Azole *N*-Oxides. Part II.[1] The Tautomerism of 3,4,5-Trimethylpyrazole 2-Oxide with 1-Hydroxy-3,4,5-trimethylpyrazole

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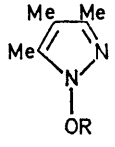
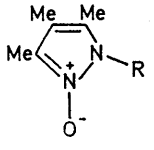
1-Hydroxy-3,4,5-trimethylpyrazole is considerably more stable than the tautomeric *N*-oxide in both aqueous and ethanolic solution.

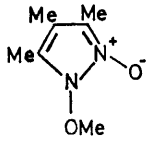
N-HYDROXYPYRAZOLES, which are potentially tautomeric with pyrazole *N*-oxides, were first described by Freeman and his co-workers [2] in 1969. We wished to study this tautomerism and chose as a representative system 1-hydroxy-3,4,5-trimethylpyrazole (1). For comparison we required 1-methoxy-3,4,5-trimethylpyrazole (2) and 1,3,4,5-tetramethylpyrazole 2-oxide (3). The methoxy-compound could be obtained by direct methylation of the 1-hydroxypyrazole or, more satisfactorily, by the deoxygenation of 1-methoxy-3,4,5-trimethylpyrazole 2-oxide (4). However, all attempts to



(1a) R = H
(2) R = Me



(1b) R = H
(3) R = Me



(4)

prepare 1,3,4,5-tetramethylpyrazole 2-oxide, either by methylation of the 1-hydroxypyrazole or by oxidation of 1,3,4,5-tetramethylpyrazole, failed. Among reagents tried for this oxidation were performic, peracetic, pertrifluoroacetic, *m*-chloroperbenzoic, perphthalic, and permaleic acids, and 90% hydrogen peroxide with polyphosphoric acid. Only unchanged starting material was isolated from all of these reactions.

EXPERIMENTAL

Basicity measurements were made potentiometrically.[3] Spectra were measured as previously described.[1] Melting points, measured on a Kofler hot-stage, are corrected.

1-*Hydroxy*-3,4,5-*trimethylpyrazole* (1) was prepared by Freeman's method [2] as white needles with m.p. 182—184° (lit.,[2] 183—184°).

1-*Methoxy*-3,4,5-*trimethylpyrazole* (2).—An excess of diazomethane in ether was added dropwise to a stirred ice-cooled solution of 1-hydroxy-3,4,5-trimethylpyrazole 2-oxide [2] (4·1 g) in dry AnalaR chloroform (50 ml) during 1·5 h. The yellow solution was stirred for 1 h and allowed to warm to room temperature; the solvents were then removed under pressure (bath temperature below 30°). The resulting 1-*methoxy*-3,4,5-*trimethylpyrazole* 2-*oxide* (4) (crude yield 4 g, 90%) exploded during an attempted distillation (*cf.* ref. 4) and in subsequent preparations was therefore used without further purification. Phosphorus trichloride (9 ml) was added dropwise to a stirred ice-cooled solution of the crude methoxy oxide (4 g) in dry AnalaR chloroform (50 ml). The resulting yellow solution was stirred for 6 h, solvent was removed under reduced pressure, and the oil was cautiously added to ice–water (200 ml). The mixture was made alkaline (pH 13) with 2N-sodium hydroxide solution

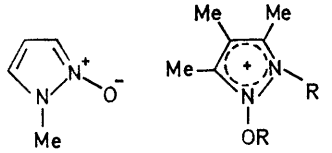
[1] Part I, F. T. Boyle and R. A. Y. Jones, *J.C.S. Perkin II*, preceding paper.
[2] J. P. Freeman, J. J. Gannon, and D. L. Surbey, *J. Org. Chem.*, 1969, **34**, 187.
[3] A. Albert and E. P. Serjeant, 'Ionisation Constants of Acids and Bases,' Methuen, London, 1962, p. 16.
[4] Part III, F. T. Boyle and R. A. Y. Jones, *J.C.S. Perkin I*, 1973, 167.

and extracted with chloroform (3 × 100 ml). The extract was dried ($MgSO_4$) and the chloroform was removed under reduced pressure. N.m.r. analysis of the oil showed that unchanged *N*-oxide was still present so it was redissolved in chloroform (50 ml) and treated as before with phosphorus trichloride (5 ml) for 2 days. After work-up to a yellow oil, distillation gave two products. The first was was *1-methoxy-3,4,5-trimethylpyrazole* (2) as a light-sensitive colourless oil (0·5 g, 12%) with b.p. 46—48°/0·015 mmHg; δ (CCl_4) 3·95 (s, OMe), 2·11(s) and 2·10(s) (3-Me, 5-Me), and 1·90 (s, 4-Me); *m/e* 140 (*M*). An accurate microanalysis could not be obtained, probably because of partial thermal degradation at boiling point, but the parent peak in the mass spectrum was accurate for $C_7H_{12}N_2O$ within 3 p.p.m. The second product was *3-chloromethyl-1-methoxy-4,5-dimethylpyrazole* (0·5 g, 10%) with b.p. 56—62°/0·15 mmHg (Found: C, 48·8; H, 6·0; N, 15·5. $C_7H_{11}ClN_2O$ requires C, 48·2; H, 6·3; N, 16·0%); δ (CCl_4) 4·50 (s, 2H, CH_2Cl), 4·04 (s, 3H, OMe), 2·08 (s, 3H, 5-Me), and 1·95 (s, 3H, 4-Me); *m/e* 174 + 176 (*M*), 159 + 161 (*M* − Me), 143 + 145 (*M* − OMe), 140 (*M* − Cl), 125 (*M* − CH_2Cl), and 109 (*M* − OMe − CH_2Cl). The formation of this product is discussed in ref. 5.

RESULTS

It is unfortunate that 1,3,4,5-tetramethylpyrazole 2-oxide (3) proved unobtainable, because it would have provided a satisfactory model for the *N*-oxide tautomer (1b). Dr. E. W. Parnell (May and Baker Ltd.) kindly supplied us with a sample of 1-methylpyrazole 2-oxide [6] (5), and we have attempted to predict the pK_{BH+} and u.v. spectrum of the tetramethylpyrazole *N*-oxide by extrapolation from those of the monomethyl *N*-oxide.

The u.v. spectra of pyrazole and of all its methylated derivatives have been reported.[7] The introduction of additional methyl groups has little effect on molar extinction coefficients, but does cause a systematic bathochromic shift in the values of $\lambda_{max.}$. By analogy we suppose that a similar effect will be found in the corresponding pyrazole *N*-oxides and we have therefore



(5) (6) R = H, Me

represented the u.v. spectrum of the inaccessible tetramethylpyrazole 2-oxide by that of 1-methylpyrazole 2-oxide shifted 11 nm to longer wavelength.

The addition of methyl groups to pyrazole [8] and imidazole [9] has an additive incremental effect on the pK_{BH+} values. A similar effect can be seen in the pyridine *N*-oxide series.[10] We have chosen incremental values of 0·45, 0·50, and 0·70 p*K* units for the 3-, 4-, and 5-methyl groups respectively, corresponding to the values for 2-, 3-, and 4-methyl groups in pyridine 1-oxide. This predicts a total difference of 1·65 p*K* units between the pK_{BH+} values of the monomethyl- and tetramethylpyrazole *N*-oxides.

Even fairly large errors in these extrapolations do not alter the conclusions of this work.

The predicted data, together with measured pK_{BH+} values and u.v. spectra for the tautomeric system (1) and for 1-methoxy-3,4-5-trimethylpyrazole, are recorded in the Table and Figures.

TABLE

Basicity data for substituted pyrazoles in aqueous solution

Substituents	Proton gain (pK_{BH+})	Proton loss (pK_a)
1-Hydroxy-3,4,5-trimethyl (1)	5·51 ± 0·06	6·11 ± 0·06
1-Methoxy-3,4,5-trimethyl [a] (2)	7·03 ± 0·03	
1-Methyl 2-oxide (5)	6·90 ± 0·03	
1,3,4,5-Tetramethyl 2-oxide (3)	8·55 [b]	

[a] 2% Ethanol present for solubility. [b] Estimated (see text).

DISCUSSION

The u.v. spectra of 1-hydroxy and 1-methoxy-3,4,5-trimethylpyrazole, and of 1-methylpyrazole 2-oxide,

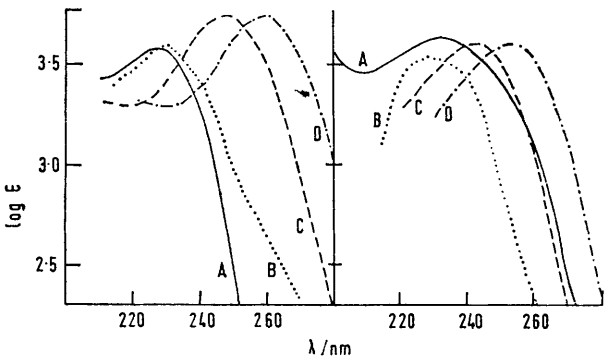


FIGURE 1 FIGURE 2

Ultraviolet spectra of pyrazoles: FIGURE 1, in ethanol; FIGURE 2, in water. A, tautomeric mixture (1); B, 1-methoxy-3,4,5-trimethylpyrazole (2); C, 1-methylpyrazole 2-oxide (5); D, conjectured spectra of 1,3,4,5-tetramethylpyrazole 2-oxide (3).

and the estimated spectrum of 1,3,4,5-tetramethylpyrazole 2-oxide in ethanol solution are illustrated in Figure 1. The spectrum of the tautomeric system (1) closely resembles that of the methoxy model compound (2), and there is no evidence of absorption corresponding to the 3,4,5-trimethylpyrazole 2-oxide tautomer (1b). In aqueous solution (Figure 2) the initial impression is that the tautomeric mixture contains significant concentrations of both tautomers (1a, 1b), but for the reasons detailed below we believe that this is not a correct interpretation.

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[6] E. W. Parnell, *Tetrahedron Letters*, 1970, 3941.

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[8] J. Elguero, E. Gonzalez, and R. Jacquier, *Bull. Soc. chim. France*, 1968, **14**, 5009.

[9] A. H. M. Kirby and A. Neuberger, *Biochem. J.*, 1938, **32**, 1146.

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The titration curve of the tautomeric system (1) shows that there is considerable overlap of separate

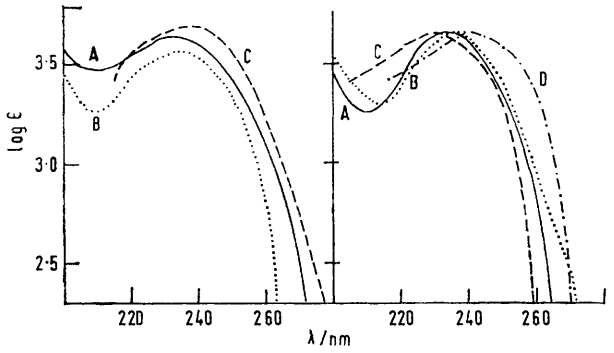

FIGURE 3

FIGURE 4

FIGURE 3 Ultraviolet spectra of 1-hydroxy-3,4,5-trimethylpyrazole (1). A, buffered at pH 6·2; B, cation in 0·001N-sulphuric acid; C, anion in N-sodium hydroxide solution. FIGURE 4 Ultraviolet spectra of cations (6) in sulphuric acid. A, 1-hydroxy-3,4,5-trimethylpyrazole (1); B, 1-methoxy-3,4,5-trimethylpyrazole (2); C, 1-methylpyrazole 2-oxide (3); D, conjectured spectrum of 1,3,4,5-tetramethylpyrazole 2-oxide (5)

cation ⇌ free base and free base ⇌ anion curves, that is that 1-hydroxy-3,4,5-trimethylpyrazole is almost as strong an acid as its cation. Thus in aqueous solutions at intermediate pH values the u.v. spectrum will not simply be that of the free base but will be a superimposition of the spectra of cation, free base, and anion. Figure 3 illustrates this at pH 6·2; the long wavelength absorption is probably mainly due not to the *N*-oxide tautomer, but to the anion.

Provided that both tautomers (1a, 1b) and both model compounds (2), (3) protonate to give structurally analogous cations (6) [and the similarity of the cation spectra (Figure 4) supports this assumption] then a quantitative estimate of the tautomeric equilibrium constant, K_T, can be obtained from the difference, ΔpK_{BH+}, between the pK_{BH+} values of the *O*- and *N*-methyl models, using Mason's equation:[11] $K_T = 10^{\Delta pK_{BH+}}$. This gives a value of $K_T = 33$, corresponding to 97% of the *N*-hydroxy-tautomer (1a). Because of the approximations involved we do not place great reliance on the accuracy of this value, but we believe that the qualitative conclusion, that in both aqueous and ethanolic solution 1-hydroxy-3,4,5-trimethylpyrazole (1a) is the overwhelming tautomer, is valid.

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[11] S. F. Mason, *J. Chem. Soc.*, 1958, 674.