Azole *N*-Oxides. Part IV. Deoxygenation and Side-chain Substitution Reactions of Some 1-Methoxypyrazole 2-Oxides [1]

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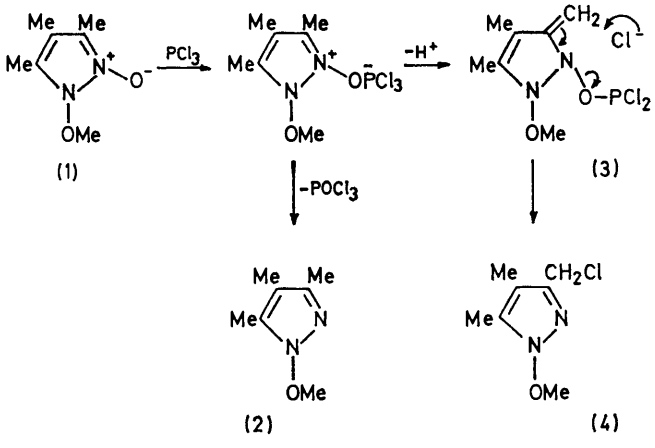
1-Methoxypyrazole 2-oxides undergo the normal acyloxy migration reaction of *N*-oxides with acetic anhydride to give 3- and 5-acetoxymethylpyrazoles. With phosphorus trichloride and with benzoyl chloride abnormal reactions were observed, leading to 3-chloromethylpyrazoles, in some cases accompanied by simple deoxygenation of the *N*-oxide.

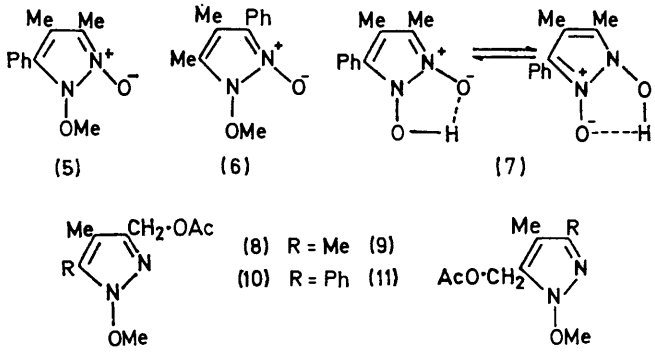
THE previous paper [1] described how we sought to prepare 1-methoxy-3,4,5-trimethylpyrazole (2) by the deoxygenation of its 2-oxide (1). Attempted reduction of (1) with triethyl phosphite proved inconclusive, but with phosphorus trichloride in chloroform [2] we obtained [3] not only the required deoxygenation product (2), but also 3-chloromethyl-1-methoxy-4,5-dimethylpyrazole (4), the product of simultaneous deoxygenation and side-chain chlorination. There appears to be no analogy for this reaction; the usual reagents for side-chain chlorination of *N*-oxides are arenesulphonyl chlorides [4] or phosphoryl chloride.[5] Certainly a possible explanation of our present observations is that phosphoryl chloride produced during the deoxygenation reaction then acts as the chlorinating reagent, but if this is so then why does the same thing not happen with, for example, 2-picoline 1-oxides which are simply deoxygenated.[6] A possible mechanism is illustrated in Scheme 1. Alternatively an intramolecular transfer of chlorine from the phosphorus atom to the 3-position methylene group is possible if anhydrobase formation is faster than cleavage of the phosphorus–chlorine bond, and this would account for the



SCHEME 1

absence of the isomeric 5-chloromethyl product; however, anhydrobase formation has been shown to be the slow step in acyloxy migration reactions with picoline *N*-oxide [7] and consequently the intermolecular path seems more likely.

Because this reaction seemed unusual we have looked at the behaviour of two other reagents which commonly lead to deoxygenation and side-chain substitution in heteroaromatic *N*-oxides, namely acetic anhydride and benzoyl chloride. We have studied their reactions with 1-methoxy-3,4,5-trimethylpyrazole 2-oxide (1), and with the two isomeric compounds 1-methoxy-3,4-dimethyl-5-phenylpyrazole 2-oxide (5) and 1-methoxy-4,5-dimethyl-3-phenylpyrazole 2-oxide (6) which are obtained [1] as a 1 : 1 mixture by the action of diazomethane on the tautomeric 1-hydroxy-3(5),4-dimethyl-5(3)-phenylpyrazole 2-oxide (7). The 5-phenyl compound (5) is sufficiently stable to be isolated and purified, but its 3-phenyl isomer (6) spontaneously rearranges too quickly.[1] The reactions of the latter compound were therefore studied by using the 1 : 1 mixture of (5) and (6).



In the reactions with acetic anhydride the *N*-methoxy-*N'*-oxides all behaved unexceptionally. The trimethyl compound (1) gave a 60 : 40 mixture of the 3- and 5-acetoxymethyl derivatives (8) and (9), as shown by n.m.r. spectra of the crude reaction product. This reaction is analogous to the reactions of 2- and 4-picoline and 2,4-lutidine 1-oxides, in which migration of the acetoxy-group to the α-position probably involves an ion-pair mechanism [8] whereas migration to the γ-position may involve ion and radical pairs.[9] The

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[2] M. Hamana, *J. Pharm. Soc. Japan*, 1955, **75**, 121.
[3] Part II, F. T. Boyle and R. A. Y. Jones, *J.C.S. Perkin II*, in the press.
[4] H. Tanida, *J. Pharm. Soc. Japan*, 1958, **78**, 611.
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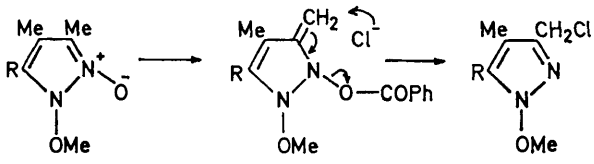
[7] V. J. Traynelis and P. L. Pacini, *J. Amer. Chem. Soc.*, 1964, **86**, 4917
[8] R. Bodalski and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1968, 831.
[9] H. Iwamura, M. Iwamura, T. Nishida, and S. Sato, *J. Amer. Chem. Soc.*, 1970, **92**, 7474.

two esters (8) and (9) proved to be inseparable and were also contaminated with the product of thermal rearrangement of the starting material [1] so that accurate elemental analyses could not be obtained. The molecular formula was confirmed by precise mass measurement of the parent peak (*m/e* 198) in the mass spectrum.

The 5-phenyl-*N*-methoxy-*N'*-oxide (5) reacted with acetic anhydride to give the 3-acetoxymethyl compound (10), which was again contaminated with products of the thermal rearrangement of starting material.[1] Since the ester (10) co-distilled with one of these, and since they also moved together both on t.l.c. plates and in preparative g.l.c., it proved impossible to obtain the ester better than 90% pure, but again its molecular formula could be confirmed by precise mass measurement. The mixture of 3- and 5-phenyl-*N*-methoxy-*N'*-oxides (5) and (6) similarly reacted to give a mixture of the 5- and 3-acetoxymethyl compounds (10) and (11) respectively; again they could not be purified, but their structures are confirmed by their n.m.r. and mass spectra.

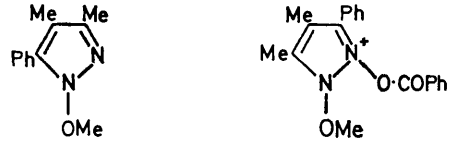
The reaction of benzoyl chloride with heteroaromatic *N*-oxides usually leads to the introduction of the benzoyloxy-group into the side-chain,[10,11] though Vozza has reported side-chain chlorination as a minor side reaction.[10] By contrast, in the reaction of the 1-methoxypyrazole 2-oxides with benzoyl chloride it is side-chain chlorination which is the main reaction. The trimethyl compound (1) gives the same chloromethyl compound (4) as was obtained in the phosphorus trichloride reaction; this is the sole product, as shown by n.m.r. analysis of the crude reaction mixture. The 5-phenyl-*N*-methoxy-*N'*-oxide (5) gave a mixture of two compounds: the 3-chloromethyl derivative (13) and, very surprisingly, the simple deoxygenation product (14); indeed, on one occasion this was the only product isolated. Deoxygenation of *N*-oxides in the absence of reducing agents, however, is not completely unknown.[12] It is not clear what process is causing the deoxygenation here, but one possibility is homolytic cleavage of the N–OCOPh bond either on the alumina during chromatography or during distillation, when a considerable quantity of polymeric material was produced. When the mixed *N*-methoxy-*N'*-oxides (5) and (6) were treated with benzoyl chloride the only isolable products were the same two compounds (13) and (14) as were obtained from the reaction of (5) alone. No product attributable to the 3-phenyl starting material (6) was detected; extensive polymerisation which occurred during work-up probably indicates the ultimate fate of the quaternary intermediate (15). We suggest that these chlorination reactions proceed as indicated in Scheme 2; the cleavage of the carbon–chlorine bond to give the anhydrobase (12) probably occurs, as in the reaction with phosphorus trichloride [*cf.* (3)], before the cleavage of the nitrogen–oxygen bond, and this accounts for the absence of any of the expected benzoyloxymethyl product (16).



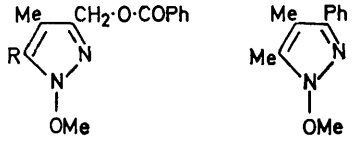
(12) R = Me, Ph (4) R = Me (13) R = Ph

SCHEME 2

This Scheme also rationalises the observation that only one of the isomeric *N*-methoxy-*N'*-oxides (5) and (6) gives a chloromethyl derivative with benzoyl chloride



(14) (15)



(16) R = Me, Ph (17)

—the isomer with a phenyl substituent vicinal to the *N*-oxide function cannot react this way—and thus confirms the assignment of structures (5) and (6) which we made [1] on the basis of their thermal rearrangement reactions.

Freeman and Gannon [13] obtained an *N*-methoxypyrazole by methylating the corresponding *N*-hydroxy-compound. They formulated it as 1-methoxy-4,5-dimethyl-3-phenylpyrazole (17) but said that their evidence in favour of this structure rather than the 5-phenyl isomer (14) was not strong. The physical and spectroscopic properties of their compound are closely similar to those we find for compound (14); of course, it would not be surprising for the two isomers to have similar properties, but it is possible that Freeman's original assignment [13] was wrong.

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, n.m.r. spectra on Perkin-Elmer R10 or R12 spectrometers, and mass spectra on Hitachi RMU-6 or A.E.I MS902 spectrometers.

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[11] I. J. Pachler, *J. Amer. Chem. Soc.*, 1953, 3026; E. Hayashi and T. Higashino, *Chem. Pharm. Bull.*, 1964, **12**, 43.
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Reaction of 1-*Methoxy*-3,4,5-*trimethylpyrazole* 2-*Oxide* (2) *with Phosphorus Trichloride.*—This reaction is described in ref. 3.

Reaction of 1-*Methoxy*-3,4,5-*trimethylpyrazole* 2-*Oxide* (1) *with Acetic Anhydride.*—Acetic anhydride (1·3 g) in methylene chloride (10 ml) was added dropwise during 10 min to an ice-cooled solution of the *N*-oxide [1] (2·0 g) in methylene chloride (29 ml) and kept overnight . The resulting yellow solution was extracted with 2N-sodium hydroxide solution (3 × 30 ml) and water (50 ml) and then dried ($MgSO_4$). The dried extract was evaporated under reduced pressure to leave a yellow oil (1·9 g, 75%) which was distilled to give a 1 : 1 mixture of 3-*acetoxymethyl*-1-*methoxy*-4,5-*dimethylpyrazole* (8) and 5-*acetoxymethyl*-1-*methoxy*-3,4-*dimethylpyrazole* (9) (0·7 g, 30%) with b.p. 88—90°/0·9 mmHg, $\nu_{max.}$ (liquid film) 2870 (methoxyl CH) and 1743 cm^{-1} (C=O); δ (CCl_4) 4·88 and 4·73 (CH_2), 3·94 and 3·91 (OMe), 2·17, 2·09, 2·03, 1·97, 1·92, and 1·92 (3-, 4-, and 5-Me, and Ac); *m/e* 198 (*M*, accurate for $C_9H_{14}N_2O_3$ within 6 p.p.m.), 167 (*M* — OMe), 155 (*M* — AcO), and 108 (*M* — OMe — AcO).

Reaction of 1-*Methoxy*-3,4-*dimethyl*-5-*phenylpyrazole* 2-*Oxide* (5) *with Acetic Anhydride.*—This reaction was carried out as above, using acetic anhydride (0·9 g) and the *N*-oxide [1] (1·0 g), except that the reaction mixture was set aside for 2 days. N.m.r. analysis of the crude product indicated that it contained 70% of 3-acetoxymethyl-1-methoxy-4-methyl-5-phenylpyrazole (10), 10% of unchanged starting material, and 20% of the products of thermal rearrangement [1] of the starting material. Distillation gave the *ester* in 90% purity, b.p. 150°/0·25 mm. $\nu_{max.}$ (liquid film) 3065 (arom. CH), 2865 (methoxyl CH), 1740 (C=O), 765 and 700 cm^{-1} (C_6H_5–); δ (CCl_4) 7·2—7·8 (m, 5H, Ph), 4·89 (s, 2H, CH_2O), 3·90 (s, 3H, OMe), 2·26 (s, 3H, 4-Me), and 2·01 (s, 3H, Ac); *m/e* 260 (*M*), 201 (*M* — AcO), and 187 (*M* — CH_2OAc). The 10% impurity was 5-methoxy-3,4-dimethyl-5-phenylpyrazole.[1]

Reaction of the Mixed N-*Oxides* (5 *and* 6) [1] *with Acetic Anhydride.*—The reaction was carried out as above. The main fraction (40%), b.p. 155—160°/25 mmHg, was 5-*acetoxymethyl*-1-*methoxy*-4-*methyl*-3-*phenylpyrazole* (11) in 80% purity; $\nu_{max.}$ (liquid film) 3030 (arom. CH), 2870 (methoxyl CH), 1743 (C=O), 772 and 699 cm^{-1} (C_6H_5–); δ (CCl_4) 7·2—7·8 (m, 5H, Ph), 5·10 (s, 2H, CH_2O), 4·15 (3H, s, OMe), 2·21 (3H, s, 4-Me), and 2·01 (s, 3H, Ac); *m/e* 260 (*M*, accurate for $C_{14}H_{16}N_2O_3$ within 10 p.p.m.), 245 (*M* — Me), 201 (*M* — AcO), and 187 (*M* — CH_2OAc). The minor fraction (20%) was the isomeric ester (10). The major impurity in both fractions was 3-methoxy-3,4-dimethyl-5-phenylpyrazole.[1]

Reaction of 1-*Methoxy*-3,4,5-*trimethylpyrazole* 2-*Oxide* (1) *with Benzoyl Chloride.*—Benzoyl chloride (2·8 g) in methylene chloride (100 ml) was added dropwise during 15 min to a stirred ice-cooled solution of the *N*-oxide [1] (3·1 g) in methylene chloride (50 ml). The resulting yellow solution was stirred for 1 h and then washed with water (50 ml), 2N-sodium hydroxide solution (3 × 50 ml), and water (50 ml); it was then dried ($MgSO_4$). The dried extract was evaporated under reduced pressure to give a brown oil (3·45 g, 100%) which was distilled to give 3-chloromethyl-1-methoxy-4,5-dimethylpyrazole [3] (4) (1·8 g, 52%) as a colourless oil, b.p. 100—106°/15 mmHg.

Reaction of 1-*Methoxy*-3,4-*dimethyl*-5-*phenylpyrazole* 2-*Oxide* (5) *with Benzoyl Chloride.*—(*a*) Benzoyl chloride (1·3 g) in methylene chloride (30 ml) was added dropwise to a stirred ice-cooled solution of the *N*-oxide [1] (1·5 g) in methylene chloride (20 ml) during 5 min. The solution was stirred for 16 h and then passed through a silica-gel column using benzene as eluant. The forerunnings contained benzoyl chloride and were rejected. The eluant was changed to ethyl acetate which gave a yellow fraction; this was concentrated to an oily solid, which proved to be impure benzoic acid. The oil was redissolved in methylene chloride (30 ml), washed with 2N hydrochloric acid (3 × 20 ml), dried ($MgSO_4$), concentrated, and distilled. Considerable decomposition occurred during distillation and the resulting oil still contained benzoic acid. It was again dissolved in methylene chloride (20 ml), and the solution was washed with 2N-sodium hydroxide solution (3 × 12 ml), dried ($MgSO_4$), concentrated, and distilled to give 1-*methoxy*-3,4-*dimethyl*-5-*phenylpyrazole* (14) as a colourless oil (0·11 g, 8%) with b.p. 114—117°/0·35 mmHg; δ (CCl_4) 7·46 (m, 5H, Ph), 3·83 (s, 3H, OMe), 2·18 (s, 3H, 3-Me), and 1·99 (s, 3H, 4-Me); *m/e* 202 (*M*) and 171 (*M* — OMe).

(*b*) The reaction was repeated under the same conditions except that, after being stirred for 16 h, the reaction mixture was washed with 2N-sodium hydroxide solution (3 × 10 ml) and dried ($MgSO_4$). Chromatography (neutral alumina, benzene–ethyl acetate 70 : 30) gave a yellow solution which was concentrated under reduced pressure. N.m.r. spectroscopy showed the resulting oil to be a mixture of the pyrazole (14) and the chloromethyl-pyrazole (13), characterised below, which could not be separated. T.l.c. indicated that no other compounds were present.

Reaction of the Mixed N-*Oxides* (5 *and* 6) *with Benzoyl Chloride.*—Benzoyl chloride (6·7 ml) was added dropwise during 15 min to a stirred ice-cooled solution of a 1 : 1 mixture of the *N*-oxides [1] in methylene chloride (100 ml). The resulting green solution was stirred for a further 1 h, and was then washed with 2N-sodium hydroxide solution (3 × 80 ml), dried ($MgSO_4$), and concentrated. The resulting yellow oil was distilled under reduced pressure; during the distillation extensive polymerisation took place. The major fraction contained the pyrazoles (13) and (14) and benzoic acid. Chromatography (neutral alumina, benzene–ethyl acetate 70 : 30) followed by vacuum distillation gave 3-*chloromethyl*-1-*methoxy*-4-*methyl*-5-*phenylpyrazole* (13) as a colourless oil (1·7 g, 29%) with b.p. 126°/0·3 mmHg (Found: N, 11·3. $C_{12}H_{13}ClN_2O$ requires N, 11·8%); δ (CCl_4) 7·1—7·7 (m, 5H, Ph), 4·50 (s, 2H, CH_2Cl), 4·08 (s, 3H, MeO), and 2·10 (s, 3H, 4-Me); *m/e* 236 + 238 (*M*, accurate for $C_{12}H_{13}ClN_2O$ within 3 p.p.m.) and 201 (*M* — Cl).

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