Tautomeric Azines. Part 6.[1] Phthalazin-1(2*H*)-one

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Phthalazin-1(2*H*)-one, its three monomethyl derivatives, and two of its dimethyl monocationic derivatives have been investigated by examining the spectra of the various charged forms and by basicity studies. The tautomeric equilibrium of the parent compound has been elucidated quantitatively, and the minor contributions of lactim and zwitterionic forms have been found. The tautomeric monocations show appreciable contributions from hydroxy-forms, which can predominate in high polarity media.

PHTHALAZIN-1(2*H*)-ONE (1) enters into 1,3-dipolar cycloadditions, and evidence has been presented [2] that it is the zwitterionic tautomer (1c) which is involved. Previous studies of the tautomerism of phthalazin-1(2*H*)-one have explicitly considered only the carbonyl (1b) and hydroxy-forms (1a): i.r.[3-5] and u.v. spectral evidence [5,6] demonstrated that the carbonyl form (1b) predominated. We have now undertaken a full study of the tautomeric equilibria of phthalazin-1(2*H*)-one (1) encompassing the three neutral tautomers and also the three tautomeric forms (5a—c) of the corresponding monocation.

Model Compounds.—Corresponding to the three tautomeric forms (1a—c) there exist three monomethyl derivatives (2)—(4). Each of these can be protonated to form a monocation which exists in two tautomeric forms: (2) ⟶ (6a and b); (3) ⟶ (7a and b); (4) ⟶ (8a and b). Three dimethyl monocations (9)—(11) should exist, as non-tautomeric species. The dications, whether parent (12), monomethyl (13)—(15), dimethyl (16)—(18), or trimethyl (19), are also not capable of prototropic tautomerism. To apply the basicity method in this series [7] we needed to make comparisons with as many of the methyl derivatives as possible.

The monomethyl derivatives (2)—(4) were prepared by known methods (see Experimental section). 1-Methoxyphthalazine (2) reacts with methyl toluene-*p*-sulphonate at 25 °C to yield the dimethyl cation (10) as the toluene-*p*-sulphonate: heating at 160 °C rearranges this salt into the isomeric (11). Attempts to prepare the other isomer (9) failed.

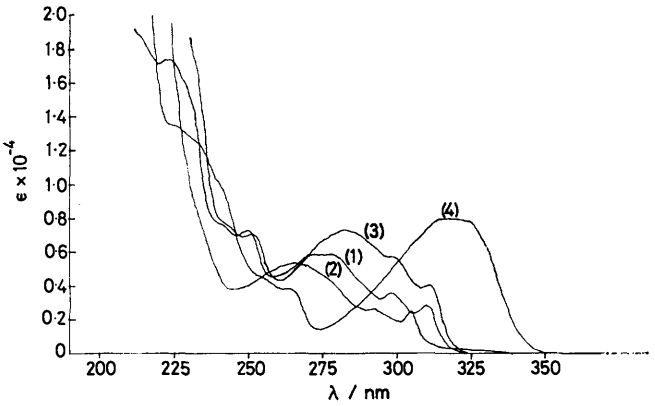


FIGURE 1 U.v. spectra in water of neutral species of 1-methoxyphthalazine (2), phthalazin-1(2*H*)-one (1), 2-methylphthalazin-1-one (3), and 3-methyl-1-oxidophthalazinium (4)

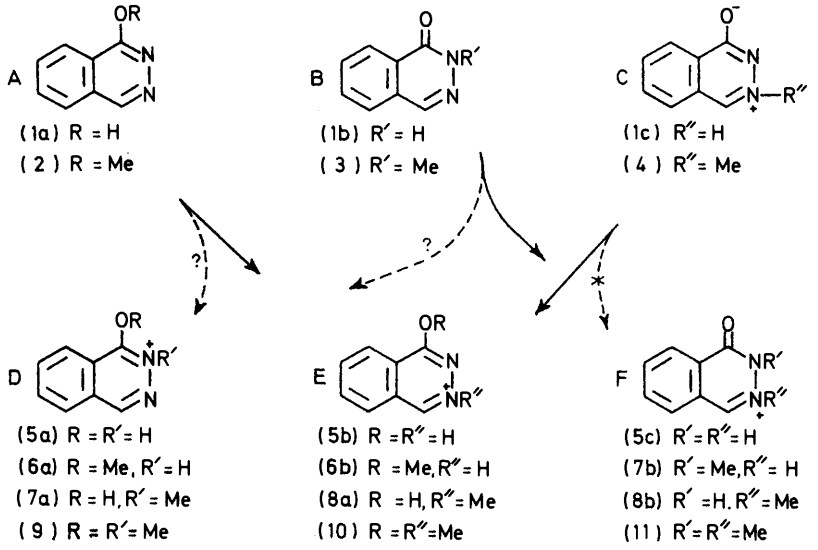
Ultraviolet Spectra (*Table* 1).—Spectra of the four neutral species are compared in Figure 1: the betaine structure (1c) is not favoured, and in view of the expected

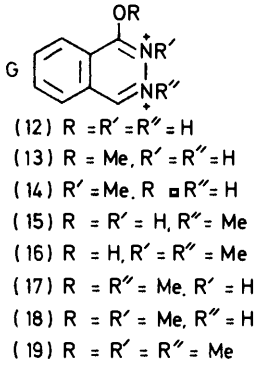
[1] Part 5, A. J. Boulton, I. J. Fletcher, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1971, 2344.
[2] N. Dennis, A. R. Katritzky, and M. Ramaiah, *J.C.S. Perkin I*, 1975, 1506.
[3] Yu. N. Sheinker and Yu. I. Pomarantsev, *Zhur. fiz. Khim.*, 1959, **33**, 1819 (*Russ. J. Phys. Chem.*, 1959, **33**, 174).
[4] S. F. Mason, *J. Chem. Soc.*, 1957, 4874.
[5] K. Mori, *Yakugaku Zasshi*, 1962, **82**, 1161.
[6] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1962, 3129.
[7] For a full discussion of the prototropic tautomerism of heteroaromatic compounds see J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, 'The Tautomerism of Heterocycles,' Academic Press, New York, 1976.

bathochromic effect of *N*-methylation, the accordance with structure (1b) is reasonable, as previously deduced.[5,6]

The monocations show two distinct spectral types (Figure 2). Spectra of the monocations bearing the 3-methyl (8) and the methoxy-substituent (6) resemble that of the dimethylated cation (10). This indicates that the predominant form of (6) is (6b) and of (8) is (8a). However, the spectrum of the monocation bearing the 2-methyl substituent (7) is distinctly different from these spectra, but does resemble that of the 2,3-dimethyl cation (11), indicating that the predominant form of (7) is (7b).

The interpretation of the spectra of the monocation (5) of the parent compound is more difficult: (5) has three possible tautomeric forms in contrast to the monomethyl derivatives which have only two each. From Figure 2, the spectrum of (5) appears to lie between those of the model fixed dimethyl cations (10) and (11).





In the above discussion, monocations of type D have been neglected: in view of the basicities of pyridine (pK_a 5.2), 2-methoxypyridine (3.3), and 3-methoxypyridine (4.9), it appears clear that D would be a minor contributor only.

The dicationic species should all be of similar type and this is borne out by the spectra (Figure 3) of [(1) ⟶] (12); [(2) ⟶] (13); [(3) ⟶] (14); [(10 ⟶] (17); and [(11) ⟶] (16). The small variations are consistent with the expected effects of *N*- and *O*-methylation.

TABLE 1

U.v. spectral maxima and intensities [a]

	Neutral species		Monocation		Dication	
Compound	Solv.	λ/nm (log ε)	H_0	λ/nm (log ε)	H_0	λ/nm (log ε)
(1)	H_2O	310 (3.46)		311 (3.69)		
(2)	H_2O	265 (3.74), 304 (3.39)	1.18	312 (3.88)		
(3)	H_2O	250 (4.30), 301 (3.54)	−6.6	217 (4.43), 227 (4.45)		312 (3.87)
(4)	H_2O	317 (3.92)	+1	315 (3.76)		Decomposes
(10)			+7	313 (3.69)	−12	316 (3.73)
(11)				307 (3.95), 320 (3.95)		323 (3.84)

[a] In aqueous H_2SO_4 unless otherwise stated.

Basicity Measurements (*Table* 2).—Comparison of the basicities for proton addition to the fixed monocations (10) and (11) (forming dications) should give a value for the tautomerism constant for the mobile monocation (8). It is clear from Table 2 that (10) and (11) have similar basicities; unfortunately the differences in the acidity

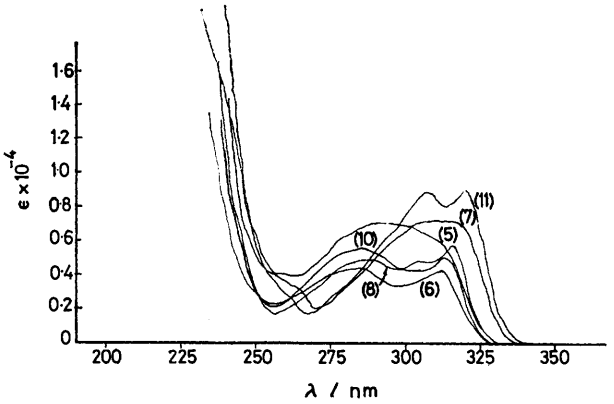


FIGURE 2 U.v. spectra of monocations of 1-methoxyphthalazine (6) (N-HCl); 3-methyl-1-oxidophthalazinium (8) (N-HCl); 1-methoxy-3-methylphthalazinium toluene-*p*-sulphonate (10) (water); phthalazin-1(2*H*)-one (5) (65.05% H_2SO_4); 2-methylphthalazin-1-one (7) (N-HCl); and 2,3-dihydro-2,3-dimethyl-1-oxophthalazinium toluene-*p*-sulphonate (11) (10% H_2SO_4)

functions followed (different values of *m*) do not allow precise conclusions. Taking this evidence in conjunction with the u.v. data, we believe that for aqueous solutions [(8a)]/[(8b)] ≃ 5.

As the methoxy- (2) and 3-methyl derivatives (4) form predominantly cations of similar type [*i.e.* (6b) and (8a),

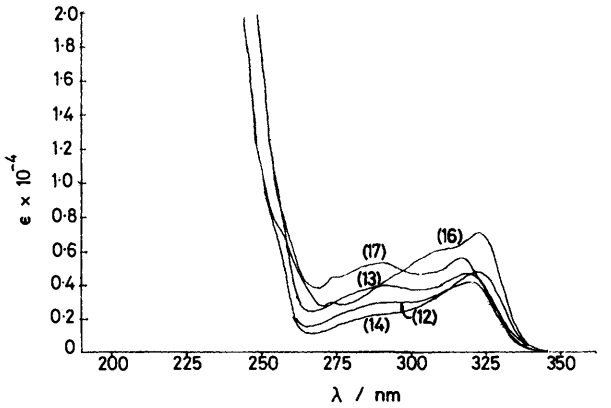


FIGURE 3 U.v. spectra in 100% H_2SO_4 of 2-methylphthalazin-1-one (14), phthalazin-1(2*H*)-one (12), 1-methoxyphthalazine (13), 1-methoxy-3-methylphthalazinium toluene-*p*-sulphonate (17), and 2,3-dihydro-2,3-dimethyl-1-oxophthalazinium toluene-*p*-sulphonate (16)

respectively], the ratio of the basicities gives directly a value for $pK_T = 1.82$ in favour of (4).

Provided monocations of type D can be neglected, the pK_a (−4.3) of the 2-methyl derivative (3) for conversion into the cation (7b) indicates that conversion of (1b) into (5b) would have pK −4.3 + 0.3 = −4.0. Hence comparison with the methoxy-compound indicates pK_T 7.8 for the equilibrium (1b) ⇌ (1a).

I.r. Spectra.—The tosylate of (8) clearly exists in structure (8a) in the solid state as shown by the absence of $\nu_{C=O}$. Such a band would be expected at 1 670 cm^{-1} and is shown by the fixed cationic tosylate of (11), but not by the fixed cationic tosylate of (10).

N.m.r. Spectroscopy.—The n.m.r. spectra of the neutral species (1)—(4) demonstrate that (1) does not exist in the hydroxy-form (1a): the H-4 signals in $(CD_3)_2SO$ occur at δ 8.42, 9.38, 8.40, and 8.39, respectively. This does not distinguish between structures (1b) and (1c).

The n.m.r. spectra of the tosylates of (8), (10), and (11), which show the H-4 signal at δ 9.85, 10.24, and 9.76, respectively, do not allow reliable conclusions regarding the tautomerism (8a) ⇌ (8b) in $(CD_3)_2SO$ solution.

Conclusions.—A consistent overall picture is revealed: phthalazin-1(2*H*)-one exists as expected predominantly in the lactam form (B), and the contributions of hydroxy- and zwitterionic forms (A and C) are minor. By contrast, mobile monocationic species show a tendency to prefer the hydroxy-structures of type E, whereas no evidence is found for type D. This behaviour is in good agreement with the known effect of substituents on tautomeric equilibria.[7]

TABLE 2

Basicity measurements at 25 °C

	Neutral → monocation		Monocation → dication			
Compd.	pK_a	λ/nm [a]	H_0 [b]	*m*	λ/nm [a]	pK_a
(1) [b]	−2.0					
(2) [c]	3.77 ± 0.045					
(3) [c]	−4.3 ± 0.2					
(4)	1.95 ± 0.02	280				
(10) [d]			−9.87	0.83		−8.19 ± 0.3
(11)			−9.36	0.91	308	−8.52 ± 0.05

[a] Analytical wavelength. [b] A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1956, 1294. [c] Ref. 6. [d] Measured by the n.m.r. method (see Experimental section).

EXPERIMENTAL

The following were prepared by the literature method cited: phthalazin-1(2*H*)-one, m.p. 186 °C (lit.,[8] 182 °C); 2-methylphthalazin-1-one, m.p. 105—108 °C (lit.,[9] 112—114 °C); 1-methoxyphthalazine, m.p. 59 °C (lit.,[10] 60—61 °C); 3-methyl-1-oxidophthalazinium, m.p. 235 °C (decomp.) (lit.,[11] 236 °C).

1-Hydroxy-3-methylphthalazinium (8) *Toluene-*p*-sulphonate.*—Phthalazin-1(2*H*)-one (1.46 g, 0.01 mol), methyl toluene-*p*-sulphonate (1.86 g, 0.01 mol), and kerosene (8 ml) were stirred at 20 °C for 1.5 h then for 6 h at 140 °C. The precipitated solid obtained after cooling was dissolved in EtOH (10 ml), and light petroleum (b.p. 40—60 °C; 30 ml) was added to give the *hydroxy-derivative*, which crystallised from EtOH as needles (3.2 g, 98%), m.p. 196 °C (Found: C, 57.6; H, 4.9; N, 8.5. $C_{16}H_{16}N_2O_4S$ requires C, 57.8; H, 4.8; N, 8.4%); $\nu_{max.}$ (Nujol) 1 605, 1 575, 1 310, 1 250, 1 150, 1 100, 1 030, 1 000, 870, and 810 cm^{-1}; $\lambda_{max.}$ (H_2O) 213 (log ε 4.60) and 319 nm (4.04); δ[$(CD_3)_2SO$] 9.85 (1 H,

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[9] S. Gabriel and F. Müller, *Ber.*, 1895, **28**, 1830.
[10] K. Adachi, *Yakugaku Zasshi*, 1955, **75**, 1426.
[11] T. Ikeda, S. Kanahara, and K. Aoki, *Yakugaku Zasshi*, 1968, **88**, 521.

s, H-4), 7.10 (2 H, d, Ts J 8 Hz), 7.35 (2 H, d, Ts), 7.32 (4 H, m, H-5—8), 4.38 (3 H, s, 3-Me), and 2.25 (3 H, s, CMe).

1,2-Dihydro-2,3-dimethyl-1-oxophthalazinium (11) *Toluene-p-sulphonate.*—2-Methylphthalazin-1-one (3) (0.160 g, 0.001 mol) and methyl toluene-*p*-sulphonate (0.186 g, 0.001 mol) were stirred at 160 °C for 2 h. MeCN (10 ml) was then added and the mixture heated under reflux for 10 min. On cooling, the *product* (11) separated as needles, which were recrystallised (EtOH–Et_2O) (0.300 g, 90%), m.p. 224—225 °C (Found: C, 58.5; H, 5.1; N, 8.3. $C_{17}H_{18}N_2O_4S$ requires C, 58.9; H, 4.9; N, 8.1%); $\nu_{max.}$ (Nujol) 1 670, 1 640, 1 600, 1 380, 1 320, 1 220, 1 120, 1 030, and 810 cm^{-1}; $\lambda_{max.}$ (H_2O) 223 nm (log ε 3.2); δ[$(CD_3)_2SO$] 9.76 (1 H, s, H-4), 7.76 (2 H, d, Ts, J 8 Hz), 7.06 (2 H, d, Ts), 8.30 (4 H, m, H-5—8), 4.45 (3 H, s, 3-Me), 2.23 (3 H, s, CMe), and 3.89 (3 H, s, 2-Me).

1-Methoxy-3-methylphthalazinium (10) *Toluene-p-sulphonate.*—1-Methoxyphthalazine (2) (0.160 g, 0.001 mol) and methyl toluene-*p*-sulphonate (0.186 g, 0.001 mol) were kept at 20 °C for 2 h. The resulting solid was triturated with MeCN (10 ml); the precipitate was crystallised from MeCN–Et_2O (50 : 50) to give the *product* (10) as needles (0.345 g, 100%), m.p. 155 °C (Found: C, 58.9; H, 5.3; N, 8.2. $C_{17}H_{18}N_2O_4S$ requires C, 58.9; H, 4.9; N, 8.1%); $\nu_{max.}$ (Nujol) 1 600, 1 580, 1 510, 1 490, 1 200, 1 120, 1 030, 960, and 760 cm^{-1}; $\lambda_{max.}$ (H_2O) 224 nm (log ε 3.71); δ [$(CD_3)_2SO$] 10.24 (1 H, s, H-4), 7.46 (2 H, d, Ts, J 8 Hz), 7.04 (2 H, d, Ts), 8.27 (4 H, m, H-5—8), 4.44 (3 H, s, 3-Me), 2.24 (3 H, s, CMe), and 4.22 (3 H, s, OMe).

Thermal Conversion of (10) *into* (11).—1-Methoxy-3-methylphthalazinium toluene-*p*-sulphonate (10) (0.080 g, 1×10^{-4} mol) was heated to 160 °C for 2.5 h with occasional stirring. The mixture was crystallised from MeCN to give 2,3-dimethyl-1-phthalazinium toluene-*p*-sulphonate (11) (0.075 g, 94.0%), m.p. 224—225 °C (mixed m.p. 224 °C).

Physical Measurements. (i) *U.v. method.* The u.v. method of measuring pK_a values is well known.[12] The pK_a of the betaine (4) was measured using aqueous buffers and dilute aqueous sulphuric acid.[12] The pK_a of the cation (11) was measured in solutions of concentrated sulphuric acid. The acidity of all sulphuric acid solutions was assigned from tables of the H_0 acidity function.[13] All optical densities were measured with a Unicam SP 500 spectrophotometer.

(ii) *N.m.r. method.* The n.m.r. method is useful when the u.v. method is inapplicable, although most authors admit an error in pK_a of ±0.3 The advantages and disadvantages have been discussed.[14] N.m.r. measurements were taken with a Perkin-Elmer R10 60 MHz spectrometer.

Solutions for measuring the pK_a of the salt (10) were prepared by adding 0.06 ml of sulphuric acid of the appropriate strength into 0.05 g samples. The solutions were immediately transferred to n.m.r. tubes and the spectra recorded between v 4 and 5 at a 100 Hz sweep width, 60 MHz, and 33 °C. The difference in δ of the two methyl peaks between δ 4 and 5 changed on ionisation from 23 to 5 Hz. Twelve separate measurements were obtained where this distance varied between 8 and 22 Hz. The constant drift of the magnetic field, significant at a 100 Hz sweep width, was corrected by sweeping the magnetic field in both directions. Six pairs of opposite sweeps were made for each sample. The acid solutions were standardised as for the measurements for the salt (11). The H_0 values used were those of ref. 13. The H_0 values were corrected by computer by means of equation (i).[13] The value of K was obtained by means of equation (ii).[13] Corrections were also

$$H_0(T) = H_0\,(25\ ^\circ C) + [K(298.15 - T)/298.15T] \quad \text{(i)}$$

$$K = -3.202\,55H_0\,(25\ ^\circ C)^3 - 56.689\,8H_0\,(25\ ^\circ C)^2 + 4.610\,41H_0\,(25\ ^\circ C) - 204.341 \quad \text{(ii)}$$

made by the computer program for the partial neutralisation of the sulphuric acid on ionising the sample.[15]

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