Syntheses of Dihydrodioxepinopyridines, Dihydrodioxocinopyridines, and a Dihydrooxazepinopyridine

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Novel classes of heterocycles, [1,4]-dioxepino[5,6-*c*]pyridine, [1,5]-dioxocino[2,3-*c*]pyridine, [1,4]-dioxepino-[6,5-*b*]pyridine and pyrido[4,3-*f*][1,4]oxazepine, were synthesized from pyridoxine and pyridoxamine.

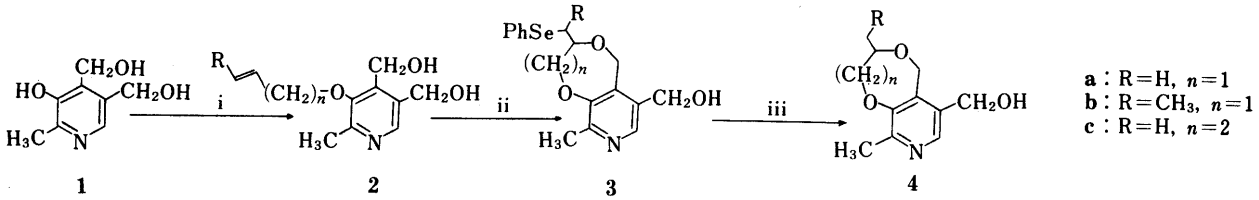
Keywords [1,4]-dioxepino[5,6-*c*]pyridine; [1,5]-dioxocino[2,3-*c*]pyridine; [1,4]-dioxepino[6,5-*b*]pyridine; pyrido[4,3-*f*][1,4]-oxazepine; pyridoxine; pyridoxamine; phenylselenenyl chloride

As a part of our studies on chemical modifications of pyridoxine and pyridoxamine, we previously reported[1] *O*-alkylations of them. Some of these compounds containing an unsaturated function in the side chain seemed to be suitable candidates for further chemical modifications. Thus we examined the intramolecular cyclization of pyridoxine and pyridoxamine derivatives having both an unsaturated group and a nucleophilic group in the molecule. We report here cyclization by means of phenylselenenyl chloride to give novel classes of heterocycles, [1,4]-dioxepino[5,6-*c*]pyridine, [1,5]-dioxocino[2,3-*c*]pyridine, [1,4]-dioxepino[6,5-*b*]pyridine, and pyrido[4,3-*f*][1,4]oxazepine.

Intramolecular cyclizations of olefinic alcohols,[2] olefinic acid,[3] and olefinic amines[4] by means of phenylselenenyl chloride have been reported, and these reactions have been carried out in the absence of water. Toshimitsu *et al.*[5] reported that the reaction of an olefin with phenylselenenyl chloride in a mixture of acetonitrile and water afforded the hydroxy group addition compound. They also observed amidoselenation reaction of olefins with acetonitrile–water in the presence of phenylselenenyl chloride and trifluoromethanesulfonic acid.[6] However, we thought it would be simpler and more convenient if the cyclization proceeded even in the presence of water. Thus we examined the reaction of 3-allyloxy-4,5-bis(hydroxymethyl)-2-methylpyridine (**2a**) with phenylselenenyl chloride in acetonitrile–water in the presence of trifluoromethanesulfonic acid; this reaction gave 2,3-dihydro-6-hydroxymethyl-9-methyl-3-[(phenylseleno)methyl]-5*H*[1,4]-dioxepino[5,6-*c*]pyridine (**3a**) in 74% yield. Similarly, cyclization of 3-(2-butenyloxy)-4,5-bis(hydroxymethyl)-2-methylpyridine (**2b**) and 3-(3-butenyloxy)-4,5-bis(hydroxymethyl)-2-methylpyridine (**2c**) were carried out to give 2,3-dihydro-6-hydroxymethyl-9-methyl-3-[1-(phenylseleno)ethyl]-5*H*[1,4]-dioxepino[5,6-*c*]pyridine (**3b**) and 3,4-dihydro-7-hydroxymethyl-10-methyl-4-[(phenylseleno)methyl]-2*H*,6*H*[1,5]-dioxocino[2,3-*c*]-pyridine (**3c**). Reductive deselenization of **3a**—**c** with nickel boride[7] gave [1,4]-dioxepino[5,6-*c*]pyridines (**4a**, **b**) and [1,5]-dioxocino[2,3-*c*]pyridine (**4c**) in 36—68% yields. An attempt at deselenization with Raney nickel catalyst according to the method of Sevrin *et al.*[8] was unsuccessful giving pyridoxine as a result of reductive cleavage of the ether bond.

[1,4]-Dioxepino[6,5-*b*]pyridines were synthesized as follows. The reaction of 3-hydroxy-2,4,5-trihydroxymethylpyridine[9] (**5**) with allyl bromide or crotyl bromide gave 3-allyloxy-2,4,5-tris(hydroxymethyl)pyridine (**6a**) or 3-(2-butenyloxy)-2,4,5-tris(hydroxymethyl)pyridine (**6b**), which were cyclized by means of phenylselenenyl chloride in the presence of trifluoromethanesulfonic acid in acetonitrile and water to give 2,3-dihydro-8,9-dihydroxymethyl-3-[(phenylseleno)methyl]-5*H*[1,4]-dioxepino[6,5-*b*]pyridine (**7a**) or 2,3-dihydro-8,9-dihydroxymethyl-3-[1-(phenylseleno)ethyl]-5*H*[1,4]-dioxepino[6,5-*b*]pyridine (**7b**). Structural confirmation of **7a** and **7b** was carried out by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy. It is known that among the three hydroxymethyl groups of **5** or **6a** the hydroxymethylene protons at the C-2 position appear at the lowest field[10] (5.34 or 5.32 ppm). Hydroxymethyl protons at C-4 and C-5 are observed at 5.27 or 5.28 and 5.13 or 5.28 ppm, respectively. Methylene protons at the C-5 position of **7a** were observed at 5.57 and 4.86 ppm as an AB quartet. Hydroxymethylene protons at the C-8 and C-9 positions, which correspond to C-5 and C-4 of **5** or **6a**, were observed at 5.12 and 4.95 ppm, respectively (Table I). This proves that the cyclization proceeded between the substituent at the C-3 position and the hydroxymethyl group at the C-2 position. Reductive deselenization of **7a** with nickel boride gave 2,3-dihydro-8,9-dihydroxymethyl-3-methyl-5*H*[1,4]-dioxepino[6,5-*b*]-pyridine (**8**).

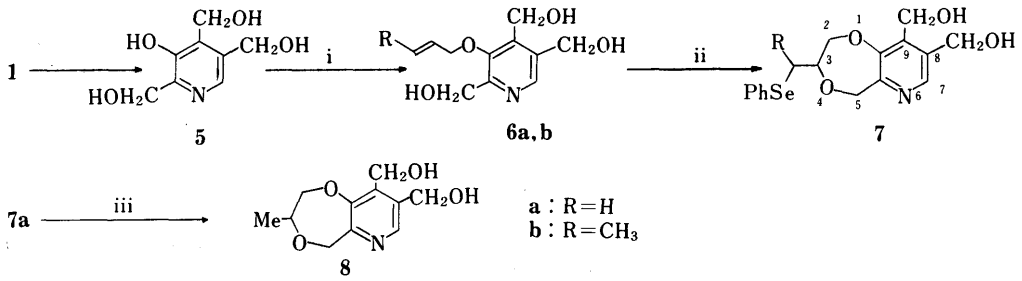
Reaction of pyridoxamine (**9**) with acryl chloride or crotonoyl chloride gave 4-(*N*-alkenoylaminomethyl)-3-hydroxy-2-methyl-5-hydroxymethylpyridine (**10a**, **b**). Cyclization of **10a** with phenylselenenyl chloride in acetonitrile in the presence of trifluoromethanesulfonic acid and



1 2 3 4

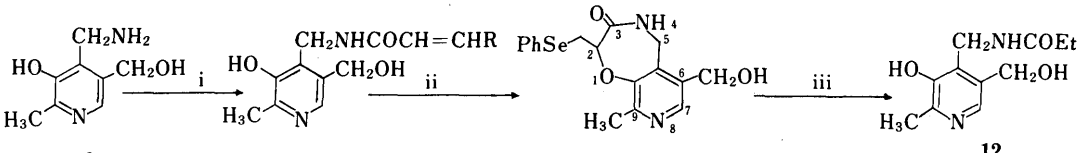
(i) $Br(CH_2)_nCH=CHR$, NaOEt, KI/acetone, reflux 10 h. (ii) PhSeCl, CF_3SO_3H–H_2O (1 : 5)/CH_3CN, reflux 1.5 h. (iii) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH–THF (1 : 9), 0°C, 5 min

Chart 1



(i) RCH=CHCH$_2$Br, NaOEt, KI/acetone, reflux 10 h. (ii) PhSeCl, CF_3SO_3H–H_2O (1 : 5)/CH_3CN, reflux 1 h. (iii) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH–THF (1 : 9), 0°C, 5 min.

Chart 2



(i) RCH=CHCOCl, 30%NaOH soln. 0°C 1 h. (ii) PhSeCl, CF_3SO_3H–H_2O (1 : 5)/CH_3CN, reflux 40 min. (iii) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH–THF (1 : 5), 0°C, 5 min.

Chart 3

TABLE I. ^{1}H-NMR Data for **5**, **6a**, **7a** and **8** Measured in Pyridine-d_5 (ppm)

Compd.	C2-CH$_2$O–	C4-CH$_2$O–	C5-CH$_2$O–	Compd.	C5-CH$_2$–	C8-CH$_2$OH	C9-CH$_2$OH
5	5.34 (2H, s)	5.27 (2H, s)	5.13 (2H, s)	**7a**	5.57 (1H, d, J=15 Hz) 4.86 (1H, d, J=15 Hz)	4.95 (2H, s)	5.12 (2H, s)
6a	5.32 (2H, s)	5.28 (2H, s)	5.28 (2H, s)	**8**	5.40 (1H, d, J=15 Hz) 4.70 (1H, d, J=15 Hz)	4.91 (2H, s)	5.08 (2H, s)

water (1 : 5) gave 6-hydroxymethyl-9-methyl-2-phenylselenomethyl-2,3,4,5-tetrahydropyrido[4,3-*f*][1,4]oxazepin-3-one (**11**) in 65% yield. The ^{1}H-NMR spectrum of **11** showed C-5 methylene proton signals at 4.03 and 4.57 ppm as an AB quartet which indicated that the cyclization had proceeded successfully. The mass (MS) spectrum and elemental analysis were consistent with the assigned structure. However, cyclization of **10b** did not proceed and **10b** was recovered. Attempted deselenization of **11** with nickel boride or Raney nickel catalyst was unsuccessful, giving ring-opened 3-hydroxy-5-hydroxymethyl-2-methyl-4-(*N*-propionylaminomethyl)pyridine (**12**).

Consequently, construction of four novel classes of heterocycles, [1,4]-dioxepino[5,6-*c*]pyridine, [1,5]-dioxocino[2,3-*c*]pyridine, [1,4]-dioxepino[6,5-*b*]pyridine, and pyrido[4,3-*f*][1,4]oxazepine has been accomplished from pyridoxine and pyridoxamine by the use of phenylselenenyl chloride. It was reported that some 3-phenylselenomethyl-3,4-dihydrocoumarin derivatives showed significant antitumor activity.[11] Thus, antitumor activity testing of some of the compounds (**3a**, **3b**, **7a**, **7b**, **11**) of the phenylselenyl group was carried out on P 388 lymphocytic leukemia. However, none of the compounds tested showed significant activity.

Experimental

All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. The infrared (IR) spectra were measured with a JASCO IR-810 spectrophotometer. MS spectra were measured with a JEOL JMS-DX 300 spectrometer. ^{1}H-NMR spectra were recorded with a JEOL JNM-MH-100 or JNM-FX-100 spectrometer using tetramethylsilane as an internal standard. Abbreviations are as follows: s, singlet; d, doublet; q, quartet, br, broad; m, multiplet.

General Procedure for the Syntheses of 3a—c by the Intramolecular Cyclization of 3-(Allyloxy, Crotonoyloxy-, and 3-Butenyloxy)-2-methyl-4,5-(bishydroxymethyl)pyridine Hydrochloride (2a, b, c) Phenylselenenyl chloride (220 mg, 1.1 mmol) and a mixture of CF_3SO_3H–H_2O (1 : 5) 270 mg were added to a suspension of compound **2a**, **2b**, or **2c** (1 mmol) in CH_3CN (20 ml). The mixture was refluxed for 1.5 h. After cooling of the mixture, saturated $NaHCO_3$ aqueous solution (50 ml) was added and the whole was extracted with $CHCl_3$. The extract was dried and the solvent was distilled off. The residue was purified by silica gel column chromatography.

2,3-Dihydro-6-hydroxymethyl-9-methyl-3-[(phenylselenomethyl]-5*H*-[1,4]-dioxepino[5,6-*c*]pyridine (3a) This compound was obtained as colorless needles (from $CHCl_3$–hexane), mp 77—78 °C, yield 74%. ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s, C9-CH_3), 2.88 and 3.09 (each 1H, dd, J=14, 6 Hz, C3-CH_2Se–), 3.68 and 4.46 (each 1H, dd, J=14, 9 Hz and J=14, 3 Hz, C2-CH_2–), 4.06 (1H, m, C3-H), 4.57 and 5.11 (each 1H, d, J=14 Hz, C5-CH_2–), 4.62 (2H, s, C6-CH_2O–), 7.32—7.50 (5H, m, Ph-Se), 7.94 (1H, s, C7-H). MS *m/z*: 365 (M^+). *Anal.* Calcd for $C_{17}H_{19}NO_3Se$: C 56.05; H, 5.26; N, 3.84. Found: C, 56.26; H, 5.30; N, 3.82.

2,3-Dihydro-6-hydroxymethyl-9-methyl-3-[1-(phenylseleno)ethyl]-5*H*-[1,4]-dioxepino[5,6-*c*]pyridine (3b) This compound was obtained as a colorless glutinous oil, yield 74%. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (3H, d, J=7 Hz, C3-CHCH_3), 2.40 (3H, s, C9-CH_3), 3.29 (1H, quintet, J=7 Hz, C3-CH(CH_3)$_2$), 3.87 (2H, m, C2-H_{ax} and C3-H), 4.57 (1H, dd, J=11, 3Hz, C2-H_{eq}), 4.61 and 5.17 (each 1H, AB q, J=14 Hz, C5-CH_2), 4.63 (2H, s, C6-CH_2O–), 7.25—7.56 (5H, m, PhSe), 7.94 (1H, s, C7-H). MS *m/z*: 379 (M^+). **3b**·HCl: mp 148—150 °C. IR (KBr): 3230 (OH), 2500 (NH^+) cm^{-1}. *Anal.* Calcd for $C_{18}H_{21}NO_3Se \cdot HCl$: C, 52.12; H, 5.35; N, 3.38. Found: C, 52.22; H, 5.23; N, 3.39.

3,4-Dihydro-7-hydroxymethyl-10-methyl-4-[(phenylseleno)methyl]-2*H*, 6*H*[1,5]-dioxocino[2,3-*c*]pyridine (3c) This compound was obtained as colorless needles (from $CHCl_3$–hexane), mp 129.5—131 °C, yield 50%.

^{1}H-NMR (DMSO-d_6–$CDCl_3$) δ: 1.89 (2H, m, C3-CH_2), 2.48 (3H, s, C10-CH_3), 2.90 and 3.18 (each 1H, dd, J=12, 6 Hz, C4-CH_2Se), 4.04 (3H, m, C2-CH_2 and C4-CH), 4.61 and 4.98 (each 1H, AB q, J=13 Hz, C6-CH_2–), 4.64 (2H, s, C7-CH_2O–), 7.24—7.50 (5H, m, PhSe–). MS m/z: 379 (M^+). **3c**·HCl: mp 130—132 °C. IR (KBr): 3330 (OH), 2600 (NH^+) cm^{-1}. *Anal.* Calcd for $C_{18}H_{21}NO_3Se$·HCl: C, 52.12; H, 5.35; N, 3.38. Found: C, 52.06; H, 5.28; N, 3.27.

2,3-Dihydro-3,9-dimethyl-6-hydroxymethyl-5*H*[1,4]-dioxepino[5,6-*c*]-pyridine (4a) $NiCl_2·6H_2O$ (285 mg, 1.2 mmol) was added with stirring to a solution of **3a** (110 mg, 0.3 mmol) in a mixture of MeOH–tetrahydrofuran (THF) (1:9; 10 ml), and then $NaBH_4$ (136 mg, 3.6 mmol) was added to the mixture. Stirring was continued for an additional 5 min, and the resulting precipitates were removed by filtration. The filtrate was evaporated to dryness. The residue was poured into 20 ml of saturated $NaHCO_3$ aqueous solution, and this mixture was extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and the solvent was evaporated off. The residue was purified by preparative thin layer chromatography (TLC) ($CHCl_3$: MeOH = 7:1), yield 43 mg (68%), colorless needles of mp 118—119 °C (from $CHCl_3$–hexane). IR (KBr): 3320 (OH) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, d, J=7 Hz, C3-CH_3), 2.44 (3H, s, C9-CH_3), 3.47 and 4.30 (each 1H, dd, J=14, 9 Hz, C2-CH_2–), 4.03 (1H, m, C3-CH–), 4.57 and 5.11 (each 1H, AB q, J=14 Hz, C5-CH_2), 4.64 (2H, s, C6-CH_2O–), 7.94 (1H, s, C7-H). MS m/z: 209 (M^+). *Anal.* Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.01; H, 7.06; N, 6.50.

3-Ethyl-2,3-dihydro-9-methyl-6-hydroxymethyl-5*H*[1,4]-dioxepino[5,6-*c*]pyridine Hydrochloride (4b) Compound **3b** was treated by similar procedures to those described for **4a** to give a colorless oil, which was dissolved in ethanol containing a small amount of HCl. The solvent was distilled off and the residue was recrystallized from EtOH–Et_2O to give colorless needles, mp 169—171 °C (from EtOH–Et_2O). Yield 59%. IR (KBr): 2800 (OH), 2550 (NH^+) cm^{-1}. ^{1}H-NMR (DMSO-d_6–$CDCl_3$) δ: 1.03 (3H, t, J=7 Hz, C3-CH_2CH_3), 1.56 (2H, quintet, J=7 Hz, C3-CH_2CH_3), 2.76 (3H, s, C9-CH_3), 3.94—4.55 (3H, m, C2-CH_2 and C3-H), 4.73 (2H, s, C6-CH_2O–), 4.76 and 5.17 (each 1H, AB q, J=15 Hz, C5-CH_2), 8.36 (1H, s, C7-H). MS m/z: 223 (M^+). *Anal.* Calcd for $C_{12}H_{17}NO_3$·HCl: C, 55.49; H, 6.99; N, 5.39. Found: C, 55.22; H, 6.67; N, 5.43.

3,4-Dihydro-4,10-dimethyl-7-hydroxymethyl-2*H*,6*H*[1,5]-dioxocino-[2,3-*c*]pyridine Hydrochloride (4c) Compound **3c** was treated by similar procedures to those described for **4b** to give colorless needles, mp 175—177 °C (from EtOH–Et_2O). Yield 36%. IR (KBr): 3310 (OH), 2540 (NH^+) cm^{-1}. ^{1}H-NMR (DMSO-d_6–$CDCl_3$) δ: 1.29 (3H, d, J=6 Hz, C4-CH_3), 1.83 (2H, m, C3-CH_2–), 2.82 (3H, s, C10-CH_3), 4.32 (3H, m, C2-CH_2 and C4-H), 4.68 (1H, d, J=15 Hz, C6-CH_2), 4.78 (2H, s, C7-CH_2O–), 4.98 (1H, d, J=15 Hz, C6-CH_2), 8.53 (1H, s, C8-H). High resolution MS m/z: Calcd for $C_{12}H_{17}NO_3$ 223.1208. Found: 223.1235.

3-Allyloxy-2,4,5-tris(hydroxymethyl)pyridine Hydrochloride (6a) A solution of sodium ethoxide (prepared from 0.55 g of sodium metal) in 100 ml of ethanol was added to a suspension of **5** (0.01 mol) in 300 ml of dry acetone with stirring. Allyl bromide (0.011 mol) and potassium iodide (4 g) were added to the mixture and the whole was refluxed for 10 h under stirring. Insoluble material was filtered off and the filtrate was evaporated. The residue was dissolved in 50 ml of aqueous saturated $NaHCO_3$ solution and extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent was distilled off. The residue was dissolved in ethanol containing a small amount of HCl. Ethanol was distilled off and the residue was recrystallized from EtOH–Et_2O to give colorless needles, mp 121—123 °C, yield 46%. ^{1}H-NMR (pyridine-d_5) δ: 4.62 (2H, d, J=5.5 Hz, C3-OCH_2–), 5.18 (4H, s, C4-CH_2O– and C5-CH_2O–), 5.23 (1H, d, J=10 Hz, *trans* H–C=C–CH_2–), 5.32 (2H, s, C2-CH_2O–), 5.49 (1H, d, J=17 Hz, *cis* H–C=C–CH_2–), 6.21 (1H, ddt, J=17, 10, 5.5 Hz, –C=C(H)CH_2–), 8.94 (1H, s, C6-H). MS m/z: 225 (M^+). *Anal.* Calcd for $C_{11}H_{15}NO_4$·HCl: C, 50.48; H, 6.16; N, 5.35. Found: C, 50.72; H, 6.04; N, 5.21.

3-Crotyloxy-2,4,5-tris(hydroxymethyl)pyridine Hydrochloride (6b) The reaction of **5** with crotyl bromide was carried out by the same procedure as described for **6a**. Colorless needles, mp 119—121 °C, yield 42%. ^{1}H-NMR (pyridine-d_5) δ: 1.59 (3H, d, J=6 Hz, CH_3–CH=C–), 4.77 (2H, d, J=6 Hz, C3-OCH_2–), 5.15 (4H, s, C4-CH_2O– and C5-CH_2O–), 5.28 (2H, s, C2-CH_2O–), 5.82 (2H, m, H–C=C–H), 8.84 (1H, s, C6-H). *Anal.* Calcd for $C_{12}H_{17}NO_4$·HCl: C, 52.27; H, 6.58; N, 5.08. Found: C, 52.00; H, 6.55; N, 5.11.

3-[(Phenylseleno)methyl]-2,3-dihydro-8,9-dihydroxymethyl-5*H*[1,4]-dioxepino[6,5-*b*]pyridine Hydrochloride (7a) Phenylselenenyl chloride (220 mg, 1.1 mmol) and a mixture of CF_3SO_3H–H_2O (1:5) (270 mg) were added to a suspension of **6a** (1 mmol) in CH_3CN (15 ml). The mixture was refluxed for 1 h. After cooling, saturated $NaHCO_3$ aqueous solution (50 ml) was added to the mixture and the whole was extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and the solvent was distilled off. The residue was purified by silica gel chromatography ($CHCl_3$: MeOH = 7:1). The eluate was concentrated and the residue was dissolved in EtOH containing a small amount of HCl. Solvent was distilled off and the residue was recrystallized from EtOH–Et_2O to give colorless needles of mp 162—164 °C, yield 66%. ^{1}H-NMR (pyridine-d_5) δ: 3.15 and 3.35 (each 1H, AB q, J=13.7 Hz, C3-CH_2Se), 3.98 and 4.61 (each 1H, dd, J=12.5, 7.5 Hz, C2-CH_2–), 4.28 (1H, m, C3-H), 4.86 and 5.57 (each 1H, AB q, J=15 Hz, C5-CH_2–), 4.95 (2H, s, C8-CH_2O–), 5.12 (2H, s, C9-CH_2O–), 7.28—7.63 (5H, m, PhSe–), 8.60 (1H, s, C7- =CH–). MS m/z: 381 (M^+). *Anal.* Calcd for $C_{17}H_{19}NO_4Se$·HCl: C, 48.99; H, 4.84; N, 3.36. Found: C, 49.19; H, 4.62; N, 3.40.

3-[1-(Phenylseleno)ethyl]-2,3-dihydro-8,9-dihydroxymethyl-5*H*[1,4]-dioxepino[6,5-*b*]pyridine Hydrochloride (7b) The reaction of **6b** with phenylselenenyl chloride was treated by the same procedure as described for **7a** to give colorless needles of mp 169—172 °C, yield 62%. ^{1}H-NMR (DMSO-d_6–$CDCl_3$) δ: 1.49 (3H, d, J=7 Hz, C3-CH(CH_3)), 3.47 (1H, quintet, J=7 Hz, C3-CH(CH_3)), 4.05 (1H, m, C3-H), 4.25 and 4.65 (each 1H, dd, J=13, 7 Hz, C2-CH_2), 4.68 (2H, s, C8-CH_2O–), 4.87 and 5.19 (each 1H, d, J=16 Hz, C5-CH_2–), 4.96 (2H, s, C9-CH_2O–), 7.35—7.53 (5H, m, PhSe–), 8.36 (1H, s, C7-H). MS m/z: 395 (M^+). *Anal.* Calcd for $C_{18}H_{21}NO_4Se$·HCl: C, 50.19; H, 5.15; N, 3.25. Found: C, 50.16; H, 5.00; N, 3.16.

2,3-Dihydro-8,9-hydroxymethyl-3-methyl-5*H*[1,4]-dioxepino[6,5-*b*]-pyridine (8) Compound **7a** (160 mg, 0.38 mmol) and $NiCl_2·6H_2O$ (185 mg, 0.78 mmol) were dissolved in 35 ml of MeOH–THF (1:9). Sodium borohydride (90 mg, 2.4 mmol) was added, and the mixture was cooled with ice and stirred for 5 min. The resulting black precipitates were filtered off. The filtrate was evaporated and the residue was purified by preparative TLC ($CHCl_3$: MeOH = 6:1) and recrystallized from $CHCl_3$–hexane to give colorless needles of mp 102—103 °C, yield 21 mg (24%). IR (KBr): 3330 (OH) cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 1.10 (3H, d, J=7 Hz, C3-CH_3), 3.49 and 4.23 (each 1H, each dd, J=13, 8 Hz and J=13, 2 Hz, C2-CH_2–), 3.93 (1H, m, C3-H), 4.70 and 5.40 (each 1H, AB q, J=14, 5 Hz, C5-CH_2–), 4.91 (2H, s, C8-CH_2O–), 5.08 (2H, s, C9-CH_2O–), 8.15 (1H, s, C7-H). MS m/z: 225 (M^+). *Anal.* Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.84; H, 6.63; N, 6.03.

4-(*N*-Acryloylaminomethyl)-3-hydroxy-5-hydroxymethyl-2-methylpyridine Hydrochloride (10a) Acryloyl chloride (3.6 mmol) and 30% NaOH aqueous solution (1 ml) was added to a suspension of pyridoxamine (0.5 g, 3 mmol) in 10 ml of water. The mixture was stirred for 1 h. The reaction mixture was neutralized with 10% HCl and extracted with AcOEt. The extract was dried over anhydrous $MgSO_4$. The solvent was distilled off and the residue was dissolved in EtOH. Hydrogen chloride gas was passed into the above solution. Ether was added to give crystals, which were collected by filtration and recrystallized from EtOH–Et_2O to give colorless needles of mp 190—193 °C, yield 52%. IR (KBr): 3310 (OH), 2700 (NH^+), 1649 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6–$CDCl_3$) δ: 2.68 (3H, s, C6-CH_2–), 4.51 (2H, d, J=6 Hz, C4-CH_2N), 4.90 (2H, s, C3-CH_2O–), 5.71 (1H, dd, J=7, 5 Hz, –COCH=C–), 6.32 (1H, d, J=5 Hz, –COC=CH–), 6.34 (1H, d, J=7 Hz, –COC=CH–), 8.15 (1H, s, C2-H), 9.72 (1H, br, NH). MS m/z: 222 (M^+). *Anal.* Calcd for $C_{11}H_{14}N_2O_3$·HCl: C, 51.07; H, 5.84; N, 10.83. Found: C, 51.02; H, 5.76; N, 10.54.

4-(*N*-Crotonoylaminomethyl)-3-hydroxy-5-hydroxymethyl-2-methylpyridine Hydrochloride (10b) Pyridoxamine and crotonoyl chloride was treated by the same procedure as described for **10a** to give colorless needles of mp 245—248 °C (dec.), yield 63%. IR (KBr): 3310 (OH), 2680 (NH^+), 1660 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6–$CDCl_3$) δ: 1.86 (3H, dd, J=6.5, 2 Hz, CH=CH(CH_3)), 2.62 (3H, s, C6-CH_3), 4.48 (2H, d, J=6 Hz, C4-CH_2NH–), 4.84 (2H, s, C3-CH_2O–), 6.05 (1H, dd, J=16, 2 Hz, –COCH=C–), 6.83 (1H, dq, J=16, 6.5 Hz, –COC=CH–), 8.14 (1H, s, C2-H), 9.50 (1H, t, J=6 Hz, –CH_2NH). MS m/z: 236 (M^+). *Anal.* Calcd for $C_{12}H_{16}N_2O_3$·HCl: C, 52.85; H, 6.28; N, 10.27. Found: C, 52.76; H, 6.17; N, 10.08.

6-Hydroxymethyl-9-methyl-2-phenylselenomethyl-2,3,4,5-tetrahydropyrido[4,3-*f*][1,4]oxazepin-3-one Dihydrochloride (11) Phenylselenenyl chloride (200 mg, 1 mmol) and a mixture of CF_3SO_3H–H_2O (1:5) (240 mg) were added to a suspension of **10a** (230 mg, 1 mmol) in CH_3CN (15 ml). The mixture was refluxed for 40 min, then allowed to cool. Saturated $NaHCO_3$ aqueous solution (30 ml) was added and the mixture was extracted with $CHCl_3$. The extract was dried over anhydrous $MgSO_4$ and the solvent was distilled off. The residue was purified by silica gel

chromatography ($CHCl_3$: MeOH = 7 : 1). The eluate was concentrated and the residue was dissolved in EtOH containing a small amount of HCl. The solvent was distilled off and the residue was recrystallized from EtOH–Et_2O to give colorless needles of mp 169—171 °C, yield 260 mg (65%). IR (KBr): 3350 (OH), 2660 (NH^+), 1630 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.68 (3H, s, C9-CH_3), 3.77 and 4.02 (each 1H, each dd, J=12, 6 Hz, C2-CH_2Se–), 4.03 and 4.57 (each 1H, AB q, J=14 Hz, C5-CH_2–), 4.83 (2H, s, C6-CH_2O–), 4.88 (1H, t, J=6 Hz, C2-CH–), 7.32—7.55 (5H, m, PhSe–), 8.22 (1H, s, C7-N=CH–). MS *m/z*: 378 (M^+). *Anal.* Calcd for $C_{17}H_{18}N_2O_3 \cdot 2HCl$: C, 45.35; H, 4.48; N, 6.22. Found: C, 45.65; H, 4.60; N, 6.09.

3-Hydroxy-5-hydroxymethyl-2-methyl-4-(*N*-propionylaminomethyl)-pyridine Hydrochloride (12) Compound **11** (80 mg, 0.18 mmol) was dissolved in 40 ml of a mixture of MeOH–THF (1 : 9). Then $NiCl_2 \cdot 6H_2O$ (170 mg, 0.71 mmol) was added. Sodium borohydride (85 mg, 2.2 mmol) was added and the mixture was stirred for 5 min. Black precipitates were removed by filtration and the filtrate was evaporated to dryness. The residue was poured into 30 ml of saturated $NaHCO_3$ aqueous solution. The mixture was extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and the solvent was evaporated off. The residue was purified by preparative TLC ($CHCl_3$: MeOH = 7 : 1) and dissolved in EtOH. Hydrogen chloride gas was passed into the above solution and ether was added to give crystals, which were recrystallized from EtOH–Et_2O to obtain colorless needles of mp 216—219 °C (dec.), yield 24 mg (52%). IR (KBr): 3320 (OH), 2700 (NH^+), 1630 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6–$CDCl_3$) δ: 1.11 (3H, t, J=7 Hz, $-CH_2\underline{CH}_3$), 2.32 (2H, q, J=7 Hz, $-\underline{CH}_2-CH_3$), 2.72 (3H, s, C6-CH_3), 4.42 (2H, d, J=6 Hz, C4-$C\underline{H}_2NH$–), 4.88 (2H, s, C3-CH_2O–), 8.16 (1H, s, –N=CH–), 9.36 (1H, t, J=6 Hz, $CH_2\underline{NH}$–). MS *m/z*: 224 (M^+). *Anal.* Calcd $C_{11}H_{16}N_2O_3 \cdot HCl$: C, 50.68; H, 6.57; N, 10.74. Found: C, 50.71; H, 6.30; N, 10.44.

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