Azole *N*-Oxides. Part III. Thermal Rearrangements of 1-Methoxypyrazole 2-Oxides [1]

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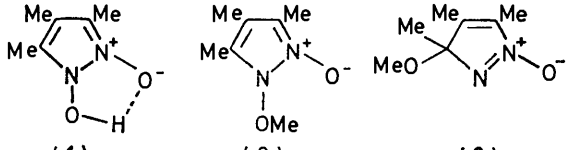
1-Methoxy-3,4,5-trimethylpyrazole 2-oxide and 1-methoxy-4,5-dimethyl-3-phenylpyrazole 2-oxide undergo spontaneous thermal rearrangements to the isomeric 5-methoxy-compounds. 1-Methoxy-3,4-dimethyl-5-phenylpyrazole 2-oxide rearranges more slowly to give a mixture of the 3-, 4-, and 5-methoxy-isomers.

As part of our studies on the tautomerism of azole *N*-oxides we wished to prepare 1-methoxypyrazoles.[1] Freeman and Gannon [2] have prepared such compounds by reducing 1-hydroxypyrazole 2-oxides, which are readily obtained from the nitrosation of αβ-unsaturated oximes, followed by methylation of the resulting 1-hydroxypyrazoles. We found that, for some compounds, the reduction step using sodium dithionite [2] gave very poor yields and attempted [3] to improve the yield by first methylating the 1-hydroxypyrazole 2-oxide to give the 1-methoxypyrazole 2-oxide [as (2)], followed by deoxygenation with a P^{III} compound such as triethyl phosphite or phosphorus trichloride. Methylation of 1-hydroxy-3,4,5-trimethylpyrazole 2-oxide (1) with diazomethane proceeded smoothly to give the 1-methoxy-2-oxide (2) and it was indeed possible to deoxygenate this compound, though with an unexpected side-reaction.[3] However, the 1-methoxy-2-oxide (2) proved to be thermally unstable, undergoing a novel type of rearrangement which is the subject of this paper. We also studied the rearrangements of the isomeric 1-methoxy-3,4-dimethyl-5-phenylpyrazole 2-oxide (11) and 1-methoxy-4,5-dimethyl-3-phenylpyrazole 2-oxide (9) which are obtained as a 1 : 1 mixture by the action of diazomethane on the tautomeric 1-hydroxy-3(5),4-dimethyl-5(3)-phenylpyrazole 2-oxide [2] (8).



(1) (2) (3)

† Except in the experimental section we have numbered the rearrangement products (3), (10), (12), (13), and (14), which are strictly speaking 3*H*-, 4*H*-, or 5*H*-pyrazole 1-oxides, as 5*H*-, 4*H*-, or 3*H*-pyrazole 2-oxides respectively, so that the substituent groups, apart from the migrating methoxy-group, retain the same positional number as in the starting materials.

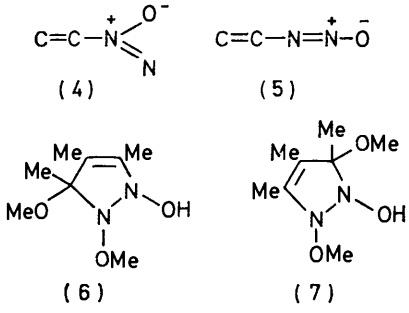
DISCUSSION

Attempted distillation of 1-methoxy-3,4,5-trimethylpyrazole 2-oxide (2) led to an explosion. N.m.r. analysis of the oil left in the remains of the condenser showed it to be different from the starting material. We subsequently found that the same reaction took place under less drastic conditions by dissolving the *N*-methoxy-*N'*-oxide (2) in carbon tetrachloride and stirring the solution at room temperature for several days. The product of reaction was shown by n.m.r., u.v., and mass spectroscopy to be the isomeric 5-methoxy-3,4,5-trimethylpyrazole 2-oxide † (3). The n.m.r. spectrum (Table) shows upfield shifts of the signals from the *O*-methyl group and from one of the *C*-methyl groups, consistent with the transfer of the methoxy-group from nitrogen to carbon, and the remaining two methyl group signals show homoallylic coupling indicating that they are attached to a localised double bond which is no longer part of an aromatic system. N.m.r. provides a simple means of monitoring the rearrangement, by following the declining intensity of the *N*-methoxy-signal and the simultaneous rise of the

N.m.r. spectra of pyrazole derivatives (δ values)

Compound	Solvent [a]	*N*-OMe	*C*-OMe	3-Me [b]	4-Me	5-Me [b]	Ph	OH
(2)	A	4·08		2·03	1·86	2·11		
(3)	A		3·05	2·07 [c]	1·83 [c]	1·46		
(6) or (7)	B	3·85	3·15	1·83 [d]	1·76	1·46 [d]		9·25
(9)	A	4·17			1·98	2·15	7·3—7·9	
(10)	A + B		3·18		2·08	1·60	7·57	
(11)	A	4·02		2·10	1·98		7·39	
(12)	A + B		3·27		2·09 [c]	1·76 [c]	7·2—7·9	
(13) [e]	A + B		3·23		1·5	2·1	7·2—7·9	
(14) [e]	A + B		3·01		1·94	1·51	7·2—7·9	

[a] A = Carbon tetrachloride; B = deuteriochloroform. [b] See footnote on this page. [c] Quartets, ^5J = 1·5 Hz. [d] Or reversed assignment for these two signals. [e] Or reversed assignment for these two compounds.



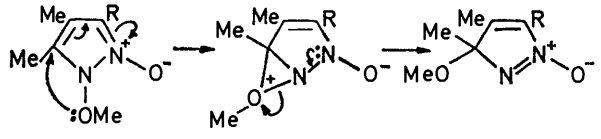
(4) (5) (6) (7)

[1] Part II, F. T. Boyle and R. A. Y. Jones, *J.C.S. Perkin II*, in the press.

[2] J. P. Freeman and J. J. Cannon, *J. Heterocyclic Chem.*, 1966, **3**, 544; *J. Org. Chem.*, 1969, **34**, 194.

[3] Part IV, F. T. Boyle and R. A. Y. Jones, following paper.

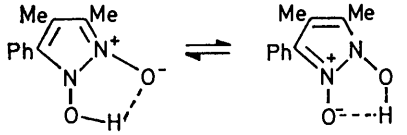
C-methoxy one. The u.v. spectrum shows no absorbance beyond about 250 nm, consistent [4] with an αβ-unsaturated azoxy-compound with partial structure (4) rather than (5). The mass spectrum shows a peak at *m/e* 156 for the molecular ion, and also peaks corresponding to the loss of the various ring substituents (see Experimental section). Further evidence for the non-aromatic structure of the rearrangement product comes from the close similarity of its n.m.r. spectrum to that of the product of the reaction of the *N*-methoxy-*N'*-oxide (2) with sodium methoxide in methanol, which we consider to have structure (6) or (7); its n.m.r. spectrum does not show significant homoallylic coupling, but this is probably because of increased buckling in the ring, relative to compound (3), arising from the increased substitution.



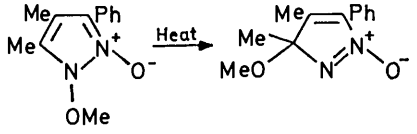
SCHEME

We are not yet in a position to substantiate a mechanism for this rearrangement for which we can find no precedent. However, by analogy with the migrations of methoxy-groups participating in solvolytic displacements [5] or with the recently reported nitrene-induced methoxy-rearrangements,[6] we suggest the methoxonium route of the Scheme (R = Me).

When 1-hydroxy-3(5),4-dimethyl-5(3)-phenylpyrazole 2-oxide [2] (8) is treated with diazomethane it gives a 1 : 1 mixture of the two isomeric methoxy-compounds (9) and (11). One of them can be isolated as a stable, crystalline solid. The other undergoes rearrangement too quickly for it to be isolated; we had to study its chemistry by using the 1 : 1 mixture. We have assigned the 5-phenyl structure (11) to the stable isomer and the 3-phenyl structure (9) to the unstable one on the basis of their rearrangement reactions. The stable isomer undergoes little or no rearrangement at room temperature in carbon tetrachloride solution, but under these conditions the unstable 3-phenyl component (9) of the 1 : 1 mixture of *N*-methoxy-*N'*-oxides rearranges completely in three days, as indicated by n.m.r. spectroscopy. The single isolable product has the structure (10) as indicated by its n.m.r. spectrum (Table), strong i.r. absorption at 1500 cm^{-1} ($\nu N{=}\overset{+}{N}{-}\bar{O}$)[2], u.v. spectrum (see Experimental section) indicative of the C=C–N(O)=N partial structure, and mass spectrum (see Experimental section). [The mass spectrum shows a feature unusual for an aliphatic ether of the one-step loss of a mass 30 fragment (218 — 188, metastable at 162); we have tentatively assigned this to a loss of C_2H_6 from the Me–C–OMe portion of the molecule, but loss of CH_2O or even NO are other possibilities and we are investigating it further.] The rearrangement is entirely analogous to that of the trimethyl compound (2) ⟶ (3) and can be rationalised by the same Scheme (R = Ph).

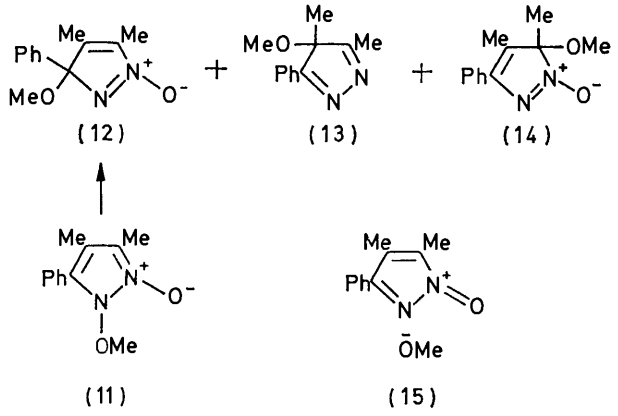


(8)



(9) (10)

The rearrangement of the 5-phenyl isomer (11) is more complex. In carbon tetrachloride solution at 30° or in acrylonitrile at room temperature a slow rearrangement leads to a mixture of two compounds. The major product is (12), as shown by its n.m.r. spectrum in which the *C*-methyl signals show homoallylic coupling, formed *via* a 1,2-shift analogous to the reactions (2) ⟶ (3) and (9) ⟶ (10). We suppose that it is formed so much more slowly because the conjugation between the benzene ring and the pyrazole π-system is disrupted during this rearrangement. The minor product is apparently either (13) or (14) formed by a 1,3-shift of the methoxy-group. At first we visualised an intermolecular mechanism *via* an intermediate such as (15), and in an attempt to intercept the methoxide ion we carried out the rearrangement of the mixed *N*-oxides (9) and (11) in ethanol. As before the 3-phenyl isomer (9) rearranged smoothly to (10), but only 20% of the 5-phenyl isomer (11) had rearranged in three months. N.m.r. spectroscopy indicated that the same two products were forming as were produced in carbon tetrachloride, and there was no evidence of the incorporation of ethoxyl, but when the reaction mixture was warmed to 45° a



(12) (13) (14)

(11) (15)

third *O*-methyl signal appeared. Rearrangement of (11) was complete in six days at this temperature. N.m.r.

[4] C. L. Stevens, B. T. Gillis, J. T. French, and T. H. Haskell, *J. Amer. Chem. Soc.*, 1958, **80**, 6088.

[5] S. Winstein, E. Alfred, R. Heck, and R. Glick, *Tetrahedron*, 1958, **3**, 1.

[6] J. I. G. Cadogan and S. Kulik, *Chem. Comm.*, 1970, 792.

analysis of the signals of the *O*-methyl groups in the δ 3·0 to 3·5 region indicated that the three products were formed in the ratios 60 : 25 : 15. The major product again is (12). We presume that the minor products are (13) and (14), but we cannot at present distinguish them, nor have we been able to separate the components of the mixture.

At present we cannot offer any evidence about the mechanisms of the 1,3-shifts of the methoxy-group in the rearrangements (11) ⟶ (13) + (14). Ionisation with intermolecular transfer of methoxide ion seems unlikely because of the lack of incorporation of ethoxyl; successive 1,2-shifts is another possibility. We are continuing investigations and initiating a study of the kinetics of the rearrangements.

EXPERIMENTAL

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, u.v. spectra on a Unicam SP 800 spectrophotometer, n.m.r. spectra (Table) on Perkin-Elmer R10 and R12 spectrometers, mass spectra on Hitachi RMU-6 or A.E.I. MS902 spectrometers.

Rearrangement of 1-*Methoxy*-3,4,5-*trimethylpyrazole* 2-*Oxide* (2).—The *N*-methoxy-*N'*-oxide [1] (0·3 g) was dissolved in carbon tetrachloride (30 ml) and stirred at room temperature for 10 days. The solvent was removed under reduced pressure while the temperature was kept below 30°, to give an orange oil (0·3 g, 100%) which slowly crystallised. Vacuum sublimation (60°/0·1 mm) gave 3-*methoxy*-3,4,5-*trimethyl*-2H-*pyrazole* 1-*oxide* (3) as colourless needles (0·1 g, 33%), m.p. 78—79° (Found: C, 53·5; H, 7·4; N, 17·6. $C_7H_{12}N_2O_2$ requires C, 53·8; H, 7·7; N, 17·9%); *m/e* 156 (*M*), 141 (*M* — Me), 125 (*M* — OMe), 110 (*M* — Me — OMe), 109 (*M* — O — OMe), and 95 (*M* — 2Me — OMe).

2-*Hydroxy*-1,5(*or* 3)-*dimethoxy*-3,4,5-*trimethyl*-3-*pyrazoline* (6) or (7).—A solution of sodium methoxide (2·4 g) in dry AnalaR methanol (50 ml) was added dropwise during 30 min to a stirred ice-cooled solution of the *N*-methoxy-*N'*-oxide (2) [1] (5·5 g) in dry AnalaR methanol (50 ml). The red solution was stirred for 16 h, by which time it had turned yellow. The solvent was removed under reduced pressure to give a yellow oil (7·15 g) which was dissolved in in 2N-sodium hydroxide solution (10 ml) and acidified (pH 1) with 10% hydrochloric acid. The resulting white emulsion was extracted into methylene chloride (3 × 40 ml) and the extract was dried ($MgSO_4$); the solvent was evaporated under reduced pressure to give a brown oil. Distillation gave a colourless oil (1·8 g, 40%) with b.p. 112—118°/0·8 mmHg, which slowly solidified. Vacuum sublimation (70°/0·25 mmHg) gave the *pyrazoline* as colourless needles with m.p. 83—84° (Found: C, 51·6; H, 8·6; N, 14·9. $C_8H_{16}N_2O_3$ requires C, 51·2; H, 8·5; N, 14·9%); $\nu_{max.}$ (Nujol) 3500—3060 (OH), 1630 (C=C), and 1440 cm^{-1} ($N-\overset{+}{N}-\overset{-}{O}$); $\lambda_{max.}$ (ethanol) 206 nm (log ε 3·81); *m/e* 171 (*M* — OH), 157 (*M* — OMe), and 139 (*M* — OH — OMe).

1-*Methoxy*-3,4-*dimethyl*-5-*phenylpyrazole* 2-*Oxide* (11).—An excess of diazomethane in ether was added dropwise to a stirred, ice-cooled suspension of the *N*-hydroxy-*N'*-oxide (8) [2] (10 g) in methylene chloride (150 ml). As the reaction proceeded the solid dissolved to give a yellow solution which was stirred for a further 1 h and then evaporated under reduced pressure to give a brown oil (10·6 g, 100%). N.m.r. analysis indicated that this was a 1 : 1 mixture of the *N*-methoxy-*N'*-oxides (9) and (11). The oil was dissolved in carbon tetrachloride (50 ml) and kept at −30° for 16 h. The *pyrazole oxide* (11) crystallised as yellow needles (1·55 g, 30%) with m.p. 92—93° (Found: C, 66·55; H, 6·5; N, 12·6. $C_{12}H_{14}N_2O_2$ requires C, 66·2; H, 6·4; N, 12·8%); $\nu_{max.}$ (Nujol) 3070 (arom. CH), 1520 ($N=\overset{+}{N}-\overset{-}{O}$), 1450 ($\overset{+}{N}-\overset{-}{O}$), 780 and 710 cm^{-1} (C_6H_5); $\lambda_{max.}$ (methanol) 229 (log ε 4·08) and 300 nm (3·99); *m/e* 218 (*M*), 202 (*M* — O), 187 (*M* — O — Me), and 171 (*M* — O — OMe).

3-*Methoxy*-3,4-*dimethyl*-5-*phenyl*-3H-*pyrazole* 1-*Oxide* (10).—The mixed *N*-methoxy-*N'*-oxides (9) and (11) (10·0 g) were dissolved in carbon tetrachloride (100 ml) and stirred at room temperature, the reaction being monitored by n.m.r. spectroscopy. After 3 days the solution was reduced to one quarter of its bulk and passed through a column of silica gel; benzene–ethyl acetate 7 : 3 was used as eluant. The eluate was concentrated under reduced pressure to give a brown oil [5·0 g, 100% based on (9)] which slowly crystallised as yellow needles. Trituration with, and recrystallisation from, ethanol gave the *pyrazole oxide* (10) as off white needles (0·75 g, 15%) with m.p. 103—104° (Found: C, 65·8; H, 6·9; N, 12·8. $C_{12}H_{14}N_2O_2$ requires C, 66·2; H, 6·4; N, 12·8%); $\lambda_{max.}$ (MeOH) 228 (log ε 4·15), 255 (3·62), and 285 nm (3·38); *m/e* 218 (*M*), 203 (*M* — Me), 188 (*M* — C_2H_6, metastable at 162), 173 (*M* — Me — C_2H_6), and 129 (*M* — Me — C_2H_6 — N_2O).

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