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An Improved Oxidation Method of Pyridoxine

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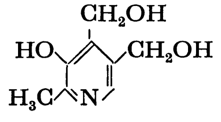
Synopsis. Manganese dioxide oxidation in the presence of primary amine was found to be an efficient oxidation system for pyridoxine.

Prevalent method to synthesize pyridoxal and its congeners from the corresponding pyridoxines has been carried out by use of "active" manganese dioxide as an effective oxidant in aqueous solution of restricted pH ranges or in chloroform.[1] The efficiency of the oxidation method seems to depend on activity of manganese dioxide, which is reported to be dependent on the preparation method,[2] and on solvent choice and reaction temperature which are proved to affect product yield as much as or more than the activity of manganese dioxide.[2,3]

In connection with our study directed toward devised molecular construction from pyridoxine to pyridinophanes with pyridoxal-like activity,[4] it was inevitably required to develop a new oxidation system by use of manganese dioxide.[5] With those above in mind and through several attempts employing pyridoxine (**1**) as a substrate model, we eventually found a new oxidation system by use of manganese dioxide[7] in the presence of amine. The present method has been successfully applied to pyridinophane congeners without exception or reduction in yield.[4]



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The fundamental reaction system consisted of **1**, manganese dioxide,[7] and an amine in the molar ratio of 1:10:2 in benzene. Pyridine was added to dissolve **1**. The mixture was heated under reflux with azeotropic removal of the resulting water. The resulting imine was subjected to transimination for isolation (path A). For the purpose of comparison of amine effect on the reaction, path C was examined as well.

$$\mathbf{1} \xrightarrow[\text{R}'\text{-NH}_2]{\text{MnO}_2} \underset{\mathbf{2}}{\text{R-CH=N-R}'} \xrightarrow{\text{R}''\text{-NH}_2} \underset{\mathbf{3}}{\text{R-CH=N-R}''} \quad \text{(path A)}$$

$$\mathbf{1} \xrightarrow[\text{R}''\text{-NH}_2]{\text{MnO}_2} \underset{\mathbf{3}}{\text{R-CH=N-R}''} \quad \text{(path B)}$$

$$\mathbf{1} \xrightarrow{\text{MnO}_2} \underset{\mathbf{4}}{\text{R-CHO}} \xrightarrow{\text{R}''\text{-NH}_2} \underset{\mathbf{3}}{\text{R-CH=N-R}''} \quad \text{(path C)}$$

$R' = \text{-CH}_2\text{CH}_2\text{NH}_2$, $\text{-CH}_3\cdot\text{HCl}$, or $\text{-CH}_2\text{CH}_2\text{CH}_2\text{N(CH}_3)_2$

$R'' = \text{-C}_6\text{H}_4\text{-}p\text{-OC}_2\text{H}_5\cdot\text{HCl}$

The results obtained are listed in Table 1. Each primary amine has a positive effect on the oxidation. Especially, 3-(dimethylamino)propylamine was the most effective of amines used.

Although we have no substantial evidence for the bimolecular oxidation mechanism,[9] the primary amino group might participate in the oxidation process by forming a transient manganese dioxide complex. The previous work on the oxidation of *β*-amino alcohols[10] could be mechanistically related to the present work.

The present method will provide "an oxidant substitute" for "active" manganese dioxide and, thus, seems to be a useful tool for the synthesis of unstable aldehydes, protected directly by coexisting primary amine to form a relatively stable Schiff base during oxidation.

Experimental

The melting point is uncorrected. The IR spectra were recorded on a Shimadzu IR-27 instrument. The UV spectra were measured with Hitachi 124 spectrophotometer. The ^{1}H-NMR spectra were recorded on a Varian HA-100D apparatus, with TMS as the internal standard and the chemical shift and coupling constant were represented by δ and Hz, respectively. Merck silica gel 60 (Art. 7734, 0.063—0.20 mm) was used for the column chromatography and Wakogel B-5 FM (Wako Pure Chem. Co., Ltd.) for analytical thin layer chromatography. The elemental analyses were performed by this Institute. All the reagents used were commercially available and employed without further purification.

Oxidation Method. The mixture consisting of **1**, manganese dioxide,[7] and an amine in the molar ratio of 1:10:2 in benzene (150 ml/g of **1**) was heated under reflux for the mentioned time with azeotropic removal of the resulting

Table 1. Manganese dioxide oxidation of pyridoxine accompanied by Schiff base formation

Reaction path	Initial amine	Reaction time/min	Amine used for isolatn	Treated time/min	Product	Yield[a]/%
C	—	120	EAN[b]	10	**3**	14
C	TEA[c]	120	EAN	10	**3**	26
B	EAN	130	—	—	**3**	57
A	EDA[d]	60	EAN	15	**3**	57
A	MA[e]	30	EAN	10	**3**	59
A	DAPA[f]	50	EAN	10	**3**	75

a) Isolated yield. b) *p*-Ethoxyaniline hydrochloride. c) Triethylamine. d) Ethylenediamine. e) Methylamine hydrochloride. f) 3-(Dimethylamino)propylamine.

water by the Dean-Stark apparatus until no more water came out. Pyridine was mixed to dissolve **1** up to fifty volume percent of benzene. The reaction mixture was then filtered, while hot, through celite (No. 545) to remove excess amount of manganese dioxide and the resulting manganese oxide, washed several times with hot pyridine. The combined filtrate was treated, after removal of the solvents under reduced pressure, with one of the following ways.

For transimination[8] (path A), the residue was dissolved into small amount of benzene–ethyl acetate (1:1 v/v), and equal weight of *p*-ethoxyaniline hydrochloride to the amine initially used was mixed, followed by addition of equal volume of water to the organic layer. By magnetic stirring, immediately, the brown solution resulted in orange-red precipitate which was recrystallized from methanol after collection by filtration. Spectral data supported that the orange red crystals are 4-(*p*-ethoxyphenyliminomethyl)-5-hydroxy-6-methylpyridine-3-methanol (**3**); mp 211—212.5 °C (decomp), needles. Found: C, 66.62; H, 6.35, N, 9.66%. Calcd for $C_{16}H_{20}O_3N_2$: C, 66.64; H, 6.99; N, 9.72%. UV (EtOH): λ_{max} (ε) 210 (19200), 224 (sh, 17700), 253 (sh, 8400), 297 (sh, 7100), 305 (sh, 7500), 350 (14700), 366 (15000), and 384 (sh, 11800) nm. UV (EtOH–0.1 M NaOH): λ_{max} (ε) 239 (18800), 310 (7000), and 410 (3400) nm. ^{1}H-NMR (DMSO-d_6): 1.34 (3H, t, J=7.0, OCH_2–$C\underline{H}_3$), 2.41 (3H, s, $C\underline{H}_3$ on the pyridine ring), 4.07 (2H, q, J=7.0, $OC\underline{H}_2CH_3$), 4.75 (2H, broad d, J=5.0, $C\underline{H}_2$–OH on the pyridine ring), 5.38 (1H, broad t, J=5.0, CH_2–$O\underline{H}$), 7.10 and 7.46 (2H each, d, J=9.0, protons on the benzene ring), 7.83 (1H, s, proton on the pyridine ring), 9.10 (1H, s, –$C\underline{H}$=N–), and 15.10 (1H, broad s, phenolic proton on the pyridine ring). IR (KBr disc): ν_{C-O-C} 1250; $\nu_{C=N}$ 1615; ν_s 1500, 1406, 1385, 1298, 1020, and 818; ν_m 1582, 1475, 1310, 1265, 1198, 1163, 1118, 1019, 860, 789, 572, and 535 cm^{-1}.

For direct isolation of **3** (path B), the residue was triturated with benzene. The precipitate was collected by filtration and recrystallized from methanol.

For (indirect) Schiff base (**3**) formation (path C), the residue was dissolved into *ca.* 20 ml of benzene followed by addition of equal weight of *p*-ethoxyaniline hydrochloride to **1** and the mixture was stirred for the mentioned time. **3** was isolated by silica gel chromatography eluted with chloroform–methanol (9 : 1 v/v).

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References

1) a) D. Heyl, *J. Am. Chem. Soc.*, **70**, 3434 (1948); b) A. N. Wilson and S. A. Harris, *ibid.*, **73**, 4693 (1951); c) W. Korytnyk, S. C. Srivastava, N. Angelino, P. G. G. Potti, and B. Paul, *J. Med. Chem.*, **16**, 1096 (1973); d) R. H. Wiley and G. Irick, *J. Med. Pharm. Chem.*, **5**, 49 (1962); *Chem. Abstr.*, **57**, 12424f (1962).

2) R. M. Evans, *Q. Rev. Chem. Soc.*, **13**, 61 (1959); A. J. Fatiadi, *Synthesis*, **1976**, 65 and 133.

3) R. J. Gritter and T. J. Wallace, *J. Org. Chem.*, **24**, 1051 (1959).

4) M. Iwata, H. Kuzuhara, and S. Emoto, *Chem. Lett.*, **1976**, 983; H. Kuzuhara, M. Iwata, and S. Emoto, *J. Am. Chem. Soc.*, **99**, 4173 (1977); M. Iwata and H. Kuzuhara, *Chem. Lett.*, **1981**, 5.

5) Under the conditions described in Ref. 1a—c with active manganese dioxide newly prepared according to the method of Attenburrow *et al.*,[6] any of modified compounds with pyridoxine-like functionality afforded insufficient yield (less than 16%).

6) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jasen, and T. Walker, *J. Chem. Soc.*, **1952**, 1094.

7) Commercially available, supplied by Junsei Chem. Co., Ltd. (Tokyo).

8) The transimination occurred quantitatively; for the essence of this reaction, see E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 826 (1962).

9) O. H. Wheeler, *Chem. Ind. (London)*, **1965**, 1769.

10) L. Birkofer and L. Erlenbach, *Chem. Ber.*, **91**, 2383 (1958).