Stepwise Oxidation of the Heteroatoms in *O*-Protected Pyridoxine-Like Pyridinophane Containing Thio Groups in the Intramolecular Bridge Chain

Makoto ANDO* and Hiroyoshi KUZUHARA*
RIKEN (The Institute of Physical and Chemical Research), Wako, Saitama 351-01
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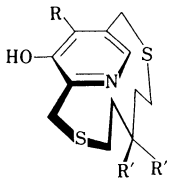
Synopsis. Racemic 14-Hydroxy-15-hydroxymethyl-*O,O'*-isopropylidene-2,8-dithia[9](2,5)pyridinophane, a model compound of our chiral pyridoxamine analogs, was oxidized under various conditions in order to examine the reactivities of the sulfur and the nitrogen atoms. Various degree of oxidized compounds, from monoxide to pentaoxide, including the desired *S,S,S',S'*-tetraoxide, were obtained.

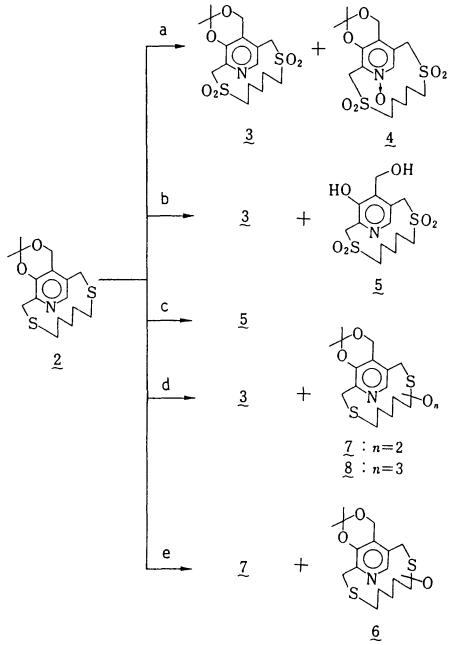
We have prepared several kinds of novel pyridinophanes with sulfur-containing intramolecular bridge chain as chiral analogs of vitamin B_6,[1,2a,3] **1a**, **1b**, and **1c**, corresponding to the *S*-enantiomers of pyridoxal, pyridoxamine, and pyridoxine analogs, respectively. Combination of **1a** or **1b** with appropriate metal ions has been successfully used for simulating the vitamin B_6-dependent enzymatic reactions with a relatively high enantioface differentiation.[1,2]



	R	R'
1a:	CHO	H or Me
1b:	CH_2NH_2	H or Me
1c:	CH_2OH	H

A consideration of the mechanism of such enzyme model reactions suggested that the bulkiness of one of the sulfur atoms in vitamin B_6 analogs might play an essential role in the asymmetric induction.[2c] The sulfonyl group is much bulkier than the corresponding thio group and has a very small tendency to chelate to metal ions. These facts suggest that a conversion of the thio group in **1a** or **1b** to the corresponding sulfonyl group might enhance their potency regarding asymmetric induction. An attempt to prepare such new vitamin B_6 analogs from **1a—c**, however, may be hampered by the fact that the oxidation of the sulfur atoms compete with that of the pyridine nitrogen atom to *N*-oxide. This paper describes the selective oxidation of those sulfides to the corresponding sulfones, employing racemic 14-hydroxy-15-hydroxymethyl-*O,O'*-isopropylidene-2,8-dithia[9](2,5)pyridinophane (**2**),[1] an *O*-protected pyridoxine analog, as a model substrate.

The oxidation of **2** with *m*-chloroperbenzoic acid (MCPBA) was studied at room temperature in various organic solvents. The employment of 5.5 mole equivalents of MCPBA to **2** in chloroform for 1 d resulted in a mixture of tetraoxide (**3**) of **2** and pentaoxide (**4**) of **2**. Unreacted MCPBA and **3** were still detectable on TLC, even if the reaction period was prolonged. With 7.5 mole equivalents of MCPBA, however, **4** was obtained in quantitative yield. In the UV spectrum of **4**, a blue shift of the absorption maxima was observed when the solvent was changed from acetonitrile to ethanol, whereas this was not observed in that of **3**. Furthermore, the ε-value of the UV absorption of **4** was somewhat larger than that of **3**. These observations elucidated the structures of **3** and **4** as 14-hydroxy-15-hydroxymethyl-*O,O'*-isopropylidene-2,8-dithia[9](2,5)-pyridinophane *S,S,S',S'*-tetraoxide and *N,S,S,S',S'*-pentaoxide, respectively[4] and showed that the oxidation of sulfur proceeded prior to that of nitrogen. However, decreasing the amount of MCPBA to 4.4—1.1 mole equivalents resulted in many products in all cases, indicating that the oxidation of sulfur proceeds without any selectivity. Although the rate of the oxidation was rather slow in dioxane, **4** was obtained in quantitative yield with 7.5 mole equivalents of MCPBA after 3 d. During these oxidation in chloroform or dioxane, we observed that **3** was once precipitated and dissolved again, giving the final product, **4**. In ethanol, **3** could be isolated in 89% yield after 1 d with **4** also obtained in 11% yield from the filtrate.



a: MCPBA/$CHCl_3$, dioxane, or ethanol, room temp.
b: catalysts[f]/aq dioxane, 60—85 °C, 3 h.
c: no catalysts/acetic acid, 60—85 °C, 3 h.
d: catalysts[f]/aq dioxane, room temp, 1 d.
e: no catalysts/aq dioxane, room temp, 3 d.
f: AcOH (1.5 wt%) + $Na_2WO_4 \cdot 2H_2O$ (0.5 wt%).

Recently, Giam et al. reported that the selective oxidation of alkyl pyridyl sulfides to the corresponding sulfones without *N*-oxide compounds proceeded in aqueous dioxane at 65—85 °C with hydrogen peroxide

and catalytic amounts of acetic acid and sodium tungustate.[5] This procedure was applied to the oxidation of **2** and found to give satisfactory results. The desired **3** (87%) and its *O,O'*-deprotected compound, 14-hydroxy-15-hydroxymethyl-2,8-dithia[9](2,5)pyridinophane *S,S,S',S'*-tetraoxide (**5**) (5%), were obtained with no *N*-oxide compounds produced. Acidic hydrolysis of **3** gave **5** which precipitated in the form of free base during the reaction. Only **5** was obtained when the oxidation was conducted in acetic acid at 60—85 °C in the absence of sodium tungustate. The hydrogen peroxide oxidation at room temperature gave monoxide (**6**), dioxide (**7**), and trioxide (**8**) of **2** depending on the reaction conditions employed (See experimental). Although **6** and **7** showed the sharp melting points, the NMR signal assignable to the proton attached to the pyridine ring in **6**, **7**, and **8**[6] appeared as 2, 4, and 2 peaks, respectively, suggesting that those compounds were the mixtures of the corresponding *S*-oxides (**6**) (assigned from IR spectrum), *S,S*- and *S,S'*-dioxides (**7**), and *S,S,S'*-trioxides (**8**) of **2**.

In conclusion, the selective oxidation of the sulfides **2** giving the corresponding sulfone derivative **3** was achieved with hydrogen peroxide-acetic acid-sodium tungustate in aqueous dioxane at 60—85 °C or with MCPBA in ethanol at room temperature.

Experimental

General. Melting points are uncorrected. IR and UV-VIS spectra were determined with a Shimadzu IR 27G and a Varian-Cary 2290 spectrometers, respectively. ^{1}H NMR spectra were recorded on a JOEL PS 100 instrument using TMS as an internal standard (100 MHz).[6] Organic extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. TLC was conducted with a precoated silica gel 60F_{254} on aluminium sheet (Merck No. 5554) with chloroform-methanol (50 : 1 or 25 : 1 v/v) as the developing solvent. Column chromatography was performed with a silica gel (Merck No. 7734) column with chloroform-methanol (100 : 1 v/v) as the eluent.

Material. Racemic 14-hydroxy-15-hydroxymethyl-*O,O'*-isopropylidene-2,8-dithia[9](2,5)pyridinophane (**2**) was prepared by the method described in previous papers.[1] Commercially available *m*-chloroperbenzoic acid (MCPBA) (85% purity, Tokyo Kasei) and an aqueous 30% hydrogen peroxide solution (Mitsubishi Gas Chemistry) were used as oxidizing reagents without accurate determination of the contents.

Oxidation of 2 with MCPBA. A typical example is described in the following. A solution of MCPBA (3.43 g, 5.5 mole equivalents to **2**) in chloroform (50 ml) was added to a stirred solution of **2** (1.00 g) in the same solvent (50 ml) cooled in an ice bath over the period of 30 min and the mixture was stirred for 1 d at room temperature. During the addition of MCPBA the precipitate appeared and then gradually dissolved within 5—6 h. After decomposition of the excess MCPBA with an aqueous sodium hydrogensulfite solution, the chloroform solution was washed with a sodium hydrogencarbonate solution and with water, dried, and chromatographed to give **3** (0.25 g, 21%) and **4** (0.91 g, 73%) in this elution order.

Compound **3**: Mp>280 °C; UV (EtOH) 298 nm (ε 6.2×10^3); (MeCN) 298 nm (ε 6.1×10^3); IR (KBr disk) 1290 and 1100 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$) δ=1.65 (6H, s, C-(C<u>H</u>$_3$)$_2$), 2.6—3.4 (10H, m), 4.14 (1H, d, J=14 Hz, 2-Py-C<u>H</u>-S), 4.23 (1H, d, J=14 Hz, 2-Py-C<u>H</u>-S), 4.28 (1H, d, J=14 Hz, 5-Py-C<u>H</u>-S), 4.76 (1H, d, J=17 Hz, Py-C<u>H</u>-O), 4.89 (1H, d, J=13 Hz, 5-Py-C<u>H</u>-S), 5.31 (1H, d, J=17 Hz, Py-C<u>H</u>-O), and 8.25 (1H, s, Py-<u>H</u>). Found: C, 49.31, H, 5.99; N, 3.46; S, 16.50%. Calcd for $C_{16}H_{23}NO_6S_2$: C, 49.34; H, 5.95; N, 3.60; S, 16.47%.

Compound **4**: Mp>280 °C; UV (EtOH) 279 (ε 7.7×10^3) and 331 nm (ε 3.5×10^3); (MeCN) 282 (ε 7.6×10^3) and 338 nm (ε 2.9×10^3); IR (KBr disk) 1300, 1280 (SO_2 and N→O), and 1120 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$) δ=1.72 (6H, s, C-(C<u>H</u>$_3$)$_2$), 2.9—3.9 (10H, m), 4.24 (2H, s, 2-Py-C<u>H</u>$_2$-S), 4.52 (1H, d, J=13 Hz, 5-Py-C<u>H</u>-S), 4.80 (1H, d, J=17 Hz, Py-C<u>H</u>-O), 5.27 (1H, d, J=16 Hz, Py-C<u>H</u>-O), 5.37 (1H, d, J=12 Hz, 5-Py-C<u>H</u>-S), and 8.25 (1H, s, Py-<u>H</u>). Found: C, 47.25; H, 5.74; N, 3.31; S, 15.85%. Calcd for $C_{16}H_{23}NO_7S_2$: C, 47.39; H, 5.72; N, 3.45; S, 15.81%.

Oxidation of 2 with Hydrogen Peroxide. a) Reaction at 60—85 °C with Catalysts: Hydrogen peroxide solution (1.5 ml) was added at 60—65 °C over the period of 30 min to a stirred solution of **2** (1.00 g), acetic acid (ca. 15 mg), and sodium tungustate dihydrate (ca. 5 mg) in dioxane (10 ml)-water (10 ml) and the mixture was stirred at 80—85 °C for further 3 h. After the mixture had been cooled, the resulting precipitate of **5** (55 mg, 5%) was filtered off, and the excess hydrogen peroxide was destroyed with an aqueous sodium hydrogensulfite solution. The resulting solution was extracted with chloroform, and the extract was washed with water, dried, and chromatographed to afford **3** (1.04 g, 87%).

Compound **5**: Mp>280 °C; IR (KBr disk) 3340 (OH), 1290, and 1100 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6) δ=2.6—3.4 (10 H, m), 4.40 (1H, d, J=13 Hz, 5-Py-C<u>H</u>-S), 4.59 (1H, d, J=16 Hz, Py-C<u>H</u>-O), 4.87 (2H, s, 2-Py-C<u>H</u>$_2$-S), 4.89 (1H, s, Py-CH$_2$-O<u>H</u>), 4.92 (1H, d, J=16 Hz, Py-C<u>H</u>-O), 5,10 (1H, d, J=13 Hz, 5-Py-C<u>H</u>-S), 8.43 (1H, s, Py-<u>H</u>), and 10.09 (1H, s, Py-O<u>H</u>). Found: C, 44.92; H, 5.48; N, 3.95; S, 18.40%. Calcd for $C_{13}H_{19}NO_6S_2$: C, 44.69; H, 5.48; N, 4.01; S, 18.35%.

b) Reaction in Acetic Acid at 60—85 °C without Catalysts: Hydrogen peroxide solution (1.5 ml) was added to a stirred solution of **2** (1.00 g) in acetic acid (10 ml) at 60—65 °C over the period of 30 min and the mixture was stirred at 80—85 °C for further 3 h. The mixture was cooled and diluted with water and the resulting precipitate of **5** (0.80 g, 75%) was collected.

c) Reaction at Room Temperature with Catalysts: Hydrogen peroxide solution (1.5 ml) was added to a stirred solution of **2** (1.00 g), acetic acid (ca. 15 mg), and sodium tungustate dihydrate (ca. 5 mg) in dioxane (30 ml)-water (10 ml) below room temperature over the period of 30 min, stirred for 1 d at room temperature, and then treated as described in a), giving **3** (0.25 g, 21%), **8** (0.66 g, 58%), and **7** (0.14 g, 13%) in this elution order.

Compound **7**: Mp 201—202 °C dec; IR (KBr disk) 1290, 1090 (SO_2 weak), and 1020 cm^{-1} (SO); ^{1}H NMR ($CDCl_3$) δ=7.91 (0.1H, s, Py-<u>H</u>), 8.03 (0.2H, s, Py-<u>H</u>), 8.15 (0.6H, s, Py-<u>H</u>), and 8.25 (0.1H, Py-<u>H</u>). Found: C, 53.53; H, 6.46; N, 3.88; S, 17.90%. Calcd for $C_{16}H_{23}NO_4S_2$: C, 53.76; H, 6.49; N, 3.92; S, 17.94%.

Compound **8**: Mp>280 °C; IR (KBr disk) 1290, 1110 (SO_2), and 1030 cm^{-1} (SO); ^{1}H NMR ($CDCl_3$) δ=8.15 (0.4H, s, Py-<u>H</u>) and 8.24 (0.6H, s, Py-<u>H</u>). Found: C, 51.03; H, 6.14; N, 3.78; S, 17.12%. Calcd for $C_{16}H_{23}NO_5S_2$: C, 51.46; H, 6.21; N, 3.75; S, 17.17%.

d) Reaction at Room Temperature without Catalysts: Hydrogen peroxide solution (1.5 ml) was added to a stirred solution of **2** (1.00 g) in dioxane (30 ml)-water (10 ml) below room temperature and the mixture was stirred for 3 d at room temperature. A similar work up gave unreacted **2** (0.25 g, 25%), **6** (0.21 g, 19%), and **7** (0.51 g, 48%) in this elution order.

Compound **6**: Mp 176—177 °C; IR (KBr disk) 1020 cm^{-1} (SO); ^{1}H NMR ($CDCl_3$) δ=7.90 (0.7H, s, Py-<u>H</u>) and 8.10

(0.3H, s, Py-H). Found: C, 55.97; H, 6.78; N, 3.89; S, 18.78%. Calcd for $C_{16}H_{23}NO_3S_2$: C, 56.27; H, 6.79; N, 4.10; S, 18.78%.

Acidic Hydrolysis of 3. A mixture of **3** (1.00 g), hydrochloric acid (2.5 ml), and water (25 ml) was stirred at 80—85 °C for 2 h and cooled and the resulting precipitate of **5** (0.83 g, 93%) was collected.

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6) Assignments, see Ref. 1b.