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INDOLE DERIVATIVES.

131.* THE BASICITY OF 5- AND 6-AMINOINDOLES

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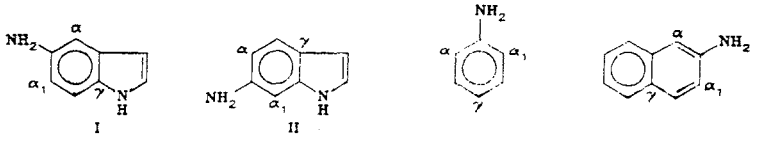
The pK_a values for the 5- and 6-aminoindoles were determined from potentiometric titration curves and from ^{13}C NMR data on the total change of the chemical shifts of the carbon atom signals on protonation of the amino group. The pK_a values obtained (5.99 and 5.53) were higher than those of aniline (3.92) or β-naphthylamine (3.39).

A number of different methods of synthesizing the 5- and 6-aminoindoles (I and II) have been reported [2-8] and a recent review describes methods of synthesizing compound I [9]. However, there is little information in the literature on the properties of these compounds and, in particular, there is no data on their basicity.



I II

*For Communication 130, see [1].

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TABLE 1. ^{1}H and ^{13}C NMR Spectroscopic Data for the 5- and 6-Aminoindoles (in $CDCl_3$)

Compound	$\delta_{^1H}$, $\delta_{^{13}C}$, ppm									J (^1H), Hz
	1-H	2-H $C_{(2)}$	3-H $C_{(3)}$	4-H $C_{(4)}$	5-H $C_{(5)}$	6-H $C_{(6)}$	7-H $C_{(7)}$	$C_{(8)}$	$C_{(9)}$	
5-Aminoindole	7,94	7,13	6,37	6,95	3,50*	6,67	7,20	—	—	$J_{12}=2,59$; $J_{23}=3,05$; $J_{13}=1,98$; $J_{37}=0,95$
	—	124,68	101,61	105,55	139,56	112,93	111,00	128,83	130,67	$J_{14}=J_{47}=0,6$; $J_{67}=8,55$; $J_{46}=2,14$
6-Aminoindole	7,88	7,00	6,42	7,41	6,58	3,00*	6,67	—	—	$J_{12}=2,28$; $J_{23}=3,05$; $J_{13}=1,97$; $J_{34}=0,91$
	—	122,11	102,53	121,33	110,85	142,12	96,55	118,94	137,14	$J_{45}=8,24$, $J_{57}=2,14$

*For amino group.

TABLE 2. pK_a Values for Aromatic Amines, Determined from ^{13}C NMR Spectroscopic Data

Compound	Solvent*	$C_{(1)}$	$C_{(\alpha)}$	$C_{(\alpha_1)}$	$C_{(\gamma)}$	$\Sigma\Delta C_{(\alpha)}\Delta C_{(\alpha_1)} \times \Delta C_{(\gamma)}$	pK_a
Naphthylamine	$CDCl_3$	144,10	108,46	118,11	127,86		
	$CDCl_3+CH_3COOH$	130,88	116,88	125,03	137,22	23,96	3,39**
Aniline	$CDCl_3$	146,41	115,03	115,03	118,40		
	$CDCl_3+CH_3COOH$	135,46	122,20	122,20	127,00	22,94	3,92
6-Aminoindole	$CDCl_3$	142,12	110,85	96,95	118,94		
	$CDCl_3+CH_3COOH$	128,48	114,38	106,99	124,90	19,93	5,49
5-Aminoindole	$CDCl_3$	139,56	105,55	112,93	130,67		
	$CDCl_3+CH_3COOH$	123,01	115,36	116,70	136,06	18,97	5,98

*For all compounds, $CDCl_3$–CH_3COOH, 1:4.
**4.11-0.72, correction obtained for aniline [9, 10].

In the present work we have determined the pK_a values of the aminoindoles I and II, and using NMR we have studied the effects of protonation of these compounds compared with model compounds, aniline and β-naphthylamine.

Compound II was synthesized by the method given in [4]. Compound I was prepared from 5-nitro-N-acetylindoline,* by a modification of the method described in [4]; the simultaneous reduction of the nitro group, removal of the protecting acetyl group, and dehydrogenation was carried out using an aluminum-nickel alloy and sodium hydroxide solution in place of a prepared catalyst. This method gave the aminoindole I as almost colorless crystals, which did not deteriorate after long exposure to light.

The pK_a of compounds I and II, determined by potentiometric titration in 50% ethyl alcohol, were 5.99 and 5.53, respectively. An aqueous—organic solvent was used because compounds I and II were not very soluble in water. The pK_a of the aminoindoles I and II, obtained from ^{13}C NMR spectroscopic data (see Tables 1 and 2) by studying the effects of protonation of the aminoindoles I and II, were very similar to values obtained from the model compounds, aniline and β-naphthylamine. The higher basicity of the aminogroup of these compounds in comparison with aniline and β-naphthylamine appears as a smaller change in the chemical shifts of the carbon atoms adjacent to the protonation center on addition of acid. Most sensitive to the effect of protonation are the ortho- ($C_{(\alpha)}$ and $C_{(\alpha_1)}$) and para- ($C_{(\gamma)}$) carbon atoms; the shifts in the signals of these carbons in acid medium mainly reflect the change in n-π-conjugation. The greater the involvement of the unshared electron pair on the nitrogen atom in the π-conjuation system of the aromatic molecule, the stronger the effect of protonation on atoms $C_{(\alpha)}$ and $C_{(\gamma)}$ and, consequently, the smaller the expected basicity of the amine. The determination of pK_a values for a monotypic series of compounds using ^{13}C NMR was suggested in [10] for isomeric pyrroloquinolines (it is indispensable in the case of compounds which are insoluble in aqueous alcohol).

Values for pK_a of 5.98 and 5.49 for compounds I and II in acetic acid were obtained, i.e., close to the values obtained by potentiometric titration. The high pK_a values for the aminoindoles I and II indicate that the indole ring is a less good electron-acceptor than benzene or naphthalene.

The slope of the straight line obtained by plotting the total change in the shifts of the carbon atoms responsible for the n-π-conjugation against pK_a gave, by analogy, known pK_a values for aminoindoles under the same conditions, [9, 10], while for β-naphthylamine, the extrapolated value of pK_a for 50% solution of water—ethanol was found in the same way as aniline [12]. The value for $\Sigma\Delta C_{(\alpha)}\Delta C_{(\alpha_1)}\Delta C_{(\gamma)}$ which we obtained for aniline agrees well with that given in [13] for protonation in acetic acid, and, consequently, is practically independent of the components of the mixture (with excess acid).

A direct relationship between the changes in chemical shifts of a carbon atom directly bonded to the protonation center and pK_a was not found (Table 2), possibly because of the sensitivity of the paramagnetic component of the chemical shift of this carbon atom to the effect of solvation.

The assignment of lines of the ^{13}C NMR spectra of the indoles I and II, aniline and β-naphthylamine were made on the basis of selectively-uncoupled spectra.

The PMR spectra revealed that compounds I and II exist in the associated state, involving hydrogen bonding of the protons of the indole NH group (proton donor) and the amino group (electron donor); at low concentrations, for the most basic aminoindole I in $CDCl_3$ (5%), the minor coupling constant in the PMR spectrum, which is associated with the hydrogen-bonded system disappears (Table 1).

An attempt to carry out the protonation of the aminoindoles I and II with trifluoroacetic acid led to the instantaneous oligomerization, which is characteristic of indoles.

EXPERIMENTAL

Basicity constants were calculated from potentiometric titration curves of $1 \cdot 10^{-3}$ M solutions in 50% ethanol at 25°C; pH was measured on a PHM-26 pH meter with glass (2222B) and calomel (K 4112) electrodes (Radiometer, Denmark). Three titrations were carried out for each

*We obtained this compound from N-acetylindoline by nitration in acetic acid (see the experimental section).

compound and 6-7 constants were determined over the neutralization range 20-80%. The standard error was less than 0.05 units of pK_a.

NMR spectra were recorded on a Bruker-WP-200-SY spectrometer, internal standard TMS. Deuterochloroform was used as solvent and internal lock.

5-Nitro-N-acetylindoline. To a solution of 11.8 g (0.07 mole) of N-acetylindoline in 95 ml of acetic acid at 9-12°C, was added dropwise over a period of one hour 11 ml of fuming nitric acid (1.5). The reaction mixture was maintained at room temperature for 1.5 h and then poured into 500 ml of ice water. The material which precipitated was filtered off, washed with water, and dried in air to give 1.5 g (77%) of 5-nitro-N-acetylindoline with mp 174-175°C.

5-Aminoindole (I). To a vigorously stirred mixture of 6.0 g (0.03 mole) of N-acetyl-5-nitroindole, 75 ml of water, and 20 g of aluminum-nickel alloy was added dropwise, over a period of 2 h, a solution of 35 g of sodium hydroxide in 100 ml of water. After stirring for 1.5 h, the hot solution was filtered to give 2.2 g (56%) of compound I with mp 130°C. Recrystallization from a mixture of benzene and petroleum ether gave colorless crystals with mp 131°C (literature value 130°C [2]).

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