U.V. and ^{15}N N.M.R. Integrated Study of the Protonation of Aminoazoles

Adele Garrone, Roberta Fruttero, Carla Tironi, and Alberto Gasco *
Dipartimento di Scienza e Tecnologia del Farmaco Corso Raffaello 31, 10125 Torino, Italy

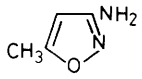
The behaviour on protonation of a series of 3-, 4-, and 5-aminoisoxazoles has been studied by ^{15}N n.m.r. spectroscopy. The results confirm that the first protonation site in the 3- and 5-amino derivatives is located at the endocyclic nitrogen atom, while in 4-amino derivatives it is at the exocyclic nitrogen. In addition, the protonation of 3-, 4-, and 5-amino substituted 1-methyl- and 1-phenyl-pyrazoles has been investigated by an integrated u.v. and ^{15}N n.m.r. approach. The first protonation site in the 5-amino derivatives is the pyridine-like endocyclic nitrogen, while in the 4-amino derivatives it is the exocyclic nitrogen. The 3-amino series behaves exceptionally because a tautomeric equilibrium is possible between the endocyclic and exocyclic monocations. In sulphuric acid the position of this equilibrium is dependent on H_2SO_4 concentration. Diprotonation of these derivatives in concentrated sulphuric acid solutions has also been studied.

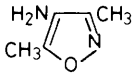
Many authors have dealt with the problem of the protonation site in amino-substituted aza-aromatic compounds. U.v. spectroscopy is a classical tool for this kind of study.[1,2] More recently, the usefulness of the n.m.r. chemical shift and coupling constant parameters has been recognized. In particular ^{13}C[3–5] and ^{15}N[6–8] spectroscopy have been employed. As regards ^{15}N n.m.r. spectroscopy, it is known that the protonation of pyridine-like nitrogen produces a large upfield shift (*ca.* −118 ppm in pyridine[9]), while the protonation of an exocyclic amino group joined to a six membered aza-aromatic ring is generally indicated by a smaller upfield shift of the amino group (*ca.* −20 ppm).[6] In addition, different spin–lattice relaxation times and n.O.e. values can be useful empirical criteria for distinguishing protonated and non-protonated nitrogen atoms: protonated nitrogen atoms usually show large n.O.e. effects and relatively short relaxation times.[8]

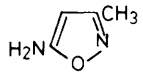
In the present work we discuss the results of a u.v. and ^{15}N n.m.r. investigation on the protonation sites of amino-substituted isoxazoles and pyrazoles in comparison with previously reported data on the subject.

Results and Discussion

Aminoisoxazoles.—Previous i.r. and n.m.r. reports on the 3-, 4-, and 5-amino derivatives (**1**) (pK_a 0.47), (**2**) (pK_a 3.8) and (**3**) (pK_a 0.64), show that all these compounds exist predominantly as such.[10]


(**1**)


(**2**)

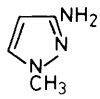

(**3**)

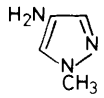
The trend of the u.v. absorptions suggests for the monocation (**2**) an exocyclic protonation and for the monocations (**1**) and (**3**) an endocyclic protonation.[10] We observed the beginning of diprotonation for (**1**) working in 70–80% H_2SO_4. Under the same conditions (**2**) was *ca.* 50% diprotonated, while no diprotonation was observed for (**3**). The ^{15}N n.m.r. spectra (see Table 1) of (**1**), (**2**), (**3**) neutral species were measured in [$^2H_6$]DMSO. The monocation of (**2**) was investigated in [$^2H_6$]DMSO as (**2**)·HCl. The spectra of the three derivatives were also recorded in TFA. On the basis of the u.v. data discussed above, all of them should exist as monocations in this medium (H_0 TFA −3.03; H_0 45% H_2SO_4 −2.85). The ^{15}N assignments are easy because the resonances of the ring nitrogen atoms occur in the typical region of isoxazole N-atoms,[11] while the resonances of exocyclic amino nitrogen atoms occur at much higher field. The strong up-field shifts (−111.2 and −134.2 ppm respectively) of the signals from the ring nitrogens of (**1**) and (**3**) observed in TFA in comparison with the corresponding signals measured in [$^2H_6$]DMSO, suggests endocyclic protonation. This protonation induces down-field shifts in the conjugated NH_2 groups as observed in amino azines.[6] Fast decomposition prevented us measuring the spectra of these two compounds in 85% H_2SO_4. The lack of a strong upfield shift of the signal related to pyridine-like nitrogen moving from (**2**) to (**2**·HCl) indicates in this model protonation occurring at the exocyclic nitrogen.

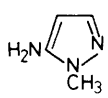
Contrary to what is observed with NH_2 groups linked to six-membered aza-aromatic rings,[6] the formation of an ammonium species induces a down-field shift. Prevalent exocyclic protonation is also suggested by the spectrum of (**2**) recorded in TFA. The −20.3 ppm high field shift of the endocyclic nitrogen is probably due to solute–solvent hydrogen bonding interactions. The ^{15}N n.m.r. spectra of (**2**) recorded in 85% H_2SO_4 ($\delta_{N(2)}$ = −100.0; δ_{NH_2} = −351.6) shows a strong upfield shift (−62.6 ppm) of the pyridine-like nitrogen atom in comparison with that of the free base. This is consistent with the prevalent diprotonation of this compound observed in the same medium by u.v.

Amino-1-methylpyrazoles and Amino-1-phenylpyrazoles.—Previous work on amino-1-substituted pyrazoles shows that all types of derivatives exist predominantly as such.[2]

Amino-1-methylpyrazoles. The problem of the first protonation site in 3- (**4**), 4- (**5**), and 5-amino-1-methylpyrazole (**6**), has been discussed by Bruix *et al.*[4] By comparison of ^{13}C n.m.r. spectra of several aminopyrazoles recorded in neutral ([$^2H_6$]DMSO) and in acidic medium (TFA), these authors showed that the predominant species obtained by dissolving (**4**) and (**6**) in TFA are the monocations protonated at N(2), the pyridine-like nitrogen. On the other hand, (**5**) was diprotonated in TFA. Monoprotonation at the exocyclic nitrogen atom was


(**4**)


(**5**)


(**6**)


(**7**)

Table 1. ^{15}N Chemical shifts for aminoisoxazoles, amino-1-methylpyrazoles, and amino-1-phenylpyrazoles.[a,b]

	Nucleus	δ_N(free base)[e] (ppm)	δ_N(hydrochloride)[d] (ppm)	δ_N(sample)[e] (ppm)
(1)	N1	−78.6		−189.7 (−111.1)
	NH_2	−357.1		−341.0 (+16.1)
(2)	N1	−37.4	−30.9 (+6.5)	−57.7 (−20.3)
	NH_2	−378.2	−363.4 (+14.8)	−372.7 (+5.5)
(3)	N1	−54.3		−188.5 (−134.2)
	NH_2	−344.7		−333.4 (+11.4)
(4)	N1	−221.5	−205.3 (+16.2)	−219.3 (+2.2)
	N2	−128.9	−115.6 (+13.3)	−208.6 (−79.7)
	NH_2	−357.7	−351.3 (+6.4)	−353.9 (+3.89)
(5)	N1	−211.3	−202.6 (8.79)	
	N2	−99.8	−96.7 (+3.1)	Decompose
	NH_2	−375.7	−365.7 +10.0	
(6)	N1	−225.2	−220.2 (+5.0)	−230.5 (−5.3)
	N2	−119.1	−244.3 (−125.2)	−242.6 (−123.5)
	NH_2	−362.5	−344.6 (+17.9)	−352.5 (+10.0)
(8)	N1	−207.0	−188.5 (+18.5)	−203.7 (+3.3)
	N2	−144.1	−116.5 (+27.6)	−198.8 (−54.7)
	NH_2	−357.4	−351.4 (+6.0)	−351.9 (+5.5)
(9)	N1	−192.4	−183.6 (+8.9)	−157.8 (+6.0)
	N2	−103.6	−99.2 (+4.4)	−148.6 (−45.0)
	NH_2	−371.2	−361.7 (+9.5)	−370.0 (+1.2)
(10)	N1	−203.5	−208.2 (−3.8)	−228.3 (−24.8)
	N2	−115.1	−227.1 (−112.0)	−232.0 (−116.9)
	NH_2	−355.6	−343.3 (+12.3)	−350.6 (+5.0)

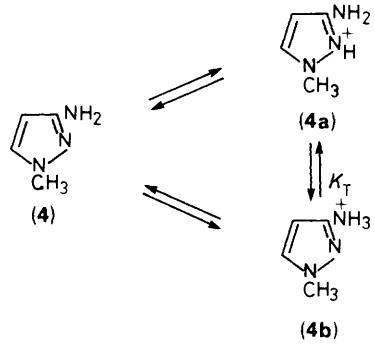
[a] In TFA the pyridine-like nitrogen of 1-methylpyrazole (**7**) and 1-phenylpyrazole (**11**) undergo upfield shift of −100 ppm and −102 ppm respectively in comparison with the free bases recorded in [$^2H_6$]DMSO. [b] The values in parentheses are the differences between the values reported in the columns *d* and *e* and those of the column *c*. [c] Spectra of the free bases recorded in [$^2H_6$]DMSO. [d] Spectra of the hydrochlorides recorded in [$^2H_6$]DMSO. [e] Spectra of the samples (free bases) dissolved in TFA.

observed by dissolving this last compound in [$^2H_6$]DMSO containing an equivalent of TFA. Theoretical calculations show that in the gas phase N(2) is the strongest basic centre in (**4**) and (**6**) while in (**5**) the amino group and pyridine-like nitrogen are centres of similar strength.[12]

N-Methylpyrazole (**7**) was taken as the reference compound for pK_a values and u.v. spectra data for 3-(**4**), 4-(**5**), and 5-amino-1-methylpyrazole (**6**), which are collected in Table 2.

The trends of absorptions suggest for the monocations (**5**) and (**6**) an exocyclic and an endocyclic protonation respectively. Both the compounds undergo double protonation: we found that (**5**) is *ca.* 50% diprotonated in 15% H_2SO_4 and completely diprotonated in 45% H_2SO_4, while (**6**) is *ca.* 50% diprotonated in 65% H_2SO_4 and completely diprotonated in 85% H_2SO_4.

The protonation of (**4**) deserves some comments. The u.v. spectrum determined in water gives an absorption at λ_{max} 233.5 nm, while the spectrum in 0.05 mol dm^{-3} H_2SO_4 (pH = 1), where only the monocation is present, shows two absorptions centred at λ_{max} 246.6 and 214.4 nm respectively [Figure 1(*a*)]. These two absorptions can be explained on the basis of the tautomerism between the two monocations (**4a**) and (**4b**). The absorption at 214.4 nm, occurring at shorter wavelength with



respect to the free base, is in practically the same position as that of the neutral form of (**7**) [Figure 1(*b*)] and can be attributed to the species (**4b**). The absorption at λ 246.6 nm, red-shifted in comparison with that of the free base, can be assigned to the species (**4a**) [Figure 1(*d*)]. The u.v. behaviour of (**4**) in H_2SO_4 solutions of different acid strengths is interesting. Moving from 0.05 mol dm^{-3} H_2SO_4 (pH 1) to 45% H_2SO_4, there is a decrease in the intensity of the absorption at 214.4 nm and an increase in that at 246.6 nm. The isosbestic point at λ 223 nm indicates an equilibrium between two species [Figure 1(*c*)].

If our hypothesis is correct we are forced to conclude that in 45% H_2SO_4 the species (**4a**) is strongly predominant. It appears, on the basis of the absorbances at λ 246.6 nm of the solution at pH 1 and of the 45% H_2SO_4 solution, that in the former medium (**4a**) and (**4b**) coexist in the ratio *ca.* 1:1. Thus the quoted[12] pK_a value for (**4**) is the macroscopic constant of the gross process for the equilibrium reported above.

U.v. spectra recorded at higher acidity values show that (**4**) is *ca.* 50% diprotonated in 60% H_2SO_4 and completely diprotonated in 85% H_2SO_4. The u.v. spectrum of the diprotonated species resembles that of the monocation of (**7**) [Figures 2(*a*) and (*b*)].

^{15}N N.m.r. spectra (see Table 1) of (**4**), (**5**), and (**6**) as neutral species were measured in [$^2H_6$]DMSO. The monocations of the three compounds were investigated in [$^2H_6$]DMSO as (**4**)–(**6**) HCl. Spectra were also recorded in TFA. Fast decomposition prevented us observing the behaviour of (**5**) in this solvent. Signals of endocyclic nitrogens occur in a region at much lower field than that in which exocyclic nitrogens absorb. As regards the former signals, the pyridine-like nitrogen was assumed to

Table 2. pK_a and u.v. spectral data of aminomethyl derivatives (4)–(7).

	Base	Monocation	Dication
(**4**) pK_a = 3.81[12]	$\lambda_{max.}$ = 233.5 nm logε_{max} = 3.69	(**4a**) λ_{max} = 246.6 nm (pH 1, H_2SO_4) (**4b**) λ_{max} = 214.4 nm (pH 1, H_2SO_4) (**4a**) λ_{max} = 246.6 nm (45% H_2SO_4) logε_{max} = 3.75	λ_{max} = 219.3 nm (85% H_2SO_4) logε_{max} = 3.75
(**5**) pK_a = 5.52[12]	$\lambda_{max.}$ = 243.5 nm logε_{max} = 3.40	λ_{max} = 214.5 nm (pH = 2.3, H_2SO_4) logε_{max} = 3.54	λ_{max} = 219.7 nm (45% H_2SO_4) logε_{max} = 3.62
(**6**) pK_a = 4.23[12]	$\lambda_{max.}$ = 225.6 nm logε_{max} = 3.81	λ_{max} = 239.2 nm (5–45% H_2SO_4) logε_{max} = 39.2	λ_{max} = 219.6 nm (85% H_2SO_4) logε_{max} = 3.80
(**7**) pK_a = 2.09[13,14]	$\lambda_{max.}$ = 216.4 nm logε_{max} = 3.58	λ_{max} = 219.8 nm (5% H_2SO_4) logε_{max} = 3.66	

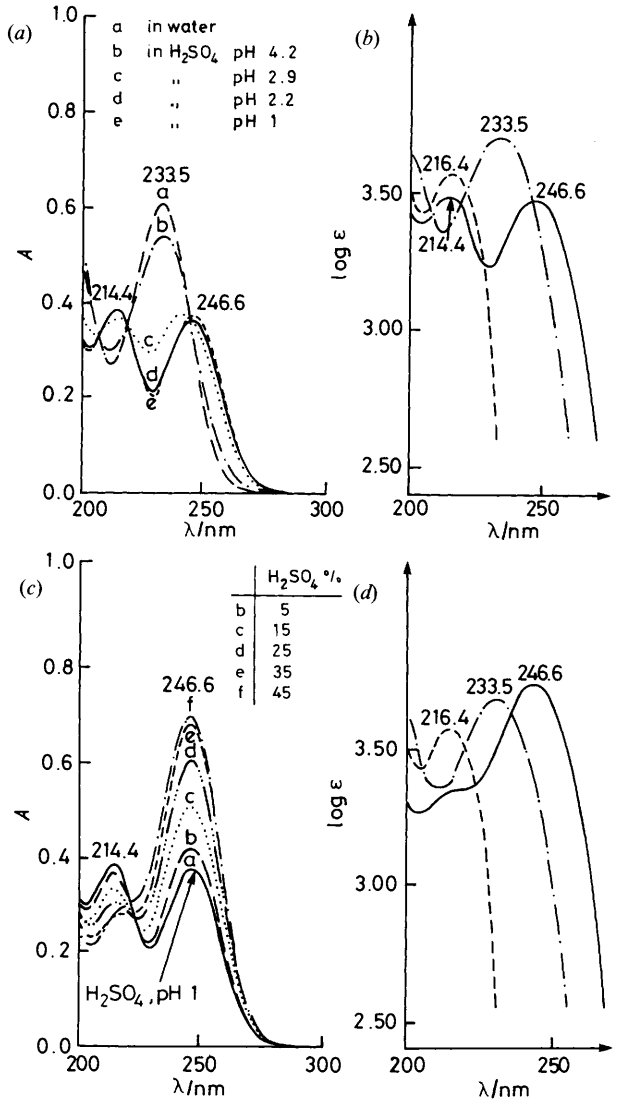


Figure 1. (*a*) λ_{max} *vs.* *A* for compound (**4**) in water–H_2SO_4 at different pH values; (*b*) λ_{max} *vs.* log ε: ——, (**4**) in H_2SO_4–water, pH 1; — · —, (**4**) in water; – – –, (**7**) in water; (*c*) λ_{max} *vs.* *A* for compound (**4**) at different H_2SO_4 concentrations; (*d*) λ_{max} *vs.* log ε: ——, (**4**) in 45% H_2SO_4; — · —, (**4**) in water; – – –, (**7**) in water.

absorb downfield of the pyrrole-like nitrogens.[15] Unambiguous assignment of the resonance lines of some protonated species in the high frequency region are difficult. An important criterion is established by recording the ^{15}N resonances both under inverse-gated-noise-decoupling techniques and under proton-noise-decoupled conditions. In this way it is possible to observe the protonated ^{15}N nuclei strongly enhanced by the large n.O.e. effect.[8] The strong upfield shift of the signal of the pyridine-like nitrogen observed in (**6**)·HCl (−125.2 ppm, [$^2H_6$]DMSO in comparison with the corresponding signal observed in (**6**), is suggestive of endocyclic protonation. As expected, the protonation of N(2) induces a downfield shift in the conjugated 5-NH_2 group.

A similar upfield shift for the pyridine-like nucleus can be observed either in the spectrum recorded in TFA, in which the predominant species is the monocation, or in 85% H_2SO_4 [$\delta_{N(2)}$ −270.0; δ_{NH_2} −365.1 ppm] in which the compound is completely diprotonated. Therefore ^{15}N n.m.r. spectra confirm the ionization behaviour of (**6**) in TFA, previously suggested by ^{13}C n.m.r. spectroscopy.[4] These results also parallel the data obtained from u.v. spectroscopy in different acidity conditions.

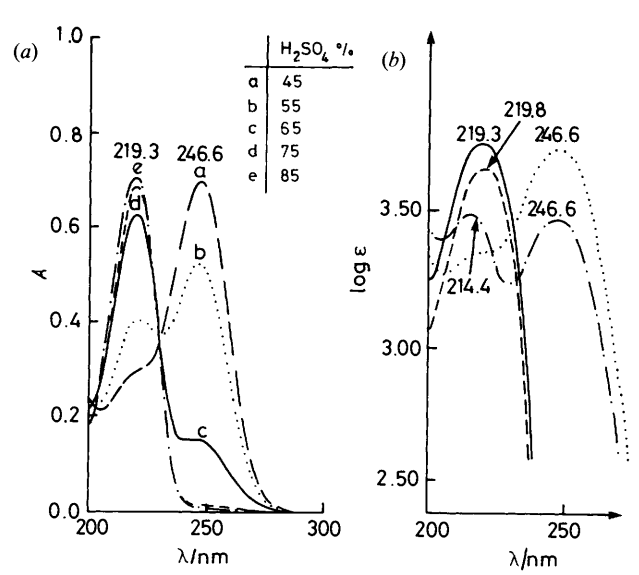
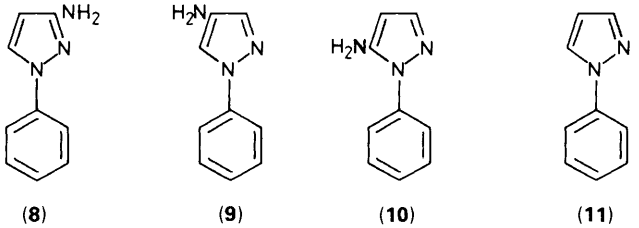


Figure 2. (*a*) λ_{max} *vs.* *A* for compound (**4**) in 45–85% H_2SO_4; (*b*) λ_{max} *vs.* log ε: ——, (**4**) in 85% H_2SO_4; — · —(**4**) in H_2SO_4–water, pH 1; – – –, (**7**) in 5% H_2SO_4; · · · ·, (**4**) in 45% H_2SO_4.

The lack of a strong upfield shift of the pyridine-like nitrogen signal on moving from (**4**) to (**4**)·HCl in [$^2H_6$]DMSO, indicates a protonation occurring at the exocyclic nitrogen. The formation of an ammonium species induces a downfield shift as already observed in the 4-aminoisoxazole derivative (**2**). A strong upfield shift for the pyridine-like nitrogen was observed when the spectrum of (**4**) was recorded in TFA solution. Since in this medium the predominant species is the monocation, we are forced to conclude that in TFA the preferred protonation site is the pyridine-like nitrogen. This conclusion is in keeping with the results reported in reference 4. This is not surprising because it is well known that K_T is dependent not only on the temperature and on the structure of the base but also on the concentration and the nature of the solvent.[2] An upfield shift of N(2) [$\delta_{N(2)}$ −204.7 ppm] with respect to the corresponding signals of (**4**) and (**4**)·HCl recorded in [$^2D_6$]DMSO, was observed in the spectrum recorded in 85% H_2SO_4. In this solvent the compound is completely diprotonated.

Analogously to (**4**), the lack of an upfield shift for N(2) moving from (**5**) to (**5**)·HCl in [$^2H_6$]DMSO, suggests an exocyclic protonation. Fast decomposition prevented us recording the spectrum of (**5**) in 85% H_2SO_4.

Amino-1-phenylpyrazoles. The problem of the determination of the first protonation site in 3-amino-1-phenylpyrazole (**8**), in 4-amino-1-phenylpyrazole (**9**), and in 5-amino-1-phenylpyrazole (**10**), has been discussed in reference 4.



(**8**) (**9**) (**10**) (**11**)

According to the authors these compounds and the corresponding 1-methyl derivatives behave similarly on ionization.

N-Phenylpyrazole (**11**) was taken as the reference compound for pK_a values and u.v. spectroscopic data for aminophenylpyrazoles (**8**)–(**10**) which are collected in Table 3. The trends of the absorptions suggest for the monocations (**9**) and

Table 3. pK_a values and u.v. spectral data of aminophenyl derivatives (**8**)–(**11**).

	Base	Monocation	Dication
(**8**) $pK_a = 2.66$[16]	$\lambda_{max} = 276.0$ nm $\log\varepsilon_{max} = 4.20$	(**8a**) $\lambda_{max} = 248.7$ nm (5% H_2SO_4) $\log\varepsilon_{max} = 4.06$ (**8b**) $\lambda_{max} = 273.4$ nm (55% H_2SO_4)	
(**9**) $pK_a = 4.60$[16]	$\lambda_{max} = 276.7$ nm $\log\varepsilon_{max} = 3.99$	$\lambda_{max} = 248.6$ nm (5% H_2SO_4) $\log\varepsilon_{max} = 4.09$	$\lambda_{max} = 248.9$ nm (65–75% H_2SO_4) $\log\varepsilon_{max} = 3.94$
(**10**) $pK_a = 3.23$[16]	$\lambda_{max} = 234.6$ nm $\log\varepsilon_{max} = 4.01$	$\lambda_{max} = 234.2$ nm (5%–55% H_2SO_4) $\log\varepsilon_{max} = 3.94$	
(**11**) $pK_a = 0.44$[13]	$\lambda_{max} = 251.0$ $\log\varepsilon_{max} = 4.10$	$\lambda_{max} = 243.5$ nm (25% H_2SO_4) $\log\varepsilon_{max} = 3.98$	

(**10**) an exocyclic and an endocyclic protonation respectively. The u.v. spectra of (**9**) recorded at concentrations up to 45% H_2SO_4 show a neat isosbestic point, while at higher H_2SO_4 concentrations the absorption positions are shifted by medium effects. Nevertheless it is possible to infer that (**9**) is *ca.* 50% diprotonated in 40% H_2SO_4 and completely diprotonated in 65–75% H_2SO_4. Compound (**10**) exists as a monocation in solutions containing up to 55% H_2SO_4. No clear information is possible from the analysis of the spectra in solutions with greater acidity function values. Compound (**8**) and the corresponding methyl derivative (**4**), behave differently in acid. In fact no tautomeric equilibrium between the endocyclic (**8a**) and exocyclic (**8b**) monocation can be detected in dilute H_2SO_4 solutions up to pH 0.0: at this pH, where only the monocation is present, the product is almost completely protonated at the exocyclic nitrogen since its spectrum resembles that of the neutral form of (**11**). The u.v. spectra of solutions in H_2SO_4 of higher acidity show that the endocyclic and exocyclic monocations of (**8**) exist in tautomeric equilibrium in the range 5–55% H_2SO_4. The endocyclic monocation appears to be the main species in 55% H_2SO_4. At concentrations higher than 55%, medium effects on the absorption positions occur, however it is possible to observe that (**8**) begins to be diprotonated in *ca.* 65% H_2SO_4.

^{15}N N.m.r. spectra in [$^2H_6$]DMSO of (**8**), (**9**), (**10**) and of their hydrochlorides are reported in Table 1. Signals of spectra recorded in TFA are also quoted. Analysis of the resonances in [$^2H_6$]DMSO solutions show that the first protonation site is exocyclic in (**8**) and (**9**) but endocyclic in (**10**). In TFA, (**8**) exists mainly as monocation, thus the upfield shift shown by the N(2) atom in this solvent (−54.7 ppm) is in keeping with the tautomeric equilibrium between endocyclic and exocyclic monocations. Since compound (**9**) is partially diprotonated in TFA, the upfield shift (−45.0 ppm) shown by the pyridine-like nitrogen is justified. In this solvent (**10**) still exists as the monocation. Upfield shifts for the N(2) nitrogens observed in 85% H_2SO_4 of (**8**), (**9**), and (**10**) are in keeping with the presence of the relevant diprotonated species.

Experimental

Materials.—3-Amino-5-methylisoxazole (**1**) and 5-amino-3-methylisoxazole (**3**) were commercial samples (Aldrich) and were purified by crystallization [(**1**), m.p. 62–63 °C from di-isopropyl ether–light petroleum (b.p. 40–60 °C); (**3**), m.p. 80–81 °C from di-isopropyl ether (b.p. 40–60 °C)].

Compounds (**2**),[17] (**4**),[18] (**5**),[12] (**6**),[19] (**7**),[20] (**8**),[21] (**9**)[22] (**10**),[23] and (**11**),[24] were obtained according to the procedure reported in the literature.

The hydrochlorides of the compounds (**2**), (**4**)–(**6**), (**8**)–(**10**), were prepared according to the following general procedure. The amino derivative (1.0 g) was dissolved or suspended in anhydrous ethanol saturated with HCl gas. After a few minutes the hydrochloride was completely precipitated by cooling and by addition of anhydrous ether.

4-*Amino*-3,5-*dimethylisoxazole hydrochloride* (**2**)·HCl. M.p. 198–200 °C decomp. from di-isopropyl ether (Found: C, 40.25; H, 6.15; N, 18.80. $C_5H_9ClN_2O$ requires C, 40.41; H, 6.10; N, 18.85%).

3-*Amino*-1-*methylpyrazole hydrochloride* (**4**)·HCl. M.p. 217–218 °C from ethanol–diethyl ether (Found: C, 36.05; H, 6.15; N, 31.40. $C_4H_8ClN_3$ requires C, 35.96; H, 6.04; N, 31.46%).

4-*Amino*-1-*methylpyrazole hydrochloride* (**5**)·HCl. M.p. 220–222 °C decomp. from ethanol–diethyl ether (Found: C, 35.95; H, 6.05; N, 31.42%).

5-*Amino*-1-*methylpyrazole hydrochloride* (**6**)·HCl. M.p. 138–139 °C from ethanol–diethyl ether (Found: C, 35.78; H, 6.12; N, 31.40%).

3-*Amino*-1-*phenylpyrazole hydrochloride* (**8**)·HCl. M.p. 162–164 °C from ethanol–diethyl ether (Found: C, 55.06; H,-5.04; N, 21.39. $C_9H_{10}ClN_3$ requires C, 55.25; H, 5.15; N, 21.48%).

4-*Amino*-1-*phenylpyrazole hydrochloride* (**9**)·HCl. M.p. 250–252 °C decomp. from ethanol–diethyl ether (Found: C, 55.26; H, 5.08; N, 21.59%).

5-*Amino*-1-*phenylpyrazole hydrochloride* (**10**)·HCl. M.p. 182–185 °C decomp. from ethanol–diethyl ether (Found: C, 55.06; H, 5.04; N, 21.39%).

U.V. Spectra.—U.v. spectra were recorded on a Perkin-Elmer Lambda 5 UV/VIS spectrophotometer. Stock solutions $5 \times 10^{-4} - 1 \times 10^{-3}$ mol dm^{-3} in water were prepared for compounds (**1**)–(**7**). Stock solutions 5×10^{-4} mol dm^{-3} in 10% ethanol–water were prepared for compounds (**8**)–(**11**). For each compound 5 cm^3 of the stock solutions were diluted at 50 cm^3 with water or with sulphuric acid of appropriate concentration. The pH of the final solutions were measured with a Beckman Model Φ 71 pH meter using a combined pH glass electrode. For H_2SO_4 concentrations of 5% w/w or higher, weighed amounts of the final solution were standardized, after dilution, by titration using 0.5 mol dm^{-3} NaOH.

N.M.R. Spectra.—The majority of the ^{15}N n.m.r. spectra were recorded with a JEOL GX 270/89 spectrometer operating at 27.25 MHz and some with a Bruker CXP-300 instrument (30.4 MHz). Samples in 0.5–1 mol dm^{-3} concentrations were contained in 10 mm o.d. tubes. Chemical shifts were determined relative to the $^{15}NH_4^+$ resonances from external 6 mol dm^{-3} $^{15}NH_4{}^{15}NO_3$ in 2 mol dm^{-3} HNO_3 and converted into the CH_3NO_2 scale with a conversion constant of −358.2 ppm. The resonances of NH_2 groups and protonated ring N atoms were obtained under complete-noise-decoupling conditions. The chemical shifts of tertiary N atoms were detected with an inverse gating decoupling technique to quench small unfavourable n.O.e., with pulse angles of *ca.* 30° and relaxation delays of up to 25 s.

Acknowledgements

We acknowledge the n.m.r. service of Consiglio Nazionale delle Ricerche (Istituto dei Composti del Carbonio Contenenti Eteroatomi e loro Applicazioni, Ozzano—Bologna) for permission to use the Bruker CXP-300 spectrometer.

References

1 A. Albert, 'Heterocyclic Chemistry,' The Athlone Press, University of London, 1968, p. 382, and references therein.
2 J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, 'The Tautomerism of Heterocycles,' Academic Press, New York, 1976, and references therein.
3 J. Riaud, *J. Chem. Soc., Chem. Commun.*, 1983, 105, and references therein.
4 M. Bruix, J. de Mendoza, R. M. Claramunt, and J. Elguero, *Magn. Reson. Chem.*, 1985, **23**, 367.
5 M. D. Treadgill, R. S. Griffin, M. F. G. Stevens, and S. K. Wong, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2229.
6 W. Stadeli, W. von Philipsborn, A. Wich, and I. Kompis, *Helv. Chim. Acta*, 1980, **63**, 504.
7 H. Fritz, *Bull. Soc. Chim. Belg.*, 1984, **93**, 559.
8 G. Anderegg, K. Popov, and P. S. Pregosin, *Helv. Chim. Acta*, 1986, **69**, 329.
9 G. J. Martin, M. L. Martin, and J. P. Gouesnard, '^{15}N NMR Spectroscopy,' Springer Verlag, Berlin, 1981.
10 A. J. Boulton and A. R. Katritzky, *Tetrahedron*, 1961, **12**, 51.
11 B. C. Chen, W. von Philipsborn, and K. Nagarajan, *Helv. Chim. Acta*, 1983, **66**, 1537.
12 J. Catalan, M. Mendez, J. Laynez, R. M. Claramunt, M. Bruix, J. de Mendoza, and J. Elguero, *J. Heterocycl. Chem.*, 1985, **22**, 997.
13 J. Elguero, E. Gonzalez, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 1968, 5009.
14 D. Dal Monte, A. Mangini, and R. Passerini, *Gazz. Chim. Ital.*, 1956, **86**, 797.
15 I. I. Shuster, C. Dyllick-Brenzinger, and J. D. Roberts, *J. Org. Chem.*, 1979, **44**, 1765.
16 A. Garrone, C. Tironi, R. Fruttero, and A. Gasco, *J. Heterocycl. Chem.*, in press. See also S. Tabak, I. I. Grandberg, and A. N. Kost, *Tetrahedron*, 1966, **22**, 2703.
17 A. Quilico and C. Musante, *Gazz. Chim. Ital.*, 1941, **71**, 327.
18 H. Dorn and R. Ozegowski, *J. Prakt. Chem.*, 1979, **321**, 93.
19 H. Dorn, G. Hilgetag, and A. Zubek, *Chem. Ber.*, 1965, **98**, 3368.
20 I. L. Finar and G. H. Lord, *J. Chem. Soc.*, 1957, 3314.
21 G. F. Duffin and J. D. Kendall, BP 743, 505/1956. *Chem. Abstr.* 50:16872, 1956.
22 I. L. Finar and R. J. Hurlock, *J. Chem. Soc.*, 1958, 3259.
23 P. Schmidt and J. Druey, *Helv. Chim. Acta*, 1958, **41**, 306.
24 I. L. Finar and R. J. Hurlock, *J. Chem. Soc.*, 1957, 3024.

Received 27*th September* 1988; *Paper* 8/03807D