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PERMANGANATE OXIDATION OF 3-METHYL-4-NITRO-5-STYRILISOXAZOLE: A CORRECTION

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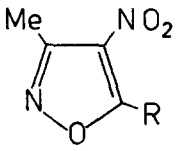
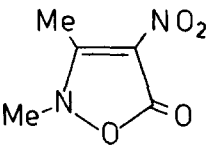
Summary: *In contrast with a previous report,permanganate oxidation of the title compound 3 gives the nitroisoxazolone 8 and not 3-methyl-4-nitroisoxazole-5-carboxylic acid 2 ; a reaction pathway, involving the spirocyclisation of the carboxylate 10, is suggested.*

In connection with our researches on new spirocyclisation reactions in the heterocyclic series[1], we became interested in the synthesis of the hitherto unknown methyl 3-methyl-4-nitroisoxazole-5-carboxylate 1. Quilico and Musante[2] first investigated the possibility of obtaining the corresponding acid 2 by oxidation of the easily available isoxazole derivative 3, but their attempts were unsuccessful. Twenty years later, Kochetkov and co-workers[3] claimed that the acid 2, mp 123°C (with frothing), could be prepared in 67% yield by treat-

ment of the same starting material with potassium permanganate in acetone in the presence of carbon dioxide.



1 R = CO_2Me
2 R = CO_2H
3 R = CH:CHPh
4 R = OMe



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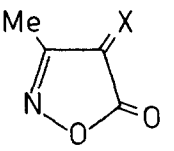
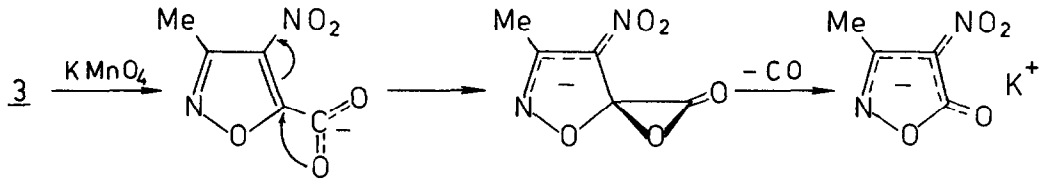


6, 7 X = NO_2Me
8 X = NO_2H
9 X = NOH

This method gave also in our hands[4], although in lower yield (ca.50%), an ivory coloured solid, mp 123-124°C dec. from anhydrous ethanol; however, to our great surprise, when it was allowed to react with ethereal diazomethane we did not obtain the expected ester 1. In fact, the reaction afforded a mixture containing (^{1}H NMR spectrum) 3-methyl-4-nitro-5-methoxyisoxazole 4, mp 89-90°C, as the main product (62%), together with minor amounts of two isomeric nitronic esters 6, mp 137-138°C, and 7, mp 66-67°C (12%), and the N-methyl derivative 5, mp 141-142°C (26%); these compounds were separated, in order of decreasing mobility, by careful column chromatography [silica gel 60 (Merck; 70-230 mesh), n-hexane - ethyl acetate 2:1 v/v], followed by preparative t.l.c. [silica gel plates (Merck F_{254}), n-hexane - ethyl acetate 1:1 v/v], and identified by spectral evidence[5].

These results, as well as a re-examination of the analytical (Calcd. for $C_4H_4N_2O_4$: C,33.34; H,2.80; N,19.44. Found: C,33.20; H,2.75; N,19.65%) and spectroscopic properties[5] of the oxidation product, led us to establish that it was not the acid 2, but 3-methyl-4-nitroisoxazolin-5-one 8; this conclusion was confirmed by comparison (mp and IR spectrum) with an authentic sample obtained from the corresponding 4-hydroxyimino derivative 9[6].

The formation of compound 8 could be rationalized on the basis of an intramolecular nucleophilic attack at the 5-position of the isoxazole ring by the oxygen of the carboxylate group of 10 leading to the spiro-α-lactone 11, followed by decarbonilation of the latter intermediate to give the salt 12.



This mechanism, highly favoured by the presence of a strongly electron-withdrawing NO_2 group at position 4, closely resembles that reported for the electrophilic bromination of sodium 3-phenylisoxazole-5-carboxylate[7], and is in accord with our recent results on the spirocyclisation reactions of some isoxazole derivatives[1c,8].

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3. N.K.Kochetkov,S.D.Sokolov,and V.M.Luboshnikova, Zh.Obshch.Khim.,32, 1778 (1962)[Chem.Abs. 3409d (1963)].

4. The work-up of the reaction products was less straightforward than that reported by the Russian authors; after removal of benzoic acid by extraction with ethyl ether at pH 1-2, compound 12, mp 262-263°C dec., was converted into the corresponding silver salt which was then treated with concentrated hydrochloric acid to give the very strong acid nitroderivative 8.

5. Spectral data of compounds 4-8 and 12 :

4 IR (KBr) 1630,1500,1460,1390,1320,1173,1108,930,820,and 765 cm^{-1};
^1H NMR ($CDCl_3$) δ 2.53 (s, 3H, 3-Me) and 4.36 (s, 3H, OMe).

5 IR (KBr) 1775,1590,1525,1470,1390,1275,1215,and 770 cm^{-1};
^1H NMR ($CDCl_3$) δ 2.72 (s, 3H, 3-Me) and 3.73 (s, 3H, NMe).

6 IR (KBr) 1770,1595,1570,1460,1065,1010,872,745,740,700,and 565 cm^{-1};
^1H NMR [$(CD_3)_2CO$] δ 2.33 (s, 3H, 3-Me) and 4.10 (s, 3H, NO_2Me).

7 IR (KBr) 1778,1590,1545,1438,1377,1360,1142,1010,980,865,752,687,and 573 cm^{-1};
^1H NMR [$(CD_3)_2CO$] δ 2.46 (s, 3H, 3-Me) and 4.12 (s, 3H, NO_2Me).

8 IR (KBr) 3300-2200(very broad),1775,1720,1568,1495,1380,1365,1250,1008,820, 752,690,and 585 cm^{-1};
^1H NMR (DMSO-d_6 + D_2O) δ 2.40 (s, 3H,3-Me);
^{13}C NMR (DMSO-d_6) δ 15.2 (q, 3-Me), 109.4 (s, C-4), 158.3 (s, C-3),and 167.4 (s, C-5).

12 IR (KBr) 1718,1690,1470,1440,1382,1260,1110,1065,770,and 590 cm^{-1}.

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