Influence of Substituents upon the Basicity, Spectral Characteristics, and Lipophilicity of a Series of 3-Aminopyridazines

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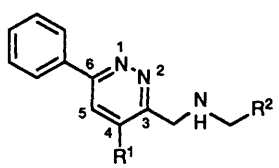
The protonation and partition thermodynamics of a series of substituted 3-aminopyridazines have been studied. The lead compound, 4-methyl-3-(2-morpholinoethylamino)-6-phenylpyridazine, minaprine, is a commercialized antidepressant drug.

The protonation constants were determined by potentiometric and/or spectrophotometric methods which also enabled us to calculate the electronic spectra of the different species. Although there are at least four potentially protonizable sites, only two constants could be determined, which correspond to the morpholino nitrogen (K_1) and to one of the nitrogen atoms of the amidino group (K_2)·log K_1 (to a smaller extent) and especially log K_2 is shown to be linearly related to the classical Taft and Hammett electronic parameters for the different substituents. However, the correlation between partition coefficients (P) or distribution coefficients at physiological pH (P') and lipophilic parameters such as those of Hansch, or the Rekker and Leo fragmental constants, is not as obvious.

4-Methyl-3-(2-morpholinoethylamino)-6-phenylpyridazine (**1**), minaprine, was synthetized by Wermuth and Exinger[1] and was recently shown to be an antidepressant drug exhibiting dopamino- and serotonino-mimetic activity but neither noradrenergic nor anticholinergic effects.[2–6] Our understanding of the mechanism through which minaprine exerts these effects requires synthesis and pharmacological as well as physicochemical studies of a great number of structural analogues. The results so far obtained by Wermuth *et al.*[6,7] show that the presence of the 3-aminopyridazine subunit, bearing small substituents in the 4-position, is necessary for the production of pharmacological activity and that the basicity of this subunit is an important factor.



(1) R^1 = Me, R^2 = morpholine

We report the acid–base and spectroscopic properties of 13 minaprine analogues (**2**)–(**14**),† differently substituted at position four of the pyridazine moiety of minaprine. The lipophilic properties of some representative derivatives have been investigated. Three additional derivatives (**15**)–(**17**)† bearing a primary amine in place of the morpholinic group [see structure (**1**)] have also been included in the study as simpler reference compounds. Some of these derivatives, bearing alcohol, aldehyde, or carboxylic groups, may likely represent metabolites of minaprine. The interest in the different substitution groups lies in the variety of pharmacological responses induced by the nature of the substituent. This variety may be accounted for, at least partly, by the modifications of the electronic distribution in the pyridazinic ring—and hence in the basicity of the amidino group—subsequent to the differences in electron-withdrawing or -donor effects of the various substituents. The objective of the present work is consequently to examine the effects of electronic perturbations upon the basicity of the amidino group.

A further aim is the collection of some experimental electronic and lipophilic parameters classically used in the establishment of quantitative structure–activity relationships (QSAR).[8]

† The differing R^1 groups in compounds (**2**)–(**14**) are indicated in Table 1. In all cases the substituent at C-3 is 2-morpholinoethylamino. Compounds (**15**)–(**17**) are defined in Table 2.

Experimental

Materials.—The 17 analogues were synthesized as described elsewhere[7,9,10] and were available either in the basic form or as the mono- or di-hydrochloride. All other materials were of analytical or reagent grade purity and were used without further purification, except octan-1-ol (Merck) which was washed successively three times with 8 mol dm^{-3} H_2SO_4, twice with distilled water, three times with 2 mol dm^{-3} NaOH, and again four times with distilled water. In each case the volume of the washing solution was 10% of the volume of the solvent, which was finally distilled at 72 °C under reduced pressure.

Protonation Constant Determinations. Potentiometric Measurements.—Back-titrations (with NaOH) of acidic solutions obtained by dissolving the ligand ($10^{-4} \leqslant C_L \leqslant 10^{-3}$ mol dm^{-3}) in a slight excess of $HClO_4$ (Prolabo RP) were performed at 25 °C. All solutions were brought to 0.1 mol dm^{-3} ionic strength with $NaClO_4$. A combined glass electrode (Beckmann reference 39501) connected to a Tacussel Ionometer was used to measure the pH-values (pH = co-logarithm of the *hydrogen ion concentration*). The standard filling solution (saturated aq. KCl) was replaced by a mixture of aq. NaCl and $NaClO_4$ (5×10^{-2} mol dm^{-3}) saturated with AgCl. The electrode was calibrated at pH 2 with a solution of 10^{-2} mol dm^{-3} $HClO_4$ in the presence of 9×10^{-2} mol dm^{-3} $NaClO_4$. As the junction potential varies exponentially with pH,[11] relationship (1) was used to correct

$$pH_{real} = pH_{measd} + a + b \cdot 10^{-pH_{measd}} \quad (1)$$

Table 1. Protonation constants (as log $K \pm 2\sigma$), and fraction of basic form ($1 - \alpha$) at plasma pH (7.4), of minaprine and its derivatives, at 25 °C (n = number of experimental points).

Compound	R^1	pH range	n	log $K_1 \pm 2\sigma$	log $K_2 \pm 2\sigma$	$1 - \alpha$
(1)	Me	3.0–9.9	305	(7.05 ± 0.07)	(4.0 ± 0.1)	0.69
(2)	Et	3.8–8.6	85	7.08 ± 0.01	4.37 ± 0.03	0.65
(3)	Ch_2Ph	0.5–8.7	308	(6.95 ± 0.07)	(3.6 ± 0.1)	0.74
(4)	H	3.2–8.1	46	6.74 ± 0.01	3.74 ± 0.03	0.82
(5)	CH_2OH	3.5–7.7	74	6.99 ± 0.01	3.81 ± 0.03	0.72
(6)	Ph	4.1–7.6	23	6.75 ± 0.02	3.42 ± 0.06	0.77
		2.0–8.6	336	(6.88 ± 0.08)	(3.3 ± 0.2)	
(7)	$CONH_2$	3.5–8.6	51	6.85 ± 0.02	2.5 ± 0.2	0.82
(8)	CO_2H	6.1–7.6	76	7.07 ± 0.01		0.68
		3.2–4.3	144		3.33 ± 0.03	
		0.5–4.3	72		log K_3 = (1.1 ± 0.3)	
(9)	CHO	6.5–7.4	4	6.89 ± 0.02		0.76
		0.1–4.2	8		(2.6 ± 0.4)	
(10)	CO_2Et	0.3–7.8	307	(6.67 ± 0.12)	(1.5 ± 0.2)	0.84
(11)	CF_3	6.1–7.4	14	6.75 ± 0.02		0.82
		1.2–3.0	32		(1.44 ± 0.08)	
(12)	Cl	5.8–7.4	12	6.64 ± 0.01		0.85
		0.1–4.2	48		(2.54 ± 0.02)	
(13)	CN	0.1–8.5	335	(6.5 ± 0.1)	(0.5 ± 0.2)	0.90
(14)	NO_2	6.0–7.4	19	6.56 ± 0.01		0.87
		0.1–0.3	31		(0.2 ± 0.1)	

Table 2. Protonation constants (as log $K \pm 2\sigma$), and fraction of basic form ($1 - \alpha$) at plasma pH (7.4), of minaprine derivatives, with $R^2 = NH_2$, at 25 °C.

Compound	R^1	pH range	n	log $K_1 \pm 2\sigma$	log $K_2 \pm 2\sigma$	$1 - \alpha$
(15)	Me	3.9–9.9	61	9.49 ± 0.01	4.67 ± 0.03	0.1
(16)	H	3.7–10.1	53	9.45 ± 0.01	3.99 ± 0.04	0.1
(17)	$CONH_2$	3.2–9.7	49	9.23 ± 0.03	2.87 ± 0.08	0.2

the observed pH, where a and b are constants and were determined by measuring the pH for 10^{-3} mol dm^{-3} $HClO_4$ (9.9×10^{-2} mol dm^{-3} in $NaClO_4$). Under our conditions a and b were, respectively, 0.085 and −8.51. Analytical concentrations and pH-values were treated by the numerical programs SCOGS[12] or MINIQUAD.[13] Thus the refined protonation constants (K) are concentration ratios.

Spectrophotometric Measurements.—In several cases the solubility or/and log K values were very low and the pH-metric method was unsatisfactory. The UV spectrophotometric method was used to determine the protonation constants; the method also provided the spectral characteristics of the various species in solution. The spectra of the ligand solutions at various pH-values were recorded between 210 and 400 nm [500 nm in the case of acidic compound (**8**)] with a Cary 17D spectrophotometer equipped with a printing device. Solutions at different pH were prepared as follows; a stock solution (5 ml) of the ligand dihydrochloride or diperchlorate (10^{-4} mol dm^{-3} $\leqslant C_L \leqslant 10^{-3}$ mol dm^{-3}) were diluted to 50 ml with 0.011 mol dm^{-3} buffers prepared from chloracetic acid ($2 \leqslant pH \leqslant 3$), formic acid ($3 \leqslant pH \leqslant 4$), acetic acid ($4 \leqslant pH \leqslant 6$), or phosphoric acid ($6 \leqslant pH \leqslant 10$). In very acidic regions ($pH \leqslant 2$) conc. hydrochloric acid was used. Except in this medium and in H_3PO_4 solutions, the ionic strength was maintained at 0.01 mol dm^{-3}. pH-Values were measured with a glass electrode standardized as described earlier. The reference solutions were the corresponding buffer solutions without ligands. The protonation constants and molar absorptivities ε, of each species were refined by means of the program LETAGROP-SPEFO,[14] which minimizes the sum U of the squares of the differences between experimental and calculated absorbances. In a few cases when the log K values were well established by pH-metry, the electronic spectra of the free ligand and of the diprotonated form were obtained from very basic and acidic solutions, respectively. Molar absorptivities of the monocationic forms were then calculated from the absorbances of a solution where LH^+ was present either with LH_2 or L, the concentrations of which were obtained from the pH and the ligand analytical concentrations by using program HALTAFALL.[15]

Partition Coefficient Determination.—Partition coefficients (P) were determined according to the method of Hansch[16] by shaking an organic phase [octan-1-ol saturated with NaOH (10^{-2} mol dm^{-3})] with a basic aqueous phase (10^{-2} mol dm^{-3} NaOH saturated with octan-1-ol) containing the ligand. An aqueous stock solution [x ml ($5 \leqslant x \leqslant 10$ ml) (10^{-5} mol $dm^{-3} \leqslant C^{\circ}_{aq} \leqslant 10^{-3}$ mol dm^{-3})] of the ligand was added to the aqueous phase [$(z - x)$ ml] and finally to the organic phase (y ml). Values of y and z were chosen according to the lipophilic character of the substituents R^1. The resulting solutions were stirred for 1 h in a thermoregulated bath maintained at 25 °C and then centrifuged at 2 000 rpm during 2 h. The ligand concentration C'_{aq} in the aqueous phase was determined by spectrophotometry at the main λ_{max} (see Table 3) and P can be described by equation (2). These values, corrected by ($1 - \alpha$),

$$P = z(C^{\circ}_{aq} - C'_{aq})/yC'_{aq} \qquad (2)$$

where α is the degree of protonation of the molecules calculated at pH 7.4, yielded the distribution coefficient P', *i.e.* the apparent partition coefficient at physiological pH.

Results and Discussion

Protonation Constants.—Protonation sites. Results of our pH-metric measurements are summarized in Tables 1 and 2; the

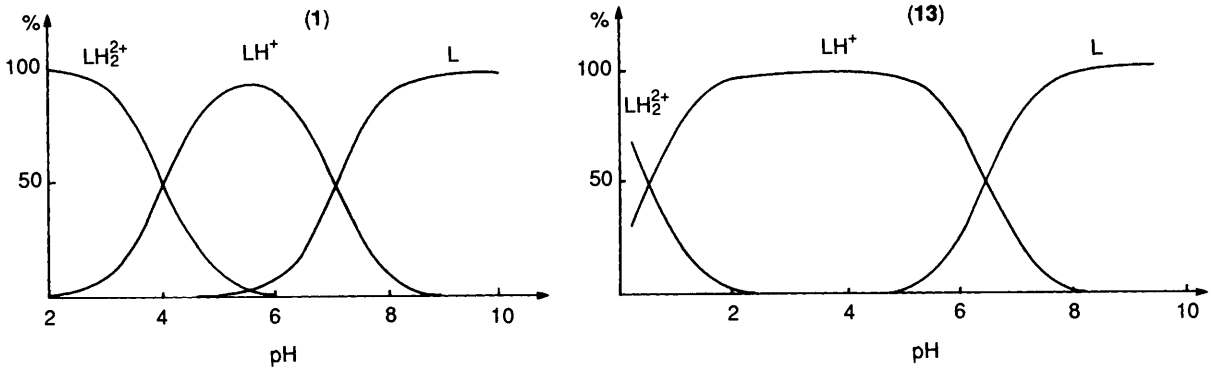


Figure 1. Distribution curves of compounds (**1**; R^1 = Me) and (**13**; R^1 = CN): percentage of ligand in the different species as a function of pH, at 25 °C, in aqueous solution.

given precision is the 95% confidence interval, *i.e.* $\pm 2\sigma$, σ being the standard deviation corresponding to the simultaneous interpretation of a minimum of two distinct experiments. Spectrophotometric results are reported in parentheses. Results for compound (**6**) show a good agreement between the two measurements.

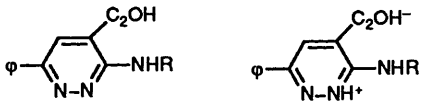
The data clearly show that, although four potential protonation sites are present in each molecule, only two protonated forms, LH^+ and LH_2^{2+}, are evidenced in the pH range explored, except for compound (**8**) (see below).

The values of log K_1 vary from 6.5 for compound (**13**) (R^1 = CN) to 7.08 for compound (**2**) (R^1 = Et) and can be compared with the values of 8.4 and 7.7 reported in the literature for morpholine and *N*-ethylmorpholine respectively.[17] Thus the first protonation site is likely to be the morpholinic nitrogen atom. Log K_2, varying from 0.25 to 4.01, corresponds to the protonation of one of the nitrogens belonging to the amidino group. These values are significantly lower than log K 5.41 which has also been determined in this work for the constitutive 3-amino-4-methyl-6-phenylpyridazine subunit. The results are consistent with the radiocrystallographic studies of some of the derivatives in the solid state, which show two protonations, on the morpholinic site and on the N-2 atom of the pyridazine moiety, respectively.[18–20]

It can be seen from Table 2 that the mean log K_1 value becomes 9.4 when the morpholino group is replaced by a primary amine (R^2 = $[CH_2]_2NH_2$). This value is comparable to that value, 10.05, found for ethylenediamine.[21] In case of log K_2 the same trend is observed but to a much lower extent.

Distribution curves. Minaprine and its derivatives, bearing two basic centres, give rise to three species in equilibrium in solution: the mono- and di-protonated cations and the basic form. Values of $(1 - \alpha)$, *i.e.* the fraction of the basic form at physiological pH (7.4), are of great importance in the bioavailability of these molecules; they can be calculated from the values of log K_1 (Tables 1 and 2). It is seen that minaprine (**1**) and compound (**2**; R^1 = Et) are the most ionized molecules, whereas compounds (**13**) and (**14**) (R^1 = CN and NO_2) are the least ionized as the amount of neutral species present is *ca.* 65% and 90%, respectively. When R^2 = $[CH_2]_2NH_2$ the monocation is predominant at physiological pH. These results are visualized on the distribution curves giving the percentage of ligand engaged in each species as a function of pH (Figure 1). They show that in any case dications do not exist at physiological pH and as a consequence the amidino group is free possibly to interact with a complementary acidic site.

Basicity of the carboxylic derivative (**8**). In the case of compound (**8**), where a carboxylic group is attached to the pyridazine moiety, three log K values were found, one of them corresponding to the carboxylic group. The higher log K_1 constant corresponds to the protonation of the morpholino nitrogen atom as in the other compounds. However, it is more difficult to assign the two lower values. Tri- and monoprotonated as well as fully deprotonated forms are well defined but LH_2^+ is not, as it may exist as one of the species (**a**) and (**b**).



(**a**) (**b**)

Our measurements do not allow us to localize the second proton of LH_2^+. However, the log K_2 value of 3.33 may be attributed to the ionization of the CO_2H group by analogy to benzoic acid (log K 3.98[21]); the very low value of log K_3 would then correspond to the protonation of the amidino group and is consistent with the base-weakening effect of the CO_2H group. In addition it is still possible to predict the acid–base behaviour of a heterocyclic amino acid such as (**a**) by means of the Hammett equations.[22] Using of the equation for substituted benzoic acids (log $K = 4.20 - \Sigma\sigma$), and σ parameters for an *ortho*-NHR substituent and for endocyclic nitrogen atoms in *meta* and *para* positions, the expected ionization constant of the carboxylic group would be 2.88 log units. The protonation constant of N-2 would be estimated to be 1.30 log units from the Hammett equation for pyridine (log $K = 5.25 - 5.90\ \Sigma\sigma$) and σ constants of substituents CO_2H (*meta*), NHR (*ortho*), and one endocyclic nitrogen atom (*ortho*). From these predictions, which show that log K for the amino group is lower than that for the acid, it can be concluded that protonation of compound (**8**) is unlikely to involve the zwitterion form (**b**) and that log K_3 = 1.1 corresponds to the protonation of the amidino group.

Influence of the substitution upon the acid–base properties. Correlation with Taft and Hammett parameters. From a qualitative point of view, log K values are consistent with inductive and resonance effects expected for the various substituents. Thus the highest values are obtained for compounds (**1**) and (**2**) bearing alkyl substitutents with positive inductive effects. On the other hand the lowest value corresponds to compound (**14**) with an NO_2 group having negative inductive effects. Table 1 shows that these effects are intense on the amidino system but much lower, though significant, on the remote morpholinic nitrogen.

Quantitative correlations between log K_2 values and the classical electronic parameters of Taft (σ^*) and Hammett (σ_m or σ_p)[22] have been performed by linear regression analysis. The results indicate that the quality of the correlation increases when going from σ^* to σ_m and σ_p. When all derivatives are treated (N = 14) the correlation coefficients r are 0.923, 0.951,

Table 3. Spectral characteristics (λ_{max}/nm and ε/dm^3 mol^{-1} cm^{-1}) of the different forms of minaprine and its derivatives.

	L		LH^+		LH_2^{2+}	
Ligand L	λ	ε	λ	ε	λ	ε
(1)	245[a]	14 900	245[a]	15 200		
	272	19 000	267	19 200	264	28 100
					325	4 600
(2)	247.5[a]	17 400	250[a]	18 300		
	272	21 000	267	21 000	264.5	31 000
	320[a]	3 400	315	3 300	324.5	5 200
(3)	255[a]	15 300	255	16 600		
	272	17 700	267	18 100	265.5	25 700
	320	2 800	320[a]	2 300	328	4 300
(4)	270.5	24 900	265	25 200	266	32 600
	320[a]	3 200	315	3 000	333	3 600
(5)					262	27 620
					322	4 640
(6)	263	24 200	263	25 000	273	27 600
	317–345	3 000	310–330[a]	3 000	310[a]	8 000
					350[a]	4 000
(7)	272.5	34 700	269	35 200	272.5	40 800
	365	4 200	353	4 600	360	5 800
(8)			267[b]	20 140	272[c]	22 600
			350[b]	2 100	380[c]	2 335
(9)			270	26 510	267	27 000
					340	5 165
(10)	271	21 200	269.5	22 200	272	24 400
	380	2 400	374	2 700	380	2 900
(11)			267	22 350	272	24 300
			340	2 660	362	4 000
(12)			252	13 700		
			267.5	15 200	270	20 650
			330	1 670	340	2 950
(13)					255	13 100
	272	25 600	268	26 200	277	27 200
	380	2 800	375	3 000	395	3 900
(14)			270	21 700	275	20 400
					420	2 470

[a] Shoulder. [b] For LH_2 species. [c] For LH_3 species.

and 0.965 respectively. The correlations with σ_m and σ_p are not very different since the substituents considered in this study have rather close σ_m- and σ_p-values.

The regression with σ_p is improved when compounds (**13**) and (**14**) (R^1 = CO_2H and CHO) are omitted (N = 12). It must be noted that the latter compound has a low solubility leading to less precise results. For the carboxylic derivative, two low values of log K could be determined despite small spectral changes in the acidic region, as explained before. If log K_2 = 3.33 instead of log K_3 = 1.1 were chosen for the protonation of the amidino group (see above) the deviation of compound (**8**) from the best-fit line would be even greater.

Correlations with σ_m and especially with σ^* are improved the same way only if compound (**12**; R^1 = Cl) is also omitted (Table 1). The chlorine atom is expected to exert electron-withdrawing inductive and donor mesomeric effects. As σ_m and σ^* are mostly related to the first mentioned effect, the rather high basicity of compound (**12**) could be explained by the predominance of the mesomeric effect of chlorine.

On the other hand, log K_1 and log K_2 are very poorly correlated: r 0.651 when all points are included in the analysis. The results show that in the analogue series of minaprine only log K_2 values can be predicted from electronic parameters, the best equation being equation (3).

$$\log K_2 = 3.56 - 4.13\,\sigma_p \quad (r = 0.965) \qquad (3)$$

Spectral Characteristics.—Assignment of the bands from pyridazine to minaprine. The spectrum of an aqueous solution of

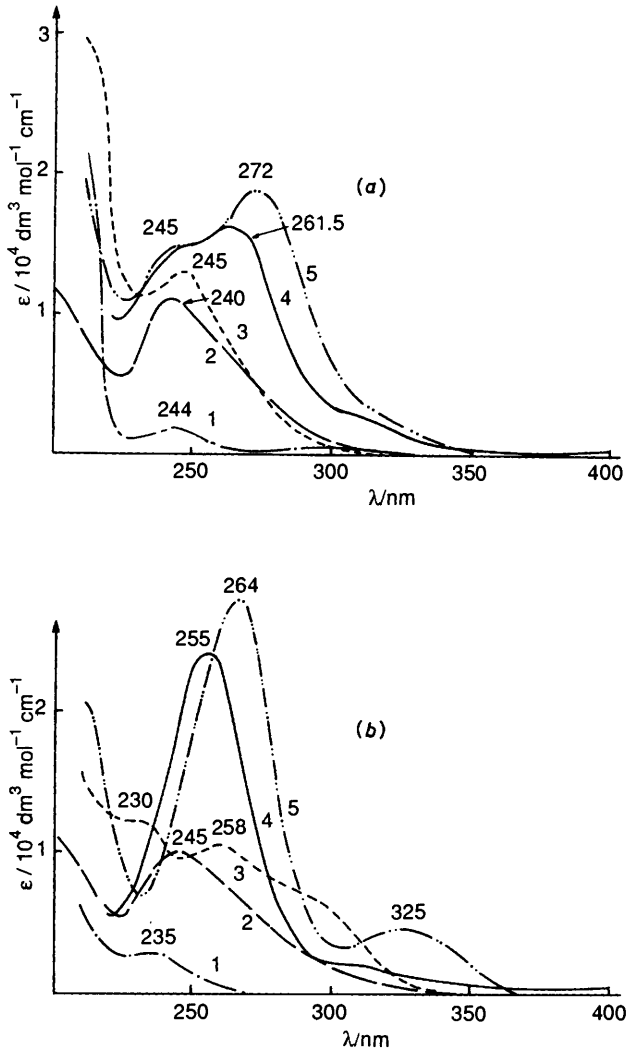


Figure 2. From pyridazine to minaprine: electronic spectra of the basic (*a*) and the protonated forms (*b*). 1, Pyridazine; 2, 6-phenylpyridazine; 3, 4-methyl-6-phenylpyridazine; 4, 3-amino-4-methyl-6-phenylpyridazine; 5, minaprine.

pyridazine [Figure 2(*a*), spectrum 1] exhibits two absorption bands at 244 nm (ε 1 800) and 296 nm (ε 470) respectively, which can be attributed to π–π* and n–π* transitions.[23] The introduction of a phenyl group in position 6 of the pyridazine ring results in an important hyperchromic effect on the π–π* band (ε 11 150) and a hypsochromic shift of 4 nm (spectrum 2). These modifications are identical with those observed on going from benzene to biphenyl (λ = 254 ⟶ 251.5 nm; ε = 204 ⟶ 18 300).

The additional substitution of a methyl group at C-4 (spectrum 3) leads to a slight bathochromic effect of 5 nm and again to a hyperchromic effect according to the effect of alkyl substituents on benzene.[23] The n–π* transition is no longer observed.

Substitution of an NH_2 group at C-3 leads to a new spectrum exhibiting three more intense bands (spectrum 4): the first two at 250 nm (ε 15 000) and 261.5 nm (ε = 16 200) most likely resulting from π–π* transitions, while the third one, at 310 nm (ε 2 700), could be attributed to an n–π* transition. Bathochromic effects expected from substituents bearing an electron lone-pair are thus observed.

Further substitution of the terminal NH_2 group by ethylmorpholine leads to minaprine, the spectrum of which (spectrum 5) shows an increased intensity of the main π–π* band.

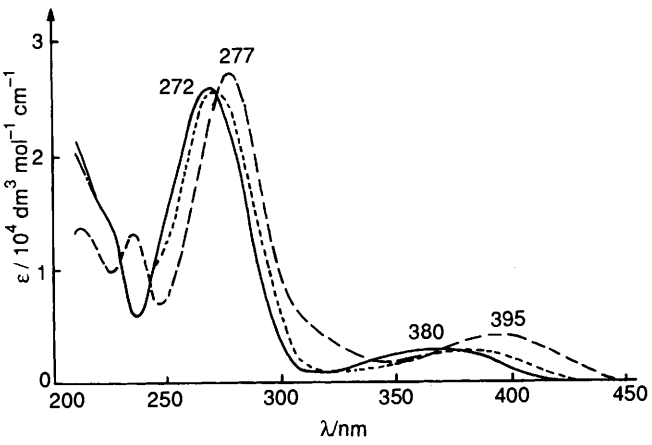


Figure 3. Electronic spectra of the different forms of compound (**13**; R = CN): L (——), LH^+ (. . .), and LH_2^{2+} (- - -).

Table 4. Values of log P, 1-α, and log P' for the transfer from water to octan-1-ol. T = 25 °C. σ = Standard deviation on the arithmetic mean of n experiments.

Compound	n	log P ± 2σ	1 − α	log P' ± 2σ
(1)	2	2.03 ± 0.01	0.69	1.87 ± 0.01
(2)	5	2.53 ± 0.04	0.65	2.34 ± 0.04
(3)	3	3.65 ± 0.04	0.74	3.52 ± 0.04
(4)	3	1.85 ± 0.01	0.82	1.76 ± 0.01
(6)	4	3.38 ± 0.01	0.77	3.26 ± 0.01
(7)	3	1.86 ± 0.05	0.82	1.77 ± 0.05
(13)	4	1.89 ± 0.05	0.90	1.84 ± 0.05

Table 5. Correlation of log P with hydrophobic parameters π, f_R, and f_L. N = Number of derivatives.

Parameters	N	r
log P, π	7	0.888
log P, f_R	7	0.915
	7[a]	0.864
log P, f_L	7	0.875
	7[a]	0.934
log P, π	5[b]	0.977
log P, f_R	5[b]	0.992
log P, f_L	5[b]	0.968

[a] Corrected for proximity of two polar fragments (ref. 22). [b] Compounds (**7**) and (**13**) omitted from the regression analysis.

This band is again bathochromically shifted so that the n–π* band is no longer visible. These spectral changes are similar to those arising when going from aniline to *N*-methylaniline.[23]

The spectra of the corresponding protonated forms (LH^+ and LH_2^{2+} for minaprine), given in Figure 2(*b*), show that protonation induces (i) the appearance of three intense bands in the spectrum of 4-methyl-6-phenylpyridazine (spectrum 3), (ii) the presence of a unique, very strong, and symmetrical π–π* band at 255 nm (ε 24 400) for the 3-amino derivatives (spectrum 4), (iii) high bathochromic and hyperchromic effects on both π–π* and n–π* transitions: λ_{max}(π–π*) when going to minaprine (spectrum 5) 255 ⟶ 264 nm, ε 24 400 ⟶ 28 100, and λ_{max}(n–π*) 310 ⟶ 325 nm, ε 2 000 ⟶ 4 600.

Discussion of the spectra in the minaprine series. Spectral characteristics of minaprine and all its derivatives, gathered in Table 3, enable us to partition these compounds into two classes. (i) Compounds substituted with alkyl, benzyl, chloro, and alcohol groups. The spectra of the basic and fully protonated forms of minaprine, shown in Figure 2(*a*) and 2(*b*), are discussed above. In general, spectra of basic and monoprotonated forms of this class of compound exhibit two strong absorption bands centred at ~250 nm and 270 nm. The n–π* band, absent from the spectrum of the minaprine, appears mostly as a shoulder in the other compounds. Diprotonation leads to an important spectral change, as a single intense absorption is then observed in this region while an n–π* band of weak intensity appears at ~325 nm. (ii) Derivatives bearing more or less electron-withdrawing substituents. These show a unique π–π* absorption band centred at ~270 nm, except for the phenyl derivative (**6**) for which λ_{max} 263 nm.† Figure 3 shows the spectra of the different forms of compound (**13**; R^1 = CN): it can be seen that the second protonation induces a slight bathochromic shift of this band together with a weak hyperchromic effect.

Diprotonated forms of all derivatives have almost the same absorption profile, exhibiting an intense π–π* band (λ_1) and a weak n–π* band (λ_2). The nature of the substituents has no significant influence on the spectra of the basic and monoprotonated forms. In contrast, λ_1 and λ_2 are very sensitive to the substituents. λ_2-values vary from 322 nm for compound (**5**; R^1 = CH_2OH) to 420 nm for compound (**14**; R^1 = NO_2) and are linearly correlated with the classical electronic parameters. The correlation coefficient is 0.916 when all the derivatives are considered and becomes 0.955 when compounds (**9**) and (**14**) are omitted from the regression. Therefore λ_2-values are also correlated to log K_2 values by means of equation (4). It is then

$$\log K_2 = 19.41 - 0.048\,\lambda_2 \quad (r = 0.963) \qquad (4)$$

possible to calculate the basicity of the amidino group of minaprine derivatives from this equation, knowing their spectra in sufficiently acidic media.

Partition Coefficients.—Table 4 shows the values of log P, 1 − α, and corresponding log P' determined for minaprine and six of its derivatives. The precision corresponds to the 95% confidence interval ±2σ, σ being the standard deviation on the arithmetic means of N experiments ($2 \leqslant N \leqslant 5$). Positive values obtained reveal the rather high lipophilicity of these compounds. It should also be noted that at plasma pH, the log P' values are not much lower than those of log P, because of the relatively high 1 − α values, ranging from 0.9 to 0.65.

Different kinds of lipophilic—or hydrophobic—parameters can be found in the literature for various substituents such as the Hansch coefficient (π) and the fragmental constants of Rekker (f_R) and of Leo (f_L).[24] Results in Table 5 show only a poor linear correlation between the experimental log P values and these parameters. A similar poor correlation is obtained with log P'. The regression is not improved if the parameters are corrected for substituents linked to aromatic nuclei. Thus the classical hydrophobic parameters do not describe the lipophilicity of this series of molecules and could not be used as such, as they often are in QSAR studies.

In fact compounds (**7**) and (**13**), bearing the less lipophilic groups ($CONH_2$ and CN respectively), with negative values for the parameters, present the greatest deviation from the regression line. The regression is not improved when a correction is brought in for the proximity of two polar fragments. If these compounds are omitted the regression between log P and f_R

† Such a hypsochromic shift was also observed on going from pyridazine to phenylpyridazine.

becomes satisfactory ($r = 0.992$); log P could then be predicted from equation (5). Taken together, our results demonstrate that

$$\log P = (0.85 \pm 0.06) f_R + (1.6 \pm 0.1) \quad (5)$$

at physiological pH (7.4) the equilibrium between the monoprotonated form and the free base is always in favour of the free base ($0.65 \leqslant 1 - \alpha \leqslant 0.90$) whatever the nature (electron donor or acceptor) of the substituent in the 4-position of the pyridazinic ring may be. In addition the logarithms of the apparent partition coefficient at pH 7.4, log P', as determined for some representative compounds, range over 1.77–3.52. The high proportion of free base and the favourable log P' values account for the excellent ability of minaprine and its analogues to cross the blood–brain barrier and thus to reach the central nervous system.

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