Azole *N*-Oxides. Part I. The Tautomerism of Benzotriazole 1-Oxide † and its 4- and 6-Nitro-derivatives with the Corresponding 1-Hydroxybenzotriazoles

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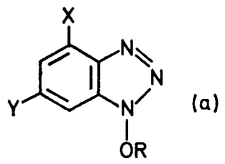
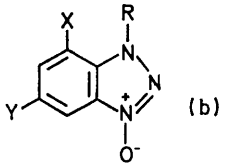
In aqueous solution benzotriazole 1-oxide and its 4- and 6-nitro-derivatives exist largely in the *N*-oxide tautomeric forms. In ethanol the unsubstituted and 6-nitro-compounds are predominantly in the *N*-hydroxy-forms, but the 4-nitro-compound exists as a mixture of comparable amounts of the two tautomers.

In 1936 Macbeth and Price [1] reported that the u.v. spectra of benzotriazole 1-oxide (1) measured in aqueous and ethanolic solution were markedly different from each other, whereas the spectra of some nitro-derivatives were similar in both solvents. They suggested that for the unsubstituted compound in ethanol both the tautomeric forms (1a and 1b) were present, that the unsubstituted compound in water existed largely as the *N*-oxide (1b), and that the nitro-derivatives were predominantly *N*-hydroxy-compounds in either solvent. As part of our studies of the chemistry of azole *N*-oxides we have re-investigated the tautomeric equilibria of benzotriazole



(a)

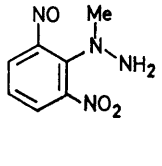


(b)

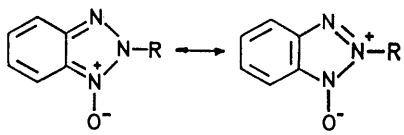
R = H		R = Me
(1)	X = Y = H	(4)
(2)	X = NO_2; Y = H	(5)
(3)	X = H; Y = NO_2	(6)

1-oxide (1) and of the 4- and 6-nitro-derivatives (2 and 3), using ultraviolet spectroscopy, basicity measurements, and acidity function correlations.

Preparation of Compounds.—Benzotriazole 1-oxide and its 4- and 6-nitro-derivatives were prepared [2] by the cyclisation of the appropriate *o*-nitrophenylhydrazine. Methylation of benzotriazole 1-oxide [3] gave a mixture of the *O*- and *N*-methyl derivatives (4). Methylation of the nitro-compounds gave only the 1-methoxy-derivatives (5a) and (6a). Dr. Roy Hull (I.C.I. Ltd., Pharmaceuticals Division) kindly supplied a sample of 3-methyl-6-nitrobenzotriazole 1-oxide (6b). The 4-nitro-analogue (5b) was obtained by cyclisation of 1-(2,6-dinitrophenyl)-1-methylhydrazine (7) with polyphosphoric acid after attempts using base [4] had led only to intractable tars. 2-Methylbenzotriazole 1-oxide (8) was obtained in very low yield by the direct oxidation of 2-methylbenzotriazole using *m*-chloroperbenzoic acid.



(7)



(8) R = Me
(10) R = H

† In order to keep the numbering of substituents in the benzene ring consistent we have numbered the triazole ring so that the nitrogen atom bearing the oxygen function is designated position 1 regardless of the tautomeric form.

[1] A. K. Macbeth and J. R. Price, *J. Chem. Soc.*, 1936, 111.
[2] O. L. Brady and J. N. E. Day, *J. Chem. Soc.*, 1923, 2258.
[3] O. L. Brady and C. V. Reynolds, *J. Chem. Soc.*, 1928, 193.
[4] B. Vis, *Rec. Trav. Chim.*, 1939, **58**, 847.

EXPERIMENTAL

Basicity Measurements.—pK_{BH^+} Values were determined spectrophotometrically.[5a] Full spectra were recorded on a Unicam SP800 spectrophotometer and precise optical densities at the selected analytical wavelengths were determined with a Unicam SP500 Series 2 spectrophotometer. The H_0 and H_A values of the solutions used were obtained from the known acid concentrations using the data of Katritzky and his co-workers.[6-8] For pK_a values in the pH region the pH values of the buffered solutions were determined using a Beckman Direct Reading Zeromatic pH meter. The pK_a of benzotriazole 1-oxide was determined potentiometrically, after the method of Albert and Serjeant.[5b] Results are recorded in Table 1.

U.v. Absorption Measurements.—U.v. spectra were recorded of solutions containing 0·7 to 1·6 × 10^{-4} mol^{-1} of compound with the pH or H_0 adjusted so that the spectrum of the required species—anion, neutral molecule, or cation—was obtained. Unicam spectrophotometers, SP800 for full spectra and SP500 Series 2 for accurate optical density measurements, were used.

Synthetic.—Elemental analyses were performed with a Technicon instrument. Melting points, measured on a Kofler hot stage, are corrected. I.r. spectra were obtained on a Perkin-Elmer 257 spectrophotometer, n.m.r. spectra on Perkin-Elmer R10 or R12 spectrometers, mass spectra on Hitachi RMU-6 or A.E.I. MS902 spectrometers.

Benzotriazole 1-oxide (1).—This compound was prepared from hydrazine hydrate and *o*-chloronitrobenzene (*cf.* ref. 2). The white needles had m.p. 157—158° (lit.,[9] 157°). Similarly 4-nitrobenzotriazole 1-oxide (2) was prepared from 2,6-dinitrochlorobenzene as red prisms with m.p. 226—228°

[5] A. Albert and E. P. Sergeant, 'Ionisation Constants of Acids and Bases,' Methuen, London, 1962; (*a*) p. 69; (*b*) p. 16.
[6] C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, 1969, **91**, 6654.
[7] K. Yates, J. B. Stevens, and A. R. Katritzky, *Canad. J. Chem.*, 1964, **42**, 1957.
[8] C. D. Johnson, A. R. Katritzky, and N. Shakir, *J. Chem. Soc.* (*B*), 1967, 1235.
[9] R. Nietzki and E. Braunschweig, *Ber.*, 1894, **27**, 3381; T. Zincke and P. Schwarz, *Annalen*, 1900, **311**, 332.

(decomp.) (lit.,[10] 229°). 6-Nitrobenzotriazole 1-oxide (3), was obtained from 2,4-dinitrophenylhydrazine with potassium hydroxide,[9] as dark yellow needles, m.p. 200—204° [lit.,[1] 206° (decomp.)].

1-*Methoxybenzotriazole* (4a) and 3-*Methylbenzotriazole* 1-*Oxide* (4b).—These compounds were prepared by methylating benzotriazole 1-oxide with sodium methoxide and methyl iodide in methanol, using the method of Brady and Reynolds.[3] 1-Methoxybenzotriazole (30%, colourless needles) had m.p. 87—88° (lit.,[3] 89°). 3-Methylbenzotriazole 1-oxide (15%, colourless needles) had m.p. 144° (lit.,[3] 145°).

TABLE 1

Dissociation constants of benzotriazole derivatives

		Proton gain				Proton loss	
		Using H_0 function		Using H_A function			
Benzotriazole substituent	λ [a] (nm)	pK_{BH^+} (±0·03)	n [b]	pK_{BH^+} (±0·03)	n [b]	λ [a] (nm)	pK_a (±0·03)
1-Oxide (1)	310	−1·06	1·33	−0·95	1·06	(P) [c]	7·88
1-Methoxy (4a)	277	−0·69	0·94				
3-Methyl 1-oxide (4b)	315	−1·07	1·40	−0·98	1·06		
2-Methyl 1-oxide (8)	315	−2·17	1·37	−1·86	1·10		
4-Nitro 1-oxide (2)	312	−2·28	1·44	−1·92	0·95	350	3·33
1-Methoxy-4-nitro (5a)	340	−2·22	1·00				
3-Methyl-4-nitro 1-oxide (5b)	300	−2·30	1·53	−1·91	1·00		
6-Nitro 1-oxide (3)	335	−2·59	1·55	−2·08	0·97	272	2·75
1-Methoxy-6-nitro (6a)	245	−2·67	1·00				
3-Methyl-6-nitro 1-oxide (6b)	240	−2·35	1·49	−1·91	0·97		

[a] Wavelength used for determining pK. [b] Coefficient in equation (1). [c] Potentiometric determination.

1-*Methoxy*-4-*nitrobenzotriazole* (5a).—A solution of 4-nitrobenzotriazole 1-oxide (2·4 g), sodium methoxide (from 0·26 g sodium), and methyl iodide (5 g) in methanol (120 ml) was boiled under reflux for 4 h. The solution was cooled and the resulting yellow precipitate was recrystallised from methanol (5 ml) to give 1-*methoxy*-4-*nitrobenzotriazole* as fine yellow needles (0·7 g, 30%), m.p. 148—149° (Found: C, 43·2; H, 3·1; N, 29·2. $C_7H_6N_4O_3$ requires C, 43·3; H, 3·1; N, 28·9%); $\lambda_{max.}$ (EtOH) 302 nm (log ε 3·92); $\nu_{max.}$ (Nujol) 3105, 3090 (arom. CH), 1588, 1495 (arom. ring), 1520, 1338 (sym. and asym. NO_2), and 950 cm^{-1} (methoxyl); δ($CDCl_3$) 8·37 (1H, q, J_o 8, J_m 2 Hz), 8·15 (1H, q, J_o 8, J_m 2 Hz), 7·78 (1H, t, J_o 8 Hz), and 4·57 (3H, s); *m/e* 194 (*M*).

1-*Methoxy*-6-*nitrobenzotriazole* (6a).—This compound was prepared in a similar manner, as pale yellow needles, m.p. 129° (lit.,[1] 130°).

1-(2,6-*Dinitrophenyl*)-1-*methylhydrazine* (7).—A solution of methylhydrazine (1·05 g) in ethanol (40 ml) was added dropwise during 15 min to a refluxing solution of 2,6-dinitrochlorobenzene (4·0 g) in ethanol (40 ml). The red solution was heated under reflux for a further 30 min and then kept at room temperature for 18 h. T.l.c. indicated that 2,6-dinitrochlorobenzene was still present so more methylhydrazine (0·5 g) in ethanol (5 ml) was added and the solution was heated under reflux for 3 h. The mixture was poured into ice–water (200 ml) and the resulting yellow solid was filtered off, dried, and recrystallised from ethanol to give the *substituted hydrazine* as yellow plates (2·5 g, 67%) with m.p. 102·5—104°. (Found: C, 39·4; H, 3·8; N, 26·2. $C_7H_8N_4O_4$ requires C, 39·6; H, 3·8; N, 26·4%).

3-*Methyl*-4-*nitrobenzotriazole* 1-*Oxide* (5b).—A mixture of the hydrazine (7) (0·4 g) and polyphosphoric acid (15 g) was gently warmed and stirred for 10 min. The resulting brown solution was cooled and poured into water (100 ml). The solution was extracted with chloroform (3 × 30 ml) and the yellow organic extract was chromatographed on basic alumina (100—200 mesh, 100 g). The unchanged hydrazine was eluted with chloroform. A second fraction was collected, concentrated under reduced pressure, and recrystallised from ethanol to give 3-*methyl*-4-*nitrobenzotriazole* 1-*oxide* as yellow plates (0·15 g, 41%), with m.p. 242—243° (Found: C, 43·4; H, 3·3; N, 29·1. $C_7H_6N_4O_3$ requires C, 43·3; H, 3·1; N, 28·9%); $\lambda_{max.}$ (EtOH) 243 (log ε 3·97) and 370 nm (3·74); $\nu_{max.}$ (Nujol) 3080, 3065 (arom. CH), 1622, 1605 (arom. ring), 1530, 1340 (sym. and asym. NO_2), and 1277 cm^{-1} ($\overset{+}{N}$–$\overset{-}{O}$); δ($CDCl_3$) 8·45 (1H, q, J_o 8, J_m 1·5 Hz), 8·40 (1H, q, J_o 8, J_m 1·5 Hz), 7·51 (1H, t, J_o 8 Hz), and 4·36 (3H, s); *m/e* 194 (*M*) and 178 (*M* − oxygen).

2-*Methylbenzotriazole* 1-*Oxide*.—A solution of *m*-chloroperbenzoic acid (5·19 g) in methylene chloride (50 ml) was added dropwise to an ice-cooled, stirred solution of 2-methylbenzotriazole [11] (3·99 g) in methylene chloride (50 ml). The solution was stirred for 12 days and then passed through a column of basic alumina (100—200 mesh, 100 g). Unchanged amine (3·1 g, 79%) was removed by washing with chloroform. A second fraction was eluted which on evaporation gave a yellow oil (more unchanged amine) and a white crystalline solid. The amine was removed by washing with cold ether (15 ml) and the solid was recrystallised from carbon tetrachloride to give 2-*methylbenzotriazole* 1-*oxide* as white plates (35 mg, 0·8%) with m.p. 96° (Found: C, 56·7; H, 4·8; N, 28·3. $C_7H_7N_3O$ requires C, 56·4; H, 4·7; N, 28·2%); $\lambda_{max.}$ (EtOH) 326 nm (log ε 3·70); $\nu_{max.}$ (Nujol) 1256 cm^{-1} ($\overset{+}{N}$–$\overset{-}{O}$); *m/e* 149 (*M*), 133 (*M* − oxygen), and 118 (*M* − oxygen and methyl).

RESULTS AND DISCUSSION

Two alternative sets of pK_{BH^+} values are recorded in Table 1: one set derived by using the H_0 function [12] in equation (1), and the other by using the H_A function.[7,8] For each set the value of the coefficient n, obtained by a least-squares analysis of the correlation between (log [cation] − log [base]) and H_0 or H_A, is also given in the Table. In general the best approximation to

[9] W. Borsch and D. Rantscheff, *Annalen*, 1911, **379**, 152.
[10] F. Krollpfeiffer, A. Rosenburg, and C. Muhlhausen, *Annalen*, 1935, **515**, 113.
[12] L. P. Hammett and A. J. Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 2721; M. J. Jorgenson and D. R. Hartter, *ibid.*, 1963, **85**, 878.

the true pK_{BH^+} value will be given by the correlation

$$pK_{BH^+} = H_O \text{ (or } H_A) + n(\log [\text{cation}] - \log [\text{base}]) \quad (1)$$

for which n is closest to unity. Good correlations with H_O (*i.e.* true Hammett bases) usually imply that protonation is occurring at nitrogen[8] and it can be seen that this applies to the 1-methoxybenzotriazoles (4a), (5a), and (6a) all of which presumably protonate on $N(3)$ to give a cation of type (9). This presumption is supported by the u.v. spectroscopic data (below). Similarly, good correlations with H_A (which is based on amide[7] and pyridine N-oxide[8] indicators) usually imply O-protonation,[8] and the fixed N-oxides (4b), (5b), and (6b) all give n values close to unity in H_A plots.

The tautomeric compounds (1)—(3) all correlate much more closely with H_A than with H_O; the n values in H_A plots lie in the range 0·95 to 1·06 whereas for H_O plots they fall between 1·33 and 1·55. This is good qualitative evidence that in aqueous solution all three systems exist predominantly in the N-oxide tautomeric forms (1b), (2b), and (3b), as their protonation behaviour resembles

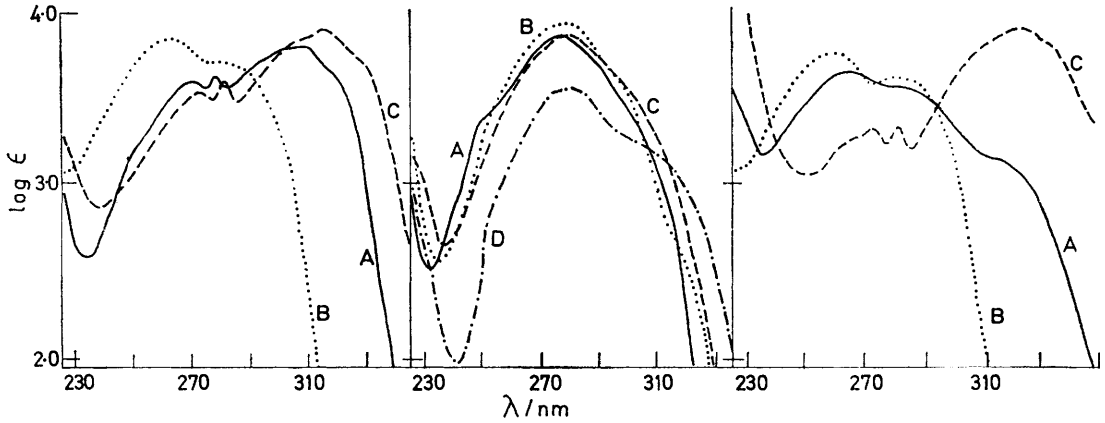


FIGURE 1 FIGURE 2 FIGURE 3

Ultraviolet spectra of benzotriazoles: FIGURE 1, free bases in aqueous solution; FIGURE 2, cations in sulphuric acid; FIGURE 3, in ethanol. A, Tautomeric system (1); B, 1-methoxybenzotriazole (4a); C, 3-methylbenzotriazole 1-oxide (4b); D, 2-methylbenzotriazole 1-oxide (8)

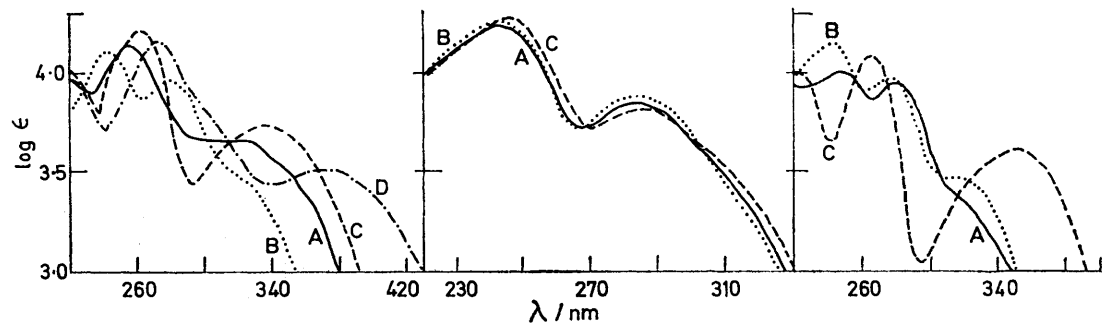


FIGURE 4 FIGURE 5 FIGURE 6

Ultraviolet spectra of 6-nitrobenzotriazoles: FIGURE 4, in aqueous solution; FIGURE 5, cations in sulphuric acid; FIGURE 6, in ethanol. A, Tautomeric system (3) as free base (buffered at pH 0·4 in Figure 4); B, 1-methoxy-6-nitrobenzotriazole (6a); C, 3-methyl-6-nitrobenzotriazole 1-oxide (6b); D, anion of tautomeric system

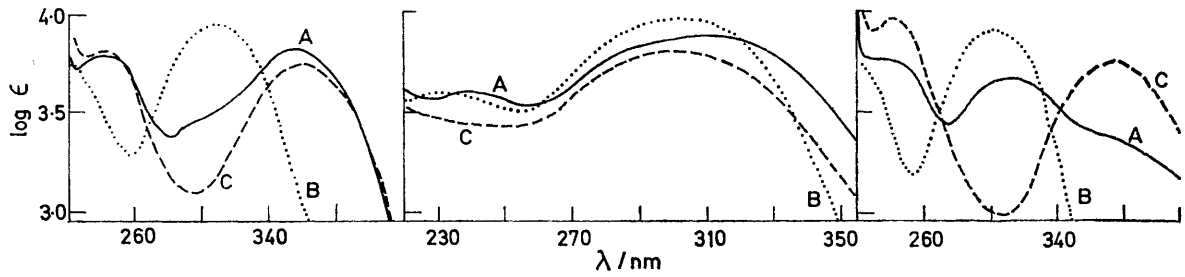


FIGURE 7 FIGURE 8 FIGURE 9

Ultraviolet spectra of 4-nitrobenzotriazoles: FIGURE 7, free bases in aqueous solution; FIGURE 8, cations in sulphuric acid; FIGURE 9, in ethanol. A, Tautomeric system (2); B, 1-methoxy-4-nitrobenzotriazole (5a); C, 3-methyl-4-nitrobenzotriazole 1-oxide (5b)

that of the *N*-oxide model compounds much more closely than that of the *N*-methoxy-models.

Mason [13] has derived equation (2) relating the difference, ΔpK_{BH^+}, between the pK_{BH^+} values of the separate tautomers (represented by their non-tautomeric model compounds) with K_T, the tautomeric equilibrium constant. For very weak bases this must be modified to

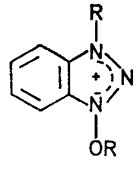
$$\log K_T = \Delta pK_{BH^+} \qquad (2)$$

equation (3), in which $H_0^t(i)$, derived as the 'pK' value from equation (1) when plotting against H_0, is actually the H_0 value for half protonation of tautomer i, and n_i is the corresponding coefficient n, also from equation (1). The modification is necessary because the comparison be-

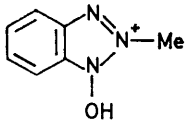
$$\log K_T = \Delta[H_0^t(i)/n_i] \qquad (3)$$

tween tautomers must be made at the same acidity, and it is therefore not permissible to compare pK_{BH^+} values derived from the H_0 scale with those derived from H_A.

This approach predicts tautomeric equilibrium constants of 1·1 (*N*-oxide favoured) for the unsubstituted system, and 0·1—0·2 (*N*-hydroxy-favoured) for the nitro-compounds. However, the differences, $\Delta[H_0^t(i)/n_i]$, between the H_0^t values for the *O*- and *N*-methyl models are too small (compared with the intrinsic errors) for us to place much reliance on the K_T values derived this way; the method is much more appropriate for systems in which there is less than 1% of the minor component. This approach suggests that in the unsubstituted benzotriazole system in aqueous solution the two tautomers are present in comparable amounts, and that the preferred tautomers of the nitro-compounds are the *N*-hydroxy-forms whereas all the other evidence suggests that the *N*-oxide is the stable tautomer in all three cases. Moreover the method is not strictly applicable to the 4-nitro-compound, since Mason's approach requires [13] that the electronic structures of the cations obtained by protonation of both tautomers and of both model compounds should be analogous. This is apparently true for the unsubstituted and 6-nitro-series; the u.v. spectra of the cations are virtually superimposable (Figures 2 and 5), suggesting that they have analogous structures (9). In the 4-nitro-series the cation spectra are less similar (Figure 8); presumably the steric interaction between the 3-methyl and 4-nitro-groups twists the chromophoric system of the *N*-methyl model so that its cation is not strictly analogous to the 3*H* cations.



(9) R = H or Me



(11)

As Spinner and Yeogh have recently pointed out,[14] if the minor tautomer exists in sufficiently high concentration for detection then a better estimate of K_T can be obtained by direct determination using equation (4), where ε^T, ε^O, and ε^N are the u.v. molar extinction coefficients at a suitable wavelength of the tautomeric mixture, and of the *O*-methyl and *N*-methyl models respectively. Spectra are illustrated in the Figures. Qualitatively they confirm the indications of the acidity function correlations, that in aqueous solution the tautomeric systems are largely in the *N*-oxide form. The resulting values of K_T, recorded in Table 2 quantify these conclusions.

$$K_T = \frac{[N^+-O^-]}{[N-OH]} = \frac{\varepsilon^T - \varepsilon^O}{\varepsilon^N - \varepsilon^T} \qquad (4)$$

In ethanol solution, however, the spectra of the tautomeric systems (1) and (3) both resemble those of the corresponding *N*-methoxy-model compounds, and the K_T values (Table 2) indicate a change in the tautomeric

TABLE 2

U.v. absorption data

Benzotriazole 1-oxide substituents	Solvent	λ [a] (nm)	ε^T [b]	ε^O [b]	ε^N [b]	K_T [c]	% *N*-oxide
None	H_2O	310	5832	270·3	6921	5·1	84
	EtOH	315	1422	14·58	6439	0·28	22
4-NO_2	H_2O	300	2960	8184	1266	3 [d]	75 [d]
	EtOH	300	4760	7842	960	0·8 [d]	45 [d]
6-NO_2	H_2O	340	4463	1911	5321	3·0	75
	EtOH	280	8056	8719	4436	0·18	15

[a] Wavelength at which extinction coefficients of *O*- and *N*-methyl models were measured (see text). [b] ε^T, ε^O, ε^N Are molar extinction coefficients of the tautomeric mixture and the *O*- and *N*-methyl models respectively. [c] Tautomeric equilibrium constant derived from equation (3). [d] Results less reliable (see text).

equilibrium to favour the *N*-hydroxy-form. This behaviour is in accord with that observed in other, related systems [15] where *N*-oxide ⇌ *N*-hydroxy tautomeric equilibria can be shifted towards the more polar *N*-oxide in water and towards the less polar *N*-hydroxy-form in less polar solvents. A similar change, but less marked, is found for the 4-nitro-compound (2), which exists in ethanol solution as almost equal proportions of the two forms. The difference presumably arises from stabilisation of the 3*H*-1-oxide tautomer (2b) by intramolecular hydrogen bonding between the 3-position hydrogen atom and the 4-nitro-group. The quantitative assessment of K_T for the 4-nitro-compound is less reliable than those for the 6-nitro- and unsubstituted compounds because, as we mentioned above, steric twisting of the chromophore of the 3-methyl-4-nitro-1-oxide renders this a less than ideal model compound.

Our result for the 6-nitro-compound differs from that of Macbeth and Price [1] who suggested that in both aqueous and ethanolic solutions the predominant tautomer was 1-hydroxy-6-nitrobenzotriazole. The discrepancy probably arises because the compound is a fairly strong acid ($pK_a = 2·75$); the spectrum recorded

[13] S. F. Mason, *J. Chem. Soc.*, 1958, 674.
[14] E. Spinner and G. B. Yeogh, *J. Chem. Soc.* (*B*), 1971, 279.
[15] (*a*) S. Takahashi and H. Kano, *Chem. Pharm. Bull.*, 1963, **11**, 1375; (*b*) D. J. Neadle and R. J. Pollit, *J. Chem. Soc.* (*C*), 1967, 1764; (*c*) S. O. Chua, M. J. Cook, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1971, 2350.

by Macbeth and Price [1] is that of the anion. When the spectrum is recorded in a solution buffered at pH 0·4, midway between the pK_a and pK_{BH+} values, it bears a close resemblance to that of the *N*-oxide model (Figure 4).

Throughout our discussion we have tacitly assumed that 2*H*-1-oxide structures (10) do not contribute significantly to the tautomeric mixtures. They are likely to be of much higher energy than the 1-hydroxy and 3*H*-1-oxide forms because they involve either the disruption of the aromaticity of the benzene ring or an increased charge separation. The u.v. spectra of 2-methylbenzotriazole 1-oxide (8) do not conclusively prove that the 2*H*-1-oxide tautomer is absent, but the difference between the spectrum of the 2-methyl cation [which presumably has structure (11) since correlation with H_A indicates *O*-protonation] and the spectra of the other cations in Figure 2 does indicate that the 3-position nitrogen atom is more basic than that at the 2-position and therefore is likely to preferentially accept the proton in a prototropic shift.

Conclusion.—In aqueous solution all the tautomeric systems studied exist predominantly in the more polar *N*-oxide form; in ethanol the equilibria are shifted towards the less polar *N*-hydroxy-tautomer. Acidity function correlations provide useful indications of tautomeric preference for weak bases. K_T Values derived from u.v. absorption studies are more reliable in these systems than those derived from basicity measurements.

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