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Protonation of Aminoindoles

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Abstract—The behaviour of 2- and 3-aminoindoles towards protonation was studied using NMR techniques. The protonation site of 2-aminoindoles **1** depends on the substituent at the adjacent 3-position. Thus, the 2-aminoindoles **1a**,**b**, with a hydrogen or a phenyl in 3-position, were protonated at the 3-position, whereas **1c**,**d**, bearing electron withdrawing groups, were protonated at the exocyclic nitrogen. In contrast, 3-aminoindoles **2** were always protonated at the amino group.

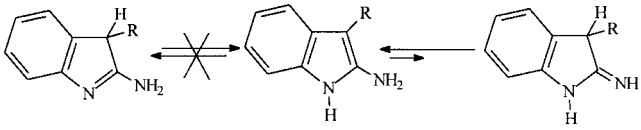
3-Aminoindoles have been utilised as key intermediates for the synthesis of compounds of pharmaceutical interest. Although little is known about the reactivity of 3-aminoindoles, they appear to behave as aromatic amines in their acylation to produce 3-acylaminoindoles and reaction with aromatic aldehydes to form imines.[1] They also undergo diazotisation to give isolable indole 3-diazonium salts or 3-diazoindoles upon neutralisation.[2] The latter compounds undergo coupling reaction with secondary amines to give the corresponding 3-triazenoindoles, which showed in vitro antileukemic activity at submicromolar concentrations.[3]

2-Aminoindoles can also be precursors of pharmacologically active compounds such as 2-diazoindoles and 2-triazenoindoles, the latter related to a triazenoimidazole derivative, dacarbazine, which is currently used in therapy against malignant melanoma and Hodgkin's disease.[4]

2-Aminoindoles are also useful building blocks for the preparation of new ring systems, such as the indolo[2,1-d]-[1,2,3,5]tetrazine related to temozolomide, the antitumour drug active against malignant melanoma, mycosis fungoide and brain tumours.[5] 2-Aminoindoles, however, are not easily available since they are unstable, difficult to handle and autoxidise extremely rapidly. Consequently, comparatively few chemical reactions have been examined and diazotisation is not among them.[6]

As protonation studies carried out on aminopyrroles[7] contributed to the understanding of the behaviour of these derivatives toward electrophiles and to the isolation of 2-diazopyrroles,[8] we prepared some 2- and 3-aminoindoles in order to study their tautomerism and their behaviour towards protonation, which should provide information about the feasibility of the diazotisation reaction of 2-aminoindoles and could lead to the unknown 2-diazoindoles.

Thus, 2-aminoindoles **1a**–**d** were prepared using known procedures.[9] The ^{1}H and ^{13}C NMR spectra of the free bases were measured in deuteriated dimethylsulfoxide. Comparison of the spectral data with those of other substituted indoles[10] shows the spectra to be compatible with the amino tautomeric form **A**, and not with an alternative imino structure **B**.



C **A** **B**

1 a-d

Only in the case of 2-aminoindole (**1a**) was the presence of a small amount (5%) of the imino tautomer **B** observed. The salient signals in the ^{1}H NMR spectrum for form **B** (Table 1) are a singlet for two protons at δ 3.50 due to the methylene at the C(3) and two exchangeable singlets for one proton each at δ 8.03 and 10.18 attributable to exocyclic and endocyclic NH, respectively. The ^{13}C NMR spectrum (Table 4) confirms the presence of the form **B**, showing a triplet at δ 37.4 for C(3) and a singlet at δ 159.1 due to C(2).

This observation contrasts with the report in which, on the basis of chemical and physico-chemical arguments, the 2-aminoindole was formulated as 2-aminoindolenine **C**.[9d,11]

Keywords: amines; indoles; tautomerism; protonation.

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Table 1. ^{1}H NMR data for 2-aminoindoles (DMSO)

Compound	Position						
	1	2	3	4	5	6	7
1a	10.07	5.16	5.21	6.89–7.19	6.56–6.79	6.56–6.79	6.89–7.19
R=H	(1H, s) **A**	(2H, s) **A**	(1H, s) **A**	(2H, m)	(2H, m)	(2H, m)	(2H, m)
A+B	10.18	8.03	3.50	**A+B**	**A+B**	**A+B**	**A+B**
	(1H, s) **B**	(1H, s) **B**	(2H, s) **B**				
1b	10.28	5.36	7.15	7.54	6.83	6.90	7.54
R=Ph	(1H, s)	(2H, s)	(2H, dt)	(1H, dd)	(1H, dt)	(1H, dt)	(1H, dd)
A			7.35				
			(3H, m)				
1c	10.57	6.69	1.32	7.56	6.87	6.95	7.11
R=CO_2Et	(1H, s)	(2H, bs)	(3H, t)	(1H, d)	(1H, t)	(1H, t)	(1H, d)
A			4.22				
			(2H, q)				
1d	10.77	7.50	2.40	7.42	6.92	7.00	7.15
R=COMe	(1H, s)	(2H, bs)	(3H, s)	(1H, dd)	(1H, dt)	(1H, dt)	(1H, dd)
A							

Table 2. ^{1}H NMR data for protonated 2-aminoindoles (DMSO/TFA)

Compound	Position						
	1	2	3	4	5	6	7
1a	12.41	9.86	4.17	7.39	7.12	7.18	7.27
R=H	(1H, s)	(1H, s)	(2H, s)	(1H, dd)	(1H, dt)	(1H, dt)	(1H, dd)
RP		10.02					
		(1H, s)					
1b	12.50	9.91	5.62	7.40–7.48	7.08–7.15	7.08–7.15	7.40–7.48
R=Ph	(1H, s)	(1H, s)	(1H, s)	(1H, m)	(1H, m)	(1H, m)	(1H, m)
RP		10.11	7.27–7.33				
		(1H, s)	(5H, m)				
1c	10.69	10.95	1.34	7.60	6.89	6.97	7.14
R=CO_2Et	(1H, s)	(3H, bs)	(3H, t)	(1H, d)	(1H, t)	(1H, t)	(1H, d)
EP			4.25				
			(2H, q)				
1d	11.19	14.32	2.53	7.49	7.03	7.03	7.19
R=COMe	(1H, s)	(3H, bs)	(3H, s)	(1H, dd)	(1H, dt)	(1H, dt)	(1H, dd)
EP							

The protonated species were generated either by addition of two-fold excess of trifluoroacetic acid to the deuteriated dimethylsulfoxide solution or by using pure trifluoroacetic acid (TFA) as a solvent, conditions that we used in our studies of the protonation of aminopyrroles.[7]

An evaluation of the ^{1}H NMR spectral data of the free bases of 2-aminoindoles and of their protonated forms in dimethylsulfoxide/trifluoroacetic acid (DMSO/TFA) indicates that the protonation site depends on the substituent in the 3-position. In fact, with **1a** and **1b** (R=H, Ph)

Table 3. ^{1}H NMR data for protonated 2-aminoindoles (TFA)

Compound	Position						
	1	2	3	4	5	6	7
1a	10.17	8.12 (1H, s)	4.26	7.35	7.43	7.43	7.26
R=H	(1H, s)	8.21 (1H, s)	(2H, s)	(1H, d)	(1H, t)	(1H, t)	(1H, d)
RP							
1b	10.11	7.44 (1H, s)	5.10 (1H, s)	7.12–7.22	7.12–7.22	7.12–7.22	7.12–7.22
R=Ph	(1H, s)	7.99 (1H, s)	6.90–7.10	(1H, m)	(1H, m)	(1H, m)	(1H, m)
RP			(5H, m)				
1c	10.68	9.52 (3H, bs)	1.46 (6H, t)	7.72	7.40	7.53	7.28
R=CO_2Et	(1H, s)	**EP**	**EP+RP**	(2H, d)	(2H, t)	(2H, t)	(2H, d)
EP+RP	**EP**	8.76 (1H, s)	4.52 (4H, q)	**EP+RP**	**EP+RP**	**EP+RP**	**EP+RP**
	10.76	**RP**	**EP+RP**				
	(1H, s)	8.88 (1H, s)	5.37 (1H, s)				
	RP	**RP**	**RP**				
1d	8.37	10.54	1.62	6.35	6.14	6.14	6.02
R=COMe	(1H, s)	(3H, bs)	(3H, s)	(1H, d)	(1H, t)	(1H, t)	(1H, d)
EP							

Table 4. ^{13}C NMR data for 2-aminoindoles (DMSO)

Compound	Position								
	C(2)	C(3)	C(3a)	C(4)	C(5)	C(6)	C(7)	C(7a)	R
1a	146.3	37.4	130.3	116.2	118.3	115.7	108.8	132.7	
R=H	(s) **A**	(t) **B**	(s) **A**	(d) **A**	(d) **A**	(d) **A**	(d) **A**	(s) **A**	
A+**B**	159.1	78.5	131.9	122.5	126.9	119.5	114.6	139.9	
	(s) **B**	(d) **A**	(s) **B**	(d) **B**	(d) **B**	(d) **B**	(d) **B**	(s) **B**	
1b	143.0	92.4	128.1	117.7	119.1	114.9	109.5	132.4	123.5 (d)
R=Ph	(s)	(s)	(s)	(d)	(d)	(d)	(d)	(s)	126.9 (d)
A									128.7 (d)
									136.4 (s)
1c	153.5	83.5	126.6	119.2	120.3	118.0	109.7	132.6	14.7 (q)
R=CO_2Et	(s)	(s)	(s)	(d)	(d)	(d)	(d)	(s)	58.0 (t)
A									165.8 (s)
1d	154.1	96.3	126.2	119.6	120.6	117.5	110.0	133.1	29.6 (q)
R=COMe	(s)	(s)	(s)	(d)	(d)	(d)	(d)	(s)	190.0(s)
A									

protonation took place at 3-position (Ring Protonation, **RP**) giving rise to a signal for two protons at δ 4.17 in the case of **1a** and a signal for one proton at δ 5.62 in the case of **1b** (Table 2). The immonium protons appear as two singlets at δ 9.86–9.91 and δ 10.02–10.11, due to a strong double bond character between C(2) and the exocyclic nitrogen. The indole NH signals were found at δ 12.41–12.50 showing a downfield shift of 2.2–2.3 ppm relative to signals for the free bases. In contrast, in the case of **1c** and **1d** (R=CO_2Et, COMe), protonation took place at the amino group (Exocyclic Protonation, **EP**). All the ^1H signals showed downfield shifts with no changes in multiplicity and there was no sign of upfield signals expected for the ring protonated species. The broadened signals attributable to the 2-amino group showed a downfield shift of about 4.3–6.8 ppm and the integration of the signals increased from two to three protons. The resonance signal for the indole NH showed 0.1–0.4 ppm downfield shift. The different reactivity between compounds **1a**,**b** and **1c**,**d** is due to the electron withdrawing effect of the acetyl and ethoxycarbonyl groups which reduce the indole ring basicity enough to allow the protonation of the amino group. Under more severe acid conditions (in pure TFA) the behaviour of 2-aminoindoles is identical to that already observed in DMSO/TFA with the sole exception of **1c** (R=CO_2Et), which is also protonated at the nucleus (87.5%) (Table 3).

It was expected that protonation of either the amino group or of the indole ring would lead to distinct changes in the ^{13}C chemical shifts of the C(2) carbon and the C(3) carbon resonances, respectively. Thus, protonation on the amino group, (**EP**), produces a non-stabilised cation but does not disrupt the aromatic character of the indole ring. Such a situation involves an upfield shift of the C(2) carbon and downfield shift of the C(3) carbon resonances. Such behaviour was shown by aniline, 3-aminothiophenes, 4-aminopyrazoles, 2- and 3-aminopyrroles.[7,12] In contrast, protonation on the ring (**RP**) produces resonance stabilised cations which involves a downfield shift of the C(2) carbon and an upfield shift of the protonated carbon C(3). This behaviour was also shown by aminopyrroles on protonation in pure TFA.[7]

Examination of the ^{13}C NMR spectra (Tables 5 and 6) confirms the site of protonation assigned from ^1H NMR data. The ^{13}C spectra of the protonated species of **1a**,**b** show a downfield shift of 25.6–30.4 ppm of the C(2) resonances in DMSO/TFA. In pure TFA, the C(2) resonances of the ring protonated species **RP** show a downfield shift of 19.0–30.4 ppm. The carbon C(3) resonances shift upfield by 39.6–42.1 ppm in DMSO/TFA and 39.6–43.7 ppm in pure TFA. The ^{13}C spectra of the conjugate acids of **1c**,**d** show that the indole ring retains aromaticity and the C(2) resonances shift upfield by 26.5–28.7 ppm in DMSO/TFA and 25.4–32.6 ppm in pure TFA and those of C(3) shift downfield by 0.5–1.9 ppm in DMSO/TFA and 5.8–11.6 ppm in pure TFA.

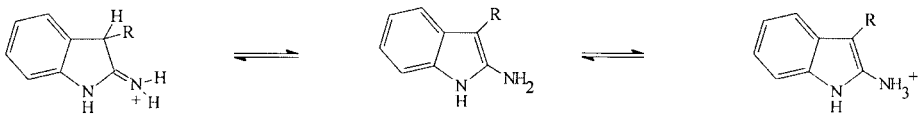
Thus, the behaviour of 2-aminoindoles differs from that of 2-aminopyrroles, which are protonated at the exocyclic nitrogen in DMSO/TFA, even in the absence of substituents on the adjacent position; in pure TFA the protonation takes place at the nucleus.[7]

The 3-aminoindoles **2a**–**c** were also prepared by standard procedures[13] and the ^1H and ^{13}C NMR spectra of the free bases and of their conjugate acids were recorded under the same conditions used for the 2-aminoindoles.

Signals for NH_2 and the indole NH of the free bases **2a**–**c** were at δ 4.48–5.49 and at δ 10.15–10.73, respectively (Table 7). The protonated forms in DMSO/TFA (Table 8) exhibited a broadened signal for three protons at δ 10.33–10.59 showing a downfield shift of 4.8–6.0 ppm relative to the free bases; the imine protons were found at δ 11.31–12.16 with downfield shift of 1.2–1.4 ppm. In pure TFA (Table 9), an upfield shift of the imine proton (0.7–1.9 ppm) and a downfield shift of the ammonium protons (2.6–4.1 ppm) were observed relative to the spectra measured in DMSO/TFA, as in the case of aminopyrroles.[7] These data are consistent with a protonation at the exocyclic nitrogen (**EP**).

Examination of the ^{13}C NMR data (Tables 10–12) confirms the protonation site assigned from ^1H NMR data, with the resonances of the carbons C(3) at δ 121.8–135.7, whereas the resonances of the carbons C(2) were at δ 107.0–123.0. The protonated forms showed the signals due to these carbons at δ 103.2–107.1 and 118.6–130.0, respectively, with upfield shift of 18.6–28.6 ppm of the carbon C(3) and a downfield shift of 6.9–11.6 ppm of the carbon C(2).

Protonation of 2-aminoindoles



1

	RP%	EP%
	DMSO/TFA (2 eq)	
a R = H	100	0
b R = Ph	100	0
c R = COOEt	0	100
d R = COMe	0	100
	pure TFA	
a R = H	100	0
b R = Ph	100	0
c R = COOEt	87.5	12.5
d R = COMe	0	100

Table 5. ^{13}C NMR data for protonated 2-aminoindoles (DMSO/TFA)

Compound	Position								
	C(2)	C(3)	C(3a)	C(4)	C(5)	C(6)	C(7)	C(7a)	R
1a	171.9	36.4	127.0	125.0	128.0	124.1	112.1	143.3	
R=H	(s)	(t)	(s)	(d)	(d)	(d)	(d)	(s)	
RP									
1b	173.4	52.8	128.9	125.0	128.8	124.4	112.5	141.9	128.6 (d)
R=Ph	(s)	(d)	(s)	(d)	(d)	(d)	(d)	(s)	129.7 (d)
RP									131.9 (s)
									136.4 (d)
1c	127.0	84.0	133.0	119.7	120.7	118.4	110.0	153.9	15.0 (q)
R=CO_2Et	(s)	(s)	(s)	(d)	(d)	(d)	(d)	(s)	58.4 (t)
EP									166.3 (s)
1d	125.4	98.2	135.0	121.6	121.9	118.9	110.7	156.0	26.6 (q)
R=COMe	(s)	(s)	(s)	(d)	(d)	(d)	(d)	(s)	185.7 (s)
EP									

In pure TFA the observed shifts were substantially identical in direction and magnitude.

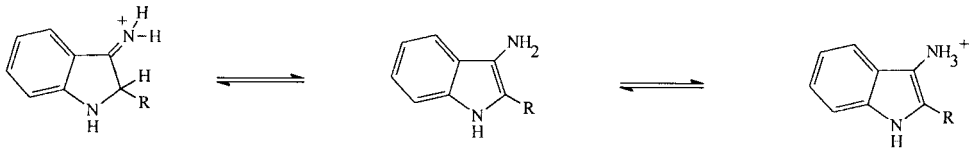
The behaviour of 3-aminoindoles, with protonation occurring at the amine nitrogen in both acid media, differs from that of 3-aminopyrroles, which are protonated at the exocyclic nitrogen in DMSO/TFA, but are protonated at the ring in pure TFA.[7]

In conclusion, an evaluation of the behaviour of aminoindoles

Table 6. ^{13}C NMR data for protonated 2-aminoindoles (TFA)

Compound	Position								
	C(2)	C(3)	C(3a)	C(4)	C(5)	C(6)	C(7)	C(7a)	R
1a	171.1	34.8	123.5	125.0	128.2	123.6	111.2	139.3	
R=H	(s)	(t)	(s)	(d)	(d)	(d)	(d)	(s)	
RP									
1b	173.4	52.8	128.9	125.0	128.8	124.4	112.5	141.9	128.6 (d)
R=Ph	(s)	(d)	(s)	(d)	(d)	(d)	(d)	(s)	129.7 (d)
RP									131.9 (s)
									136.4 (d)
1c	128.1	95.1	134.1	125.3	128.5	124.0	111.5	162. 9	11.3 (q) **EP**
R=CO_2Et	(s) **EP**	(s) **EP**	(s) **EP**	(d) **EP**	(d) **EP**	(d) **EP**	(d) **EP**	(s) **EP**	11.5 (q) **RP**
EP+RP	172.5	52.1	125.1	125.7	130.0	124.8	112.3	139.5	64.9 (t) **RP**
	(s) **RP**	(d) **RP**	(s) **RP**	(d) **RP**	(d) **RP**	(d) **RP**	(d) **RP**	(s) **RP**	65.4 (t) **EP**
									166.3 (s) **RP**
									167.3 (s) **EP**
1d	121.5	102.1	136.0	123.4	126.1	119.9	110.5	158.3	19.9 (q)
R=COMe	(s)	(s)	(s)	(d)	(d)	(d)	(d)	(s)	173.8 (s)
EP									

Protonation of 3-aminoindoles in DMSO/TFA or pure DMSO



2

	RP%	EP%
a R = COOEt	0	100
b R = Ph	0	100
c R = 4-ClC$_6$H$_4$	0	100

Table 7. ^{1}H NMR data for 3-aminoindoles (DMSO)

Compound	Position						
	1	2	3	4	5	6	7
2a	10.15	1.38 (3H, t)	5.49	7.69	6.88	7.17	7.24
R=CO_2Et	(1H, s)	4.32 (2H, q)	(2H, s)	(1H, d)	(1H, t)	(1H, t)	(1H, d)
EP							
2b	10.50	6.90 (1H, t)	4.48	7.68	7.05	7.17	7.25
R=Ph	(1H, s)	7.40 (2H, t)	(2H, s)	(1H, d)	(1H, t)	(1H, t)	(1H, d)
EP		7.80 (2H, d)					
2c	10.73	7.02 (1H, d)	4.58	7.73–7.85	7.44	7.44	7.73–7.85
R=4-ClC_6H_4	(1H, s)	7.18–7.26 (2H, m)	(2H, s)	(1H, m)	(1H, t)	(1H, t)	(1H, m)
EP		7.73–7.85 (1H, m)					

against protonation allows us to be confident of the feasibility of the diazotisation reaction, at least for derivatives bearing electron withdrawing substituents, particularly under weakly acid reaction conditions. In fact, 3-aminoindoles that very easily undergo diazotisation to give either diazonium salts or diazo compounds are protonated at the exocyclic nitrogen both in DMSO/TFA and pure TFA. 2-Aminoindoles, which instead undergo exocyclic protonation, need an electron withdrawing group at the 3-position.

Table 8. ^{1}H NMR data for protonated 3-aminoindoles (DMSO/TFA)

Compound	Position						
	1	2	3	4	5	6	7
2a	11.30	1.37 (3H, t)	10.33	7.86	7.05	7.30	7.39
R=CO_2Et	(1H, s)	4.37 (2H, q)	(3H, bs)	(1H, d)	(1H, t)	(1H, t)	(1H, d)
EP							
2b	11.90	7.25 (1H, t)	10.37	7.86	7.17	7.50	7.49
R=Ph	(1H, s)	7.60 (2H, t)	(3H, bs)	(1H, d)	(1H, t)	(1H, t)	(1H, d)
EP		7.79 (2H, d)					
2c	12.10	7.21–7.25 (1H, m)	10.59	7.90–7.94	7.76–7.80	7.76–7.80	7.90–7.94
R=4-ClC_6H_4	(1H, s)	7.47–7.63 (3H, m)	(3H, bs)	(1H, m)	(1H, m)	(1H, m)	(1H, m)
EP							

Table 9. ^{1}H NMR data for protonated 3-aminoindoles (TFA)

Compound	Position						
	1	2	3	4	5	6	7
2a	9.45	1.13 (3H, t)	8.10	7.22	6.83	6.98	7.06
R=CO_2Et	(1H, s)	4.12 (2H, q)	(3H, bs)	(1H, d)	(1H, t)	(1H, t)	(1H, d)
EP							
2b	8.63	7.26	8.39	7.34	6.98	7.06	7.18
R=Ph	(1H, s)	(5H, s)	(3H, bs)	(1H, d)	(1H, t)	(1H, t)	(1H, d)
EP							
2c	9.01	7.15 (2H, d)	8.64	7.48–7.51	7.41–7.45	7.41–7.45	7.48–7.51
R=4-ClC_6H_4	(1H, s)	7.27 (2H, d)	(3H, bs)	(1H, m)	(1H, m)	(1H, m)	(1H, m)
EP							

Table 10. ^{13}C NMR data for 3-aminoindoles (DMSO)

Compound	Position								
	C(2)	C(3)	C(3a)	C(4)	C(5)	C(6)	C(7)	C(7a)	R
2a	107.0	135.7	118.7	120.3	125.8	117.3	112.0	136.6	14.7 (q)
R=CO_2Et	(s)	(s)	(s)	(d)	(d)	(d)	(d)	(s)	59.0 (t)
EP									162.4 (s)
2b	123.0	122.9	118.9	118.3	121.9	117.3	110.8	135.0	125.0 (d)
R=Ph	(s)	(s)	(s)	(d)	(d)	(d)	(d)	(s)	125.1 (d)
EP									128.7 (d)
									133.6 (s)
2c	122.5	121.8	120.4	121.5	125.4	117.5	112.2	133.1	123.7 (s)
R=4-ClC_6H_4	(s)	(s)	(s)	(d)	(d)	(d)	(d)	(s)	125.1 (d)
EP									128.6 (d)
									133.0 (s)

Table 11. ^{13}C NMR data for protonated 3-aminoindoles (DMSO/TFA)

Compound	Position								
	C(2)	C(3)	C(3a)	C(4)	C(5)	C(6)	C(7)	C(7a)	R
2a	118.6	107.1	119.8	120.1	126.1	119.1	112.6	1359	14.4 (q)
R=CO_2Et	(s)	(s)	(s)	(d)	(d)	(d)	(d)	(s)	60.2 (t)
EP									161.5 (s)
2b	130.0	103.4	122.9	120.3	123.1	117.7	112.1	134.4	128.1 (d)
R=Ph	(s)	(s)	(s)	(d)	(d)	(d)	(d)	(s)	128.9 (d)
EP									129.3 (d)
									131.1 (s)
2c	129.4	103.2	123.7	122.8	128.9	116.8	113.6	132.7	124.6 (s)
R=4-ClC_6H_4	(s)	(s)	(s)	(d)	(d)	(d)	(d)	(s)	127.9 (d)
EP									129.1 (d)
									132.5 (s)

Table 12. ^{13}C NMR data for protonated 3-aminoindoles (TFA)

Compound	Position								
	C(2)	C(3)	C(3a)	C(4)	C(5)	C(6)	C(7)	C(7a)	R
2a	117.6	110.6	119.3	122.5	127.6	116.6	112.2	134.6	11.6 (q)
R=CO_2Et	(s)	(s)	(s)	(d)	(d)	(d)	(d)	(s)	63.4 (t)
EP									162.4 (s)
2b	126.1	100.1	120.4	120.7	123.4	114.7	111.0	133.5	127.0 (d)
R=Ph	(s)	(s)	(s)	(d)	(d)	(d)	(d)	(s)	128.6 (d)
EP									129.2 (d)
									132.0 (s)
2c	128.3	101.1	121.7	121.9	127.4	114.9	112.1	131.6	123.4 (s)
R=4-ClC_6H_4	(s)	(s)	(s)	(d)	(d)	(d)	(d)	(s)	127.0 (d)
EP									127.9 (d)
									131.3 (s)

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 410 spectrophotometer; ^1H and ^{13}C NMR spectra were measured at 200 and 50.3 MHz, respectively, with TMS as internal reference in DMSO-d_6 solution using a Bruker AC series 200 MHz spectrometer. Protonation was achieved by adding two equivalents of trifluoroacetic acid to the DMSO solutions or dissolving the samples directly in TFA.

Preparation of 2-aminoindoles 1a–d

2-Aminoindole (**1a**) was prepared from 2-nitrophenylacetonitrile by catalytic reduction and successive ring closure of the corresponding amino derivative, according to the procedure described in the literature.[9a] Yield 85%, mp 148°C; IR: 3447, 3353 and 3205 (NH_2 and NH) cm^{-1}.

2-Amino-3-phenylindole (**1b**) was prepared as the hydrochloride from 1-phenyl-2-phenylacetylhydrazine and phosphorous oxychloride according to the procedure described in the literature.[9b] Yield 50%, mp 212°C; IR: 3200–2750 (=NH_2^+ and NH) cm^{-1}. The free base was obtained just before its use since it is very easily oxidised in air. The hydrochloride was shaken in an aqueous solution of sodium carbonate (10%) under nitrogen. After 15 min, dichloromethane was added and the free base extracted. The organic layer was then evaporated under reduced pressure and the resultant oil was kept under nitrogen which was maintained even in the NMR tube during the measurements of the spectra.

Ethyl 2-aminoindole-3-carboxylate (**1c**) was prepared from 2-chloronitrobenzene and the sodium salt of ethyl cyanoacetate and followed by reduction according to the procedure described in the literature.[9c] Yield 65%, mp 182°C, IR: 3461, 3353–3300 (NH_2 and NH), 1650 (CO) cm^{-1}.

2-Amino-3-acetylindole (**1d**) was prepared from 2-aminoindole (**1a**) by two sequences of acetylation/hydrolysis according to the procedure described in the literature.[9d] Overall yield 38%, mp 176°C; IR: 3379, 3346 and 3281 (NH_2 and NH), 1595 (CO) cm^{-1}.

Preparation of 3-aminoindoles 2a–c

Ethyl 3-aminoindole-2-carboxylate (**2a**) was prepared by reaction of 2-aminobenzonitrile and ethyl bromoacetate, followed by cyclisation with potassium *t*-butoxide according to the procedure described in the literature.[13a] Yield 90%, mp 150–152°C, IR: 3460, 3347 and 3250 (NH_2 and NH), 1742 (CO) cm^{-1}.

3-Amino-2-phenylindole (**2b**) and 3-amino-2-(4-chlorophenyl)indole (**2c**) were prepared by reduction of the corresponding nitroso derivatives according to the procedure described in the literature.[13b] **2b**: yield 97%, mp 179°C; IR: 3420, 3310 and 3260 (NH_2 and NH) cm^{-1}. **2c**: yield 88%, mp 205°C, IR: 3406, 3330 and 3165 (NH_2 and NH) cm^{-1}.

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