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## Study of Imidazo[1,2-*a*]pyridin-8-ol. 2. Crystal Structure

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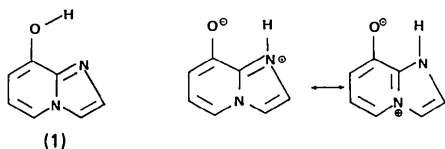
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**Abstract.** C<sub>7</sub>H<sub>6</sub>N<sub>2</sub>O, *M<sub>r</sub>* = 134.048, monoclinic, *P*2<sub>1</sub>/*c*, *a* = 13.432 (9), *b* = 13.071 (8), *c* = 13.678 (9) Å, β = 148.05 (8)°, *V* = 1270.8 Å<sup>3</sup>, *Z* = 8, *D<sub>x</sub>* = 1.401 g cm<sup>-3</sup>, Mo *K*α, λ = 0.7107 Å, μ = 0.917 cm<sup>-1</sup>, *F*(000) = 560, *T* = 293 K, *R* = 0.046 for 1021 observed reflections. The molecule is nearly planar and the structure is stabilized by the formation of intermolecular N–H...O hydrogen bonds 2.646 and 2.631 Å, ∠N–H...O 171 and 164°, between two molecules forming infinite helices. The two molecules analysed by high-resolution solid-state CP/MAS <sup>13</sup>C NMR show two different signals for five of the seven carbons in accordance with different packing in the solid state.

**Introduction.** The title compound (1) contains a phenolic group and two basic sites, thus allowing the possibility of several tautomeric forms (Rydzkowski, Blondeau, Sliwa & Cazé, 1986).



Infrared spectral data give no information on which structure is adopted. UV spectra recorded at different pH's clearly show a zwitterionic structure in neutral

aqueous solution, in equilibrium with the neutral structure. A <sup>13</sup>C NMR study performed in neutral, basic and acidic aqueous solutions afforded the conclusion that the zwitterionic tautomer predominates in the neutral medium. A potentiometric study gives all the dissociation constants. These values are in favour of the zwitterionic structure in neutral aqueous conditions.

A careful <sup>1</sup>H NMR study shows that intermolecular hydrogen bonding occurs in a neutral aprotic medium (CDCl<sub>3</sub>) in place of an intramolecular bond.

Despite this fact, we enhanced the solid-state study by determining first the X-ray structure and secondly <sup>13</sup>C NMR spectral data because, in the solid state, as for pyridoxal and pyridoxamine dihydrate (MacLaurin & Richardson, 1985), it was possible for our compound to crystallize in the dipolar (zwitterionic species) structure or in a non-polar form.

**Experimental.** The title compound was obtained by a previously described procedure (Rydzkowski, Blondeau, Sliwa & Cazé, 1986). After several recrystallizations from water and ethanol, a crystal of about 0.3 × 0.3 × 0.4 mm was obtained. Lattice parameters from 25 reflections with θ < 10°. Intensities measured by an ω–2θ scan in the range 2 < θ < 30° on a Philips PW1100 automated four-circle diffractometer with graphite-monochromatized Mo *K*α radiation, ω-scan width 1.40°, scan speed 0.03° s<sup>-1</sup> and background counts of each extremity for half the scan time. 1021

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independent reflections were obtained;  $-15 \leq h \leq 15$ ,  $-15 \leq k \leq 0$ ,  $0 \leq l \leq 16$ . No absorption correction was applied. Three standard reflections ( $1\bar{2}\bar{3}$ ,  $1\bar{3}1$ ,  $23\bar{2}$ ) showed no significant variation in intensity. The structure was solved with the *MULTAN* system of computer programs (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). 200 reflections and 2000  $\Sigma_2$  relationships were used in the phase-determining procedure.

An *E* map computed with the phases from the set with the highest combined figure of merit revealed peaks for all non-hydrogen atoms. Least-squares refinement on *F* of all non-hydrogen atomic positions with anisotropic thermal parameters gave an *R* value of 0.08. From a difference Fourier synthesis, all H-atom positions could be found unambiguously.

Further least-squares refinement with unit weights for all atoms (Stewart, Kruger, Ammon, Dickinson & Hall, 1972) resulted in an *R* value of 0.046 and *wR* value of 0.045 with isotropic thermal parameters for the H atoms.\* ( $I/\sigma$ )<sub>max</sub> = 0.5; max.  $\Delta\rho$  = 0.30 e Å<sup>-3</sup>; atomic scattering factors from *International Tables for X-ray Crystallography* (1974). The plotter program *ORTEP* (Johnson, 1976), amended for a Hewlett Packard 9825 computer by G. Nowogrocki, was also used.

High-resolution NMR spectra were obtained as follows.

(a) *CP/MAS spectra*. The <sup>13</sup>C NMR spectra were obtained on a Bruker CXP-300 Fourier-transform NMR spectrometer. 100–200 mg samples were measured in 6.3 mm i.d. boron nitride rotors. CP/MAS was used with alternative inversion of the 90° pulse phase. The proton 90° pulse length was 4.5 μs, the contact time was 3 ms and repetition time 4–6 s. The spinning speed ranged from 3.5 to 5 kHz. The chemical shifts were referenced to tetramethylsilane by using the carbonyl signal of glycine as a secondary standard (170.09 p.p.m.).

(b) *Solution NMR spectra*. <sup>13</sup>C NMR spectra of solutions were recorded on a WP-80 Fourier-transform NMR spectrometer using proton broadband decoupling. The solution was recorded for a 0.1M concentration in a 10 mm sample tube. The chemical shifts were referenced to tetramethylsilane by using the chemical shifts of the methyl carbons in (CD<sub>3</sub>)<sub>2</sub>SO at 39.6 p.p.m. from Me<sub>4</sub>Si.

**Discussion.** The compound (1), shown in Fig. 1, exists in non-dipolar form in the crystal. The imidazopyridine ring is essentially planar as is usually observed in pyridine-condensed nuclei.

\* Lists of structure factors, anisotropic thermal parameters, bond angles, atomic coordinates of H atoms and mean-planes data have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44706 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

The interesting feature of the molecular packing is that the –OH group of the six-membered ring is engaged in an intermolecular hydrogen bond with the N atom of the other molecule (the dihedral angle between the two molecules is 73.48°). We therefore observed two types of molecules, as indicated in Table 1, with very close equivalent bond distances and angles (see Table 2). These molecules are closely similar but are non-characteristic of a zwitterion: *e.g.* the C–O distance is shorter (1.345–1.351 Å) than in derivatives with an un-ionized phenolic group (1.374 Å) and is not in agreement with a dipolar form (1.290–1.327 Å) (Longo, Franklin & Richardson, 1982; MacLaurin & Richardson, 1985). This indicates that the phenolic proton has not been transferred from the phenolic group to the N atom of the imidazolic nucleus.

The N...O distances of the intermolecular hydrogen bonds are 2.646 and 2.631 Å, the N...H bond distances 1.778 and 1.779 Å and the angles at H 164 and 171°. These values are in good accordance with an intermolecular hydrogen bond.

The existence of two molecules with a different environment prompts us to examine the <sup>13</sup>C NMR (CP/MAS) high-resolution spectra. <sup>13</sup>C NMR spectra in solids have become readily measurable by using the combined techniques (CP/MAS) of high-power decoupling, cross polarization and magic-angle sample spinning (Mehring, 1983).

In general, the observed isotropic chemical shifts in the solid state are usually very close to the corresponding chemical shifts in solutions (Imashiro, Maeda, Takegoshi, Terao & Saika, 1982). However, in the case of the existence of several different conformations or different environments in the solid state for a given nucleus, we can have different resonances (Dalling, Zilm, Grant, Hoeschen, Horton & Pugmire, 1981; Vanderhart, 1981; Pease, Frey & Opella, 1981).

The dedoubled signals for C(8), C(7), C(6), C(5) and C(9) (Fig. 2) show that the two molecules are not equivalent in the solid state, as was observed by X-ray diffraction for compound (1) (Table 3).

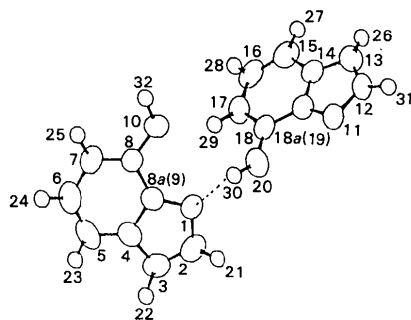


Fig. 1. *ORTEP* drawing (Johnson, 1976) of the structurally different molecules, showing one of the intermolecular hydrogen bonds. The thermal ellipsoids of the non-hydrogen atoms are drawn for 50% probability.

Table 1. Atomic coordinates ( $\times 10^4$ ) (with *e.s.d.*'s in parentheses) and equivalent isotropic temperature factors ( $B_{eq}$ ) for non-hydrogen atoms and atomic coordinates ( $\times 10^3$ ) and isotropic temperature factors for H atoms involved in hydrogen bonds

$$B_{eq} = \frac{4}{3} \sum_i \sum_j \beta_{ij} a_i \cdot a_j$$

	x	y	z	$B_{eq} (\text{\AA}^2)$
N(1)	5858 (5)	9607 (3)	3094 (5)	4.4 (4)
C(2)	6705 (7)	10539 (4)	3961 (7)	5.2 (5)
C(3)	7608 (7)	10896 (4)	3918 (7)	5.2 (5)
N(4)	7350 (5)	10147 (3)	2990 (5)	4.4 (4)
C(5)	7942 (7)	10100 (4)	2512 (7)	5.4 (6)
C(6)	7402 (7)	9296 (4)	1537 (7)	5.1 (6)
C(7)	6255 (7)	8510 (4)	954 (6)	4.5 (5)
C(8)	5964 (6)	8556 (4)	1433 (5)	4.0 (4)
C(9)	6264 (6)	9380 (3)	2501 (6)	3.9 (4)
O(10)	4576 (4)	7864 (3)	951 (4)	5.4 (3)
N(11)	1715 (5)	7951 (3)	2628 (5)	4.2 (4)
C(12)	98 (7)	7783 (4)	1787 (7)	4.6 (5)
C(13)	-1438 (7)	8069 (4)	8 (7)	5.0 (6)
N(14)	-773 (5)	8443 (3)	-328 (5)	4.2 (4)
C(15)	-1716 (7)	8834 (4)	-1915 (7)	4.9 (5)
C(16)	-687 (8)	9133 (4)	-1813 (7)	5.3 (6)
C(17)	1296 (8)	9069 (4)	-176 (7)	4.7 (6)
C(18)	2227 (7)	8688 (3)	1388 (6)	4.1 (5)
C(19)	1171 (6)	8362 (3)	1324 (6)	3.8 (5)
O(20)	4160 (5)	8606 (3)	3047 (5)	5.6 (3)
H(30)	469 (6)	888 (4)	303 (6)	5.6
H(32)	378 (8)	756 (4)	-10 (8)	5.4

Table 2. Bond lengths ( $\text{\AA}$ ) with *e.s.d.*'s in parentheses

N(1)-C(2)	1.376 (6)	N(11)-C(12)	1.361 (12)
N(1)-C(8a)	1.340 (14)	N(11)-C(18a)	1.338 (11)
C(2)-C(3)	1.347 (17)	C(12)-C(13)	1.341 (7)
C(3)-C(4)	1.393 (11)	C(13)-C(14)	1.394 (15)
C(4)-C(5)	1.395 (16)	C(14)-C(15)	1.383 (10)
C(4)-C(8a)	1.387 (9)	C(14)-C(18a)	1.386 (5)
C(5)-C(6)	1.330 (10)	C(15)-C(16)	1.324 (17)
C(6)-C(7)	1.408 (11)	C(16)-C(17)	1.412 (8)
C(7)-C(8)	1.355 (16)	C(17)-C(18)	1.359 (12)
C(8)-C(8a)	1.408 (9)	C(18)-C(18a)	1.411 (15)
C(8)-O(10)	1.352 (9)	C(18)-O(20)	1.346 (5)

Table 3.  $^{13}\text{C}$   $\delta$  for (1) in the solid state and in solution ( $\text{Me}_2\text{SO}-d_6$ )

	Solid state	Solution
C(2)	128.24	131.1
C(3)	111.26	112.98
C(5)	114.00	114.13
	112.97	
C(6)	104.42	104.8
	104.09	
C(7)	116.96	118.13
	115.76	
C(8)	147.25	146.48
	144.17	
C(8a)	139.33	139.94
	138.9	

The average chemical shifts (half-sum of dedoubled peaks) for (1) agree well with the corresponding chemical shifts in solution, as shown in Fig. 3.

This study demonstrates that it is possible to correlate X-ray data with  $^{13}\text{C}$  NMR spectra for a compound in the solid state for which two molecules or more are located in different sites.

The authors are grateful to A. Pagelot for his technical assistance in recording  $^{13}\text{C}$  NMR (CP/MAS)

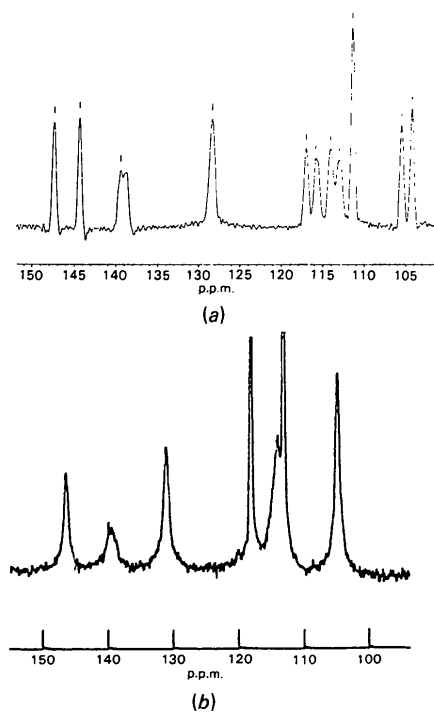


Fig. 2.  $^{13}\text{C}$  NMR spectrum of the title compound (a) in the solid state, (b) in  $\text{Me}_2\text{SO}-d_6$ .

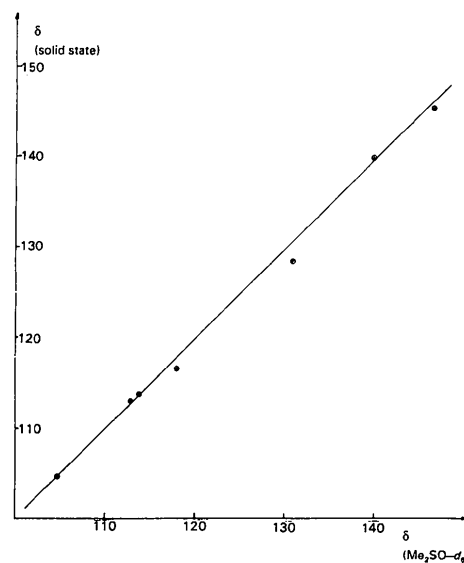


Fig. 3.  $^{13}\text{C}$  NMR chemical shifts for (1) in the solid state in relation to those in  $\text{Me}_2\text{SO}-d_6$  solution.

spectra performed at the Bruker Center, 67160 Wisssembourg, France.

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## Structure of the Radiation Protection Agent S-3-(3-Methylaminopropylamino)propylphosphorothioic Acid (WR 151,327)

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**Abstract.**  $C_7H_{19}N_2O_3PS.3H_2O$ ,  $M_r = 296.3$ , triclinic,  $P\bar{1}$ ,  $a = 6.859$  (2),  $b = 7.077$  (2),  $c = 16.326$  (5) Å,  $\alpha = 96.64$  (2),  $\beta = 100.66$  (2),  $\gamma = 105.82$  (2)°,  $V = 737.7$  Å<sup>3</sup>,  $Z = 2$ ,  $D_x = 1.337$  g cm<sup>-3</sup>,  $MoK\alpha$ ,  $\lambda = 0.71073$  Å,  $\mu = 3.33$  cm<sup>-1</sup>,  $F(000) = 320$ , room temperature, final  $R = 8.4\%$  for 1614 reflections with  $|F_o| > 3\sigma$ . The overall conformation of the molecule is linear with a bend at the terminal N atom. The molecule is a double zwitterion with the two phosphate hydrogens residing on the two N atoms, and the three P–O bonds are of equal length at approximately 1.51 Å. The S–P bond is unusually long at 2.13 Å. Each H atom on each N atom and in each water molecule participates in hydrogen bonding. Within the crystalline lattice the molecule forms head-to-tail dimers.

**Introduction.** The title compound is a member of a family of phosphorothioate compounds which have shown activity as a protective agent against the damaging and/or lethal effects of ionizing X- or  $\gamma$ -radiation (Sweeney, 1979). One-half of the maximum

tolerated dose of WR 151,327 resulted in a dose reduction factor of 1.9 as indicated by 30 day survival following irradiation of mice with <sup>137</sup>Cs  $\gamma$ -rays (Brown, Pittcock & Rubenstein, 1982). In more recent studies with higher-energy neutron radiation, WR 151,327 has demonstrated a dose reduction factor of 1.2 to 2.2 in mouse 6 to 100 day survival studies (Sigdestad, Grdina, Connor & Hanson, 1986; Steel, Jacobs, Giambarresi & Jackson, 1987).

The ultimate goal of the US Army radioprotection program is to provide field personnel with an orally effective non-toxic radioprotector. The best known and studied radioprotective agent, S-2-(3-aminopropylamino)ethylphosphorothioic acid (WR 2721,  $C_5H_{15}N_2O_3PS$ ), has limitations with respect to limited radioprotection following oral administration and a relatively short duration of radioprotection (Davidson, Grenan & Sweeney, 1980). The three-dimensional crystal structure of WR 151,327 was established to compare the overall conformation and the interatomic distance between the potentially pharmacologically