 33.6 (t) 55.0 (d)		117.2 (s)	
$R_1 = CH_2Ph$ $R_3 = H$ $R_4 = CN$ $R_5 = H$	132.6 (s)	95.5 (d)	89.3 (s)	124.6 (d)	48.2 (t) 126.8 (d) 127.1 (d) 128.1 (d) 136.2 (s		116.4 (s)	

pyrroles undergo similar protonation. The ^1H nmr spectra of the 2-amino derivatives were measured and, as expected, protonation at 5 and/or 3 position of the ring was observed (Table 5). In fact the 2-amino-3-cyano-4,5-dimethylpyrrole (**7a**) was protonated at position 5 as demonstrated by the doublet-quartet pattern. The immonium protons appear as two singlets for one proton each due to the strong double bond character between C-2 and the exocyclic nitrogen. Analogous behaviour was shown by derivatives **7b-d**. The 1-substituted 2-amino-4-cyano derivatives, **7e,f**, having positions 3- and 5-unsubstituted, undergo protonation either at the 3- or at the 5-position. The electron withdrawing cyano group deactivates the 5-position so that the protonation predominantly occurs at the 3-position. This could be explained according to the larger transmission of electronic effects between the 4- and 5-positions (hyper-*ortho*) than between the 4- and 3-positions (hypo-*ortho*) due to the high "bond fixation" which gives rise to C-4–C-5 bond with a high π bond order as already pointed out in the thiophene ring [15]. Thus in the case of the 2-amino-3-phenyl-4-acetyl-5-methylpyrrole (**7g**), protonation exclusively occurs at the 3-position. Also in this case examination of the ^{13}C nmr data confirms the protonation site assigned by ^1H nmr data (Table 6). Protonation at the 5-position generates a 2*H*-pyrrole-like structure which shows a marked downfield shift of the C-2 and C-4 and an upfield shift of the C-5 carbon atom resonances. In fact the spectra of derivatives **7a-d** show C-2 resonances at 177-188 ppm, the C-4 resonances at 165-171 ppm and the C-5 resonances at 57-75 ppm. Such chemical shift values are in good agreement with those typical of nuclear carbon atoms in 2*H*-pyrrole structures [16].

Table 5

^{1}H NMR Data for 2-Aminopyrroles in TFA

Substituent Compound	R_1	R_2	R_3	R_4	R_5
R_1 = H	9.12 (1H, s)	7.91 (1H, s)		2.64 (3H, s)	1.24 (3H, d)
R_3 = CN		8.14 (1H, s)			5.36 (1H, q)
R_4 = Me					
R_5 = Me					
A					
R_1 = H	8.89 (1H, s)	7.79 (1H, s)		2.59 (3H, s)	3.00 (1H, dd)
R_3 = CN		7.95 (1H, s)			3.50 (1H, dd)
R_4 = Me					5.17 (1H, t)
R_5 = CH_2Ph					7.24 (2H, m)
A					7.38 (3H, m)
R_1 = H	9.28 (1H, s)	8.05 (1H, s)		2.36 (3H, s)	5.85 (1H, s)
R_3 = CN		8.30 (1H, s)			7.23 (2H, d)
R_4 = Me					7.53 (3H, t)
R_5 = Ph					
A					
R_1 = H	9.05 (1H, s)	7.84 (1H, s)		7.68 (2H, t)	5.32 (2H, s)
R_3 = CN		8.11 (1H, s)		7.80 (1H, t)	
R_4 = Ph				8.04 (2H, d)	
R_5 =H					
A					
R_1 = H	10.75 (1H, bs)	8.31 (1H, s)	5.32 (1H, s)	2.71 (3H, s)	2.22 (3H, s)
R_3 = Ph		9.09 (1H, s)	7.29 (2H, d)		
R_4 = Ac			7.82 (3H, t)		
R_5 = Me					
B					
R_1 = C_6H_{11}	1.43-2.19 (10H, m) A+B	7.90 (1H, s) A	4.37 (2H, s) B		4.95 (2H, s) A
R_3 = H	4.17 (1H, m) A+B	8.20 (1H, s) A	7.47 (1H, s) A		7.80 (1H, s) B
R_4 = CN		8.69 (1H, s) B			
R_5 = H		9.03 (1H, s) B			
A+B (1:2)					
R_1 = CH_2Ph	4.34 (2H, s) B	7.88 (1H, s) A	5.06 (2H, s) B		4.73 (2H, s) A
R_3 = H	4.98 (2H, s) A	8.27 (1H, s) A	7.40 (1H, s) A		7.36 (1H, s) B
R_4 = CN	7.33 (2H, d) A+B	8.57 (1H, s) B			
R_5 = H	7.50 (3H, t) A+B	9.06 (1H, s) B			
A+B (1:4.5)					

Table 6

^{13}C NMR Data for 2-Aminopyrroles in TFA

Substituent Compound	C-2	C-3	C-4	C-5	R_1	R_3	R_4	R_5
R_1 = H	188.3 (s)	104.9 (s)	170.8 (s)	67.7 (d)		109.8 (s)	15.6 (q)	16.8 (q)
R_3 = CN								
R_4 = Me								
R_5 = Me								
A								
R_1 = H	186.6 (s)	105.7 (s)	164.7 (s)	72.7 (d)		109.7 (s)	16.3 (q)	39.0 (t)
R_3 = CN								130.5 (d)
R_4 = Me								130.6 (d)
R_5 = CH_2Ph								131.3 (d)
A								134.7 (s)
R_1 = H	187.3 (s)	104.8 (s)	165.3 (s)	75.4 (d)		109.9 (s)	16.0 (q)	128.7 (d)
R_3 = CN								131.1 (d)
R_4 = Me								132.0 (d)
R_5 = Ph								133.0 (s)
A								
R_1 = H	176.9 (s)	98.6 (s)	167.2 (s)	57.5 (t)		112.1 (s)	129.1 (s)	
R_3 = CN							130.4 (d)	
R_4 = Ph							132.0 (d)	
R_5 = H							138.2 (d)	
A								

Table 6 (continued)

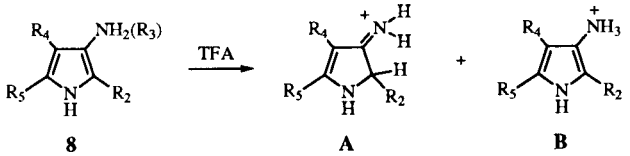
Substituent Compound	C-2	C-3	C-4	C-5	R_1	R_3	R_4	R_5
R_1 = H R_3 = Ph R_4 = Ac R_5 = Me **B**	163.3 (s)	57.3 (d)	124.8 (s)	157.3 (s)		129.9 (d) 132.2 (d) 132.3 (d) 133.4 (s)	29.8 (q) 177.7 (s)	15.2 (q)
R_1 = C_6H_{11} R_3 = H R_4 = CN R_5 = H **A+B** (1:2)	163.6 (s) A 171.8 (s) B	58.7 (t) B 146.9 (d) A	97.2 (s) B 130.4 (s) A	58.7 (t) A 137.1 (d) B	26.0 (t) A 26.1 (t) B 32.6 (t) A 32.8 (t) B 41.3 (t) A+B 58.9 (d) A 59.4 (d) B		111.3 (s) A 112.6 (s) B	
R_1 = CH_2Ph R_3 = H R_4 = CN R_5 = H **A+B** (1:4.5)	164.8 (s) A 172.3 (s) B	41.3 (t) B 149.2 (d) A	96.6 (s) B 131.4 (s) A	62.0 (t) A 136.7 (d) B	52.1 (t) A 52.5 (t) B 129.8 (d) A 129.8 (d) A 130.6 (s) A 131.6 (d) B 131.7 (d) B 131.8 (d) A 132.0 (d) B 132.5 (s) B		111.2 (s) B 112.4 (s) A	

Protonation at the 3-position gives rise to a 3*H*-pyrrole-like structure for which a downfield shift of the C-2 carbon and an upfield shift of the C-3 carbon has to be expected. In fact derivatives **7e-g** show the C-2 resonances at 163-172 ppm, and the C-3 resonances at 41-59 ppm. Also these chemical shift values are in agreement with those of 3*H*-pyrrole structures [17].

A series of 3-aminopyrroles **8a-c** was prepared [13] and their ^1H and ^{13}C nmr spectra in trifluoroacetic acid were measured.

The ^1H nmr spectra in trifluoroacetic acid of 3-aminopyrroles are indicative of protonation of the 2-position of the ring (Table 7). In fact an upfield signal at about 6 ppm due to the proton bounded to the C-2 carbon was observed and the amine protons appeared as two singlets for one proton each at 7.4-8.3 and 7.9-9.8 ppm evidencing, also in this case, the strong character of double bond between the amino nitrogen and the *ipso* carbon. In the cases of derivatives **8b,c**, bearing electron withdrawing groups on the 4-position, in addition to the signals in agreement with the ring protonation, a set of signals compatible with an aromatic pyrrole structure was observed, indicating that protonation of the amino group has also occurred, although to a smaller extent, due to the decreased electron density on the ring.

Scheme 3



8 **A** **B**

a R_2 = R_5 = Ph, R_4 = H; **b** R_2 = Ph, R_4 = Ac, R_5 = Me; **c** R_2 = Ph, R_4 = COOEt, R_5 = Me

The ^{13}C nmr spectra of derivatives **8** show sets of signals consistent with a structure arising from the protonation at the 2-position of the ring (Table 8). In particular the resonances of C-2 carbons were found at 70-72 ppm showing, with respect to the free bases, an upfield shift of 39-44 ppm; the C-3 carbon resonances were found at 181-185 ppm, shifted 49-52 ppm downfield as well as the C-5 carbon resonances which were found at 180-183 ppm; the C-4 carbon signals show slight upfield shift, 2-5 ppm, being found at 95-109 ppm [7]. Such chemical shifts are substantially in agreement with those of the protonated form of the 3-methoxy-1-phenylpyrrole which shows, by comparison with the unprotonated species, upfield shifts of 42.6 and 1.7 ppm for C-2 and C-4 carbons respectively and downfield shifts of 37.5 and 51.1 ppm for C-3 and C-5 carbons respectively [18]. In the case of derivatives **8b,c** the presence of sets of signals compatible with the exocyclic protonation was also observed. The pattern of these sets of signals is similar to that previously reported for the protonation of 3-aminopyrroles with the only difference being the magnitude of the downfield shift of C-2 carbon atom and of the upfield shift of the C-3 carbon atom resonances is larger being about 20 and 21 ppm respectively. Thus, in trifluoroacetic acid 2- and 3-aminopyrroles behave similarly.

In conclusion, in any case 2- and 3-aminopyrroles show identical behaviour towards protonation. Thus it can be expected that 2- and 3-aminopyrroles will also react similarly with other electrophiles and the failure in undergoing

Table 7

^{1}H NMR Data for 3-Aminopyrroles in TFA

Substituent Compound	R_1	R_2	R_3	R_4	R_5
R_2 = Ph R_4 = H R_5 = Ph **A**	8.88 (1H, s)	5.85 (1H, s) 7.51-7.75 (5H, m)	7.36 (1H, s) 7.94 (1H, s)	6.27 (1H, s)	7.51-7.75 (5H, m)
R_2 = Ph R_4 = Ac R_5 = Me **A+B** (3:1)	9.93 (1H, s) A 10.03 (1H, s) B	5.90 (1H, s) A 7.28 (5H, s) B 7.53 (5H, s) A	8.26 (1H, s) A 9.06 (3H, s) B 9.85 (1H, s) A	2.95 (3H, s) A+B	2.76 (3H, s) A+B
R_2 = Ph R_4 = COOEt R_5 = Me **A+B** (4:1)	9.66 (1H, s) A+B	5.95 (1H, s) A 7.30 (5H, m) B 7.51 (5H, m) A	7.82 (1H, s) A 8.81 (1H, s) A 8.96 (3H, s) B	1.51 (3H, t) A+B 4.52 (2H, q) A+B	2.65 (3H, s) B 2.86 (3H, s) A

Table 8

^{13}C NMR Data for 3-Aminopyrroles in TFA

Substituent Compound	C-2	C-3	C 4	C-5	R_2	R_4	R_5
R_2 = Ph R_4 = H R_5 = Ph **A**	71.8 (d)	181.3 (s)	94.8 (d)	180.5 (s)	129.2 (d) 130.0 (d) 132.5 (d) 132.9 (s)		128.2 (s) 131.5 (d) 131.8 (d) 137.1 (d)
R_2 = Ph R_4 = Ac R_5 = Me **A+B** (3:1)	70.6 (d) A 130.2 (s) B	183.3 (s) A 111.9 (s) B	109.4 (s) A 115.7 (s) B	183.2 (s) A 142.5 (s) B	128.3 (s) B 129.2 (d) A 129.4 (d) A 131.0 (s) A 131.4 (d) A 132.0 (d)B 132.2 (d) B	29.4 (q) B 29.7 (q) A 200.9 (s) A 204.2 (s) B	19.4 (q) A 15.7 (q) B
R_2 = Ph R_3 = COOEt R_5 = Me **A+B** (4:1)	71.3 (d) A 131.4 (s) B	184.6 (s) A 111.5 (s) B	100.2 (s) A 106.9 (s) B	182.4 (s) A 140.6 (s) B	129.2 (d) A 129.2 (d) A 131.2 (d) A 131.8 (d) B 132.9 (d) B	18.6 (q) A+B 65.2 (t) A 67.8 (t) B 167.8 (s) A 170.6 (s) B	14.1 (q) B 14.5 (q) A

typical aromatic amine reactions shown by 2-aminopyrroles has to be attributed to unsuitable reaction conditions. We believe, therefore, that it should be possible to isolate 2-diazopyrroles by diazotization of the corresponding 2-amino derivatives and successive neutralization.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary apparatus and are uncorrected; ir spectra were determined in bromoform with a Jasco FT/IR 5300 spectrophotometer. The ^{1}H and ^{13}C nmr spectra were measured in DMSO solutions, at 250 and 62.8 MHz respectively using a Bruker AC-E series 250 MHz spectrometer (TMS as internal reference); protonation was achieved by adding two equivalents of trifluoroacetic acid to the DMSO solutions or dissolving the samples directly in TFA. Mass spectra were obtained with a JEOL JMS-01 SG-2 double focusing mass spectrometer operating with an electron beam energy of 75 eV and 10 Kv accelerating voltage and with a HP 5890 Series II and HP 5989A GC/MS apparatus.

Preparation of 2-Amino-3-cyanopyrroles **7a-d**.

These derivatives were prepared from 3-acetamidobutan-2-one [19,20], or 1-acetamido-1-phenylpropan-2-one [19,20], or 3-acetamido-4-phenylbutan-2-one [19,21] or ω-acetamidoacetophenone [22] and malononitrile according to the procedure described in the literature [23].

2-Amino-3-cyano-4,5-dimethylpyrrole (**7a**) was recrystallized from ethanol, yield 76%, mp 171-173°, (lit [24] mp 163-164°); ir: 3366, 3308 and 3215 (NH_2 and NH), 2189 (CN) cm^{-1}.

2-Amino-5-benzyl-3-cyano-4-methylpyrrole (**7b**) was recrystallized from methanol, yield 82%, mp 119-120° (lit [23] mp 119-120°); ir: 3433, 3337 and 3262 (NH_2 and NH), 2197 (CN) cm^{-1}.

2-Amino-3-cyano-4-methyl-5-phenylpyrrole (**7c**) was recrystallized from methanol, yield 74%, mp 137.5-138.5° (lit [22] mp 134-135.5°); ir: 3385, 3325 and 3249 (NH_2 and NH), 2204 (CN) cm^{-1}.

2-Amino-3-cyano-4-phenylpyrrole (**7d**) was recrystallized from benzene/ethanol, yield 80%, mp 172-173° (lit [24] mp 172-173°); ir: 3389, 3312 and 3256 (NH_2 and NH), 2199 (CN) cm^{-1}.

Preparation of 1-Substituted 2-Amino-4-cyanopyrroles **7e,f**.

These derivatives were prepared from the sodium-salt derivative of formylsuccinonitrile [25] and the appropriate amine according to the procedure described in the literature [26].

2-Amino-4-cyano-1-cyclohexylpyrrole (**7e**) was purified by column chromatography using dichloromethane as eluant, yield 88%, mp 91-92°; ir: 3408 and 3337 (NH_2), 2218 (CN) cm^{-1}.

2-Amino-1-benzyl-4-cyanopyrrole (**7f**) was purified by column chromatography using dichloromethane as eluant, yield 85%, mp 62°; ir: 3410 and 3335 (NH_2), 2220 (CN) cm^{-1}.

Preparation of 4-Acetyl-2-amino-5-methyl-3-phenylpyrrole (**7g**).

To a stirred solution of 4-nitroaniline (40 mmoles) in 6*N* hydrochloric acid (30 ml), a solution of sodium nitrite in water (30%, 15 ml) was added dropwise, at 0-5°. The mixture, cooled at 0°, was treated with 4-acetyl-5-methyl-3-phenylpyrrole [27] (40 mmoles) dissolved in buffered acetic acid (200 ml added with sodium acetate (10 g)). After being stirred for 1 hour, the mixture was poured onto crushed ice. The solid product was collected and washed with water/ethanol (9:1). The 4-acetyl-5-methyl-2-(4-nitrophenylazo)-3-phenylpyrrole was recrystallized from ethanol, yield 100%, mp 238°; ir: 3150 (NH), 1625 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.99 (3H, s, CH_3), 2.55 (3H, s, CH_3), 7.47-8.35 (9H, m, C_6H_5 and C_6H_4), 11.72 (1H, s, NH); ms: m/z 348.

Anal. Calcd. for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.38; H, 4.54; N, 15.98.

To a stirred solution of stannous chloride (80 g) in acetic acid (80 ml) heated at 80° (steam bath), 4-acetyl-5-methyl-2-(4-nitrophenylazo)-3-phenylpyrrole (40 mmoles) was added in small portions. The reactants were stirred until the mixture became colourless, then they were cooled to room temperature. The mixture was added to a solution of aqueous potassium hydroxide (25%, 800 ml) with stirring. After 0.5 hour, the solid precipitate was filtered off and recrystallized from ethanol, yield 76%, mp 222-224°; ir: 3410, 3330 and 3150 (NH_2 and NH), 1610 (CO) cm^{-1}; ms: m/z 214.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 73.02; H, 6.44; N, 13.15.

Preparation of 3-Amino-2-phenylpyrroles **8a-c**.

3-Amino-2,5-diphenylpyrrole (**8a**) yield 93%, mp 187° (lit [28] mp 187°) was prepared by catalytic reduction of the corresponding nitroso compound [29], using a procedure analogous to that described for the reduction of the nitropyrroles.

4-Acetyl-3-amino-5-methyl-2-phenylpyrrole (**8b**) yield 55%, mp 223° (lit [30] mp 218-220°) and 3-amino-4-ethoxycarbonyl-5-methyl-2-phenylpyrrole (**8c**) yield 41%, mp 105° (lit [31] mp 105°) were prepared from 2-amino-2-phenylacetonitrile and the appropriate 1,3-dicarbonyl compound, according to the procedure described in literature [30].

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