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Chemistry of Chiral Vitamin B_6 Analogs. IV. Syntheses of Chiral Pyridoxal and Pyridoxamine Analogs Having a Branched "Ansa Chain" between 2′- and 5′-Positions

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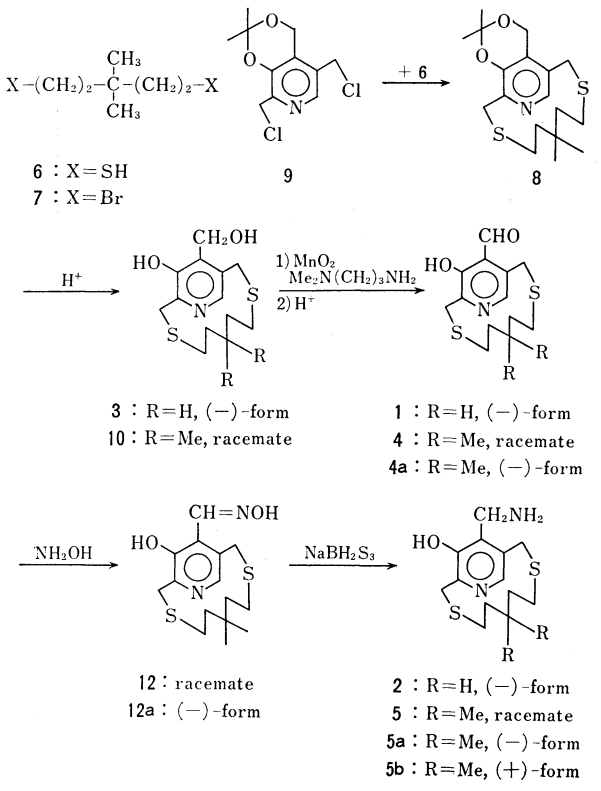
Racemic 15-formyl-14-hydroxy-5,5-dimethyl-2,8-dithia[9](2,5)pyridinophane (**4**), an analog of pyridoxal having a branched "ansa chain" between 2′- and 5′-positions, was synthesized from 2,5-bis(chloromethyl)-3-hydroxy-*O*,*O*′-isopropylidene-4-pyridinemethanol. Optical resolution of **4** was achieved *via* the formation of Schiff base with 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-glucofranose, giving the levorotary enantiomer of **4** (**4a**). Racemic 15-aminomethyl-14-hydroxy-5,5-dimethyl-2,8-dithia[9](2,5)pyridinophane (**5**), the same type of pyridoxamine analog as **4**, and its levorotary enantiomer were synthesized from the corresponding **4** and **4a**. Both levorotary and dextrorotary enantiomers of **5** were also obtained by the optical resolution of the racemate *via* the formation of chiral dibenzoyltartaric acid salts of **5**.

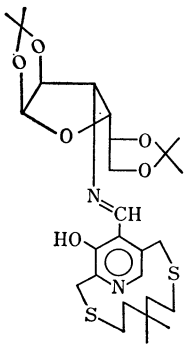
In the course of our study on mimics of vitamin B_6-dependent enzymes, we have prepared a new type of chiral analogs of pyridoxal (**1**),[1] pyridoxamine (**2**),[2] and pyridoxine (**3**)[3] which have a straight "ansa chain" between 2′- and 5′-positions. In the presence of a suitable metal ion, **1**[1] and **2**[2] have proved very active in the enzyme-mimics reactions such as racemization or transamination of amino acids. Although such reactions proceed *via* the formation of Schiff base[4] stereospecifically and/or stereoselectively owing to the chirality of the B_6 analogs used, the degree of such steric effects is rather limited in comparison to the corresponding enzymic reactions. This will be because the "ansa chain" to which the B_6 analogs owe their planer chirality is too small and separated too far from the reaction center in the transition state. This prompted us to replace the straight "ansa chain" by a more bulky one. We prepared new B_6 analogs having a branched "ansa chain".

This paper deals with 15-formyl-14-hydroxy-5,5-dimethyl-2,8-dithia[9](2,5)pyridinophane (**4**) and 15-aminomethyl-14-hydroxy-5,5-dimethyl-2,8-dithia[9]-(2,5)pyridinophane (**5**), a new type of pyridoxal and pyridoxamine analogs, and their optical resolution. The levorotary enantiomer of **5** (**5a**) was also obtained by derivation from the corresponding enantiomer of **4** (**4a**).

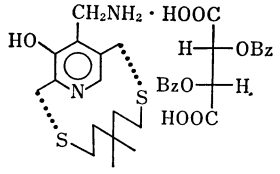
3,3-Dimethyl-1,5-pentanedithiol (**6**) was prepared by the reaction of 1,5-dibromo-3,3-dimethylpentane (**7**)[5] with thiourea and subsequent alkaline hydrolysis. The ansa compound (**8**) was obtained by slow addition of a benzene solution of an equimolar mixture of **6** and 2,5-bis(chloromethyl)-3-hydroxy-*O*,*O*′-isopropylidene-4-pyridinemethanol (**9**)[1] to a dilute solution of sodium ethoxide in ethanol at 0 °C. Removal of the isopropylidene group in **8** by acidic hydrolysis afforded an analog of pyridoxine (**10**), which was oxidized with manganese(IV) oxide in the presence of *N*,*N*-dimethyl-1,3-propanediamine in pyridine–benzene.[6] The resulting Schff base was hydrolyzed with acid to give racemic 15-formyl-14-hydroxy-5,5-dimethyl-2,8-dithia[9](2,5)pyridinophane (**4**). The optical resolution of **4** was performed by forming the Schiff base (**11**) by treatment with 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-glucofranose.[1] Levorotary enantiomer of **4** (**4a**) was obtained by recrystallization of one of the less soluble diastereomers of the Schiff base (**11a**) from benzene and subsequent acidic hydrolysis of **11a**. Compounds **4** and **4a** were treated with hydroxylamine in ethanol to give the corresponding (±)-oxime (**12**) and (−)-oxime (**12a**), respectively. Reduction of **12** and **12a** to the corresponding pyridoxamine analogs, **5** and **5a**, were performed with sodium (dihydrotrithio)borate in tetrahydrofuran, following the earlier synthesis of **2**.[2]

We also succeeded in the optical resolution of **5**; that is, when **5** was treated with (−)-(*R*,*R*)-dibenzoyltartaric acid in ethanol, the crude (−)-dibenzoyltartaric acid salt of **5** (neutral equimolar salt) (**13a**) contaminated with its diastereomeric salt was prepared. Owing to the poor solubility of the salt in the usual solvents, fractional crystallization of **13a** proved very difficult. Therefore, such crude **13a** was treated with aqueous sodium hydrogencarbonate to give crude **5a**

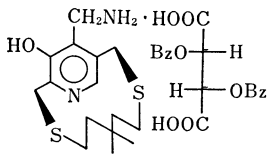




11 : mixture of diastereomer
11a : (−)-form



13a



13b

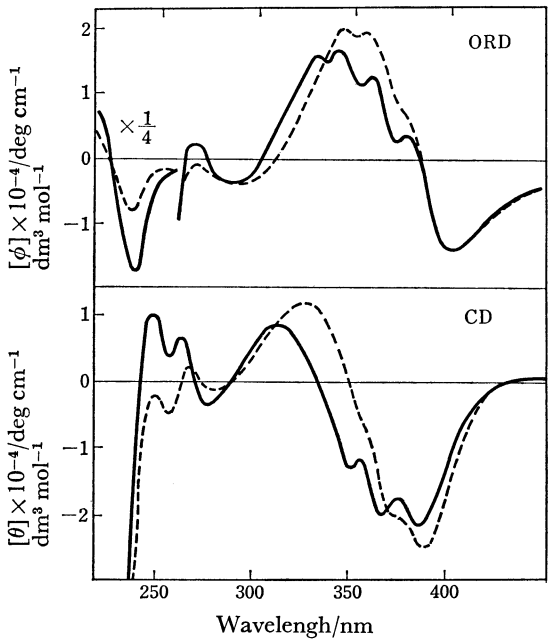


Fig. 1. ORD and CD spectra of **4a** and **1** (1.76×10^{-4} M solution in MeCN at 21 °C.).
4a: ——, **1**: ----.

including a little (+)-enantiomer (**5b**). This was repeatedly treated as described above and gave **5a**. Using (+)-(*S,S*)-dibenzoyltartaric acid in the same way resulted in (+)-enantiomer (**5b**). The physical properties, including optical rotation, of **5a** obtained by the resolution of **5** completely agreed with those of **5a** prepared from **12a**.

In order to determine the absolute configuration of **4a**, its ORD and CD spectra were measured. They were very similar to those of **1** (Fig. 1), indicating that **4a** has the same configuration as **1** has. Because **1** had been shown to have *S*-configuration on the basis of the results of X-ray analysis of (−)-pyridoxine analog (**3**) derived from **1**,[3] the absolute configuration of **4a** was determined to be *S*. Therefore, **5a** and **12a** derived from **4a** also had *S*-configuration and the enantiomer **5b** had *R*-configuration.

Studies on the function of these new B_6 analogs with definite configuration are under way. These indicate that in some systems they are very superior to the former analogs, **1** and **2**. The results will be reported in the near furture.

Experimental

All melting and boiling points are uncorrected. Optical rotations were measured with a Perkin-Elmer 241MC polarimater. UV, IR, and ^{1}H NMR spectra were recorded on a Hitachi 124 Spectrophotometer, a Shimadzu IR-27G infrared spectrophotometer, and a JEOL PS-100 spectrometer, respectively. ORD and CD spectra were obtained using a JASCO J20A automatic recording spectropolarimeter. Column chromatography was performed on a Merck silica gel 60 (No. 7734).

*3,3-Dimethyl-1,5-pentanedithiol (**6**).* A stirred mixture of 1,5-dibromo-3,3-dimethylpentane (**7**)[5] (64.8 g), thiourea (61.0 g), and water (45 ml) was refluxed for 20 h. A solution of potassium hydroxide (100 g) in water (200 ml) was added all at once to the resulting solution at room temperature, refluxed for 6 h with stirring, diluted with water, and extracted with ether. The aqueous layer was acidified with hydrochloric acid and extracted with ether. The ethereal extract was dried ($MgSO_4$), concentrated, and distilled, giving 35.8 g (82%) of **6**: bp 100—101 °C/7 mmHg (1 mmHg≈133 Pa); n_D^{23} 1.5141; IR (film) 2550 cm^{-1} (SH). Found: C, 50.84; H, 9.73; S, 39.07%. Calcd for $C_7H_{16}S_2$: C, 51.17; H, 9.81; S, 39.02%.

*14-Hydroxy-15-hydroxymethyl-O,O′-isopropylidene-5,5-dimethyl-2,8-dithia[9](2,5)pyridinophane (**8**).* A solution of **6** (4.6 g) and 2,5-bis(chloromethyl)-3-hydroxy-*O,O′*-isopropylidene-4-pyridinemethanol (**9**)[1] (6.9 g) in benzene (500 ml) was added to a stirred solution of sodium ethoxide (prepared from sodium (1.7 g) in ethanol (2.5 l)) over a period of 6 h in an ice bath and kept overnight at 0 °C. The solvents were removed and the residue was extracted with chloroform–water. The organic layer was washed with water, dried ($MgSO_4$), concentrated, and chromatographed. Elution with dichloromethane gave 7.5 g (81%) of **8**: mp 139—140 °C; UV_{max} (MeCN) 297 (ε 6.3×10^3) and 211 nm (ε 15.0×10^3); ^{1}H NMR ($CDCl_3$) δ=7.94; (1H, s), 5.26 (1H, d, J=16 Hz), 4.77 (1H, d, J=16 Hz), 4.15 (1H, d, J=12 Hz), 3.73 (1H, d, J=12 Hz), 3.61 (1H, d, J=13 Hz), 3.50 (1H, d, J=13 Hz), 1.63 (3H, s), 1.59 (3H, s), and 0.70 (6H, s). Found: C, 61.23; H, 7.67; N, 3.92; S, 18.11%. Calcd for $C_{18}H_{27}NO_2S_2$: C, 61.15; H, 7.70; N, 3.96; S, 18.14%.

*14-Hydroxy-15-hydroxymethyl-5,5-dimethyl-2,8-dithia[9](2,5)-pyridinophane (**10**).* A stirred mixture of **8** (7.3 g) in 1 M (1 M=1 mol/dm^3) hydrochloric acid (240 ml) was heated at 80—85 °C for 1 h. Soon **8** was dissolved and the hydrochloride of **10** was deposited. The mixture was made basic with solid sodium hydrogencarbonate and stirred for 1 h at room temperature. Separation of the precipitates gave 5.2 g of **10**. Additional **10** (1.2 g; total 99%) was recovered by concentrating the filtrate to dryness, extracting the residue with pyridine, and removing the pyridine; mp> 280 °C. Found: C, 57.49; H, 7.36; N, 4.30; S, 20.44%. Calcd for $C_{15}H_{23}NO_2S_2$: C, 57.47; H, 7.40; N, 4.47; S,

20.45%.

Hydrochloride: Mp 208—209 °C dec Found: C, 51.50; H, 6.90; Cl, 10.11; N, 3.97; S, 18.38%. Calcd for $C_{15}H_{24}ClNO_2S_2$: C, 51.49; H, 6.91; Cl, 10.13; N, 4.00; S, 18.32%.

*(±)-15-Formyl-14-hydroxy-5,5-dimethyl-2,8-dithia[9](2,5)-pyridinophane (**4**).* A stirred mixture of *N,N*-dimethyl-1,3-propanediamine (7.2 ml), manganese(IV) oxide (27.0 g), and a solution of **10** (5.2 g) in pyridine (100 ml) and benzene (70 ml) was refluxed for 4 h while the generated water was azeotropically separated.[6] The insoluble material was filtered off with celite and the filtrate was evaporated to dryness. Dioxane (100 ml) and 1.2 M hydrochloric acid (65 ml) were added to the residue and stirred for 1 h at room temperature. Dilution of the solution with water (*ca.* 1 l) and adjustment of pH to *ca.* 3 with aqueous sodium hydroxide gave precipitates. These were passed through a silica-gel column with dichloromethane, giving 3.6 g (70%) of **4**: mp 147—148 °C; IR (KBr) 1660 cm^{-1} (C=O). Found: C, 57.82; H, 6.73; N, 4.41; S, 20.54%. Calcd for $C_{15}H_{21}NO_2S_2$: C, 57.85; H, 6.80; N, 4.50; S, 20.59%.

*(−)-Schiff Base of **4** with 3-Amino-3-deoxy-1,2:5,6-di-O-isopropylidene-D-glucofranose (**11a**).* A solution of **4** (6.24 g) and 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-glucofranose[1] (5.74 g) in benzene (500 ml) was refluxed for 2 h while the generated water was azeotropically separated. Evaporating the solution to *ca.* 100 ml afforded crude **11a**, which was recrystallized twice from benzene, giving 4.17 g (75% based on half of **4**) of **11a**: mp>280 °C; UV_{max} ($CHCl_3$) 353 nm (ε 4.9×10^3); IR (KBr) 1660 cm^{-1} (C=N); $[\alpha]_D^{26}$ −337° (*c* 0.392, $CHCl_3$). Found: C, 58.90; H, 7.30; N, 4.98; S, 11.37%. Calcd for $C_{27}H_{40}N_2O_6S_2$: C, 58.67; H, 7.29; N, 5.07; S, 11.60%.

*(−)-15-Formyl-14-hydroxy-5,5-dimethyl-2,8-dithia[9](2,5)-pyridinophane (**4a**).* To a solution of **11a** (3.98 g) in dioxane (400 ml) was immediately added 1 M hydrochloric acid (60 ml). The mixture was stirred for 1 h at room temperature. Treating the solution as described in the preparation of **4** gave 1.80 g (80%) of **4a**: mp 93 °C; $[\alpha]_D^{24}$ −422° (*c* 0.264, $CHCl_3$); UV_{max} (MeCN) 360 (ε 4.0×10^3), 248 (ε 8.2×10^3), and 225 nm (ε 10.8×10^3); IR (KBr) 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=10.53 (1H, s), 8.06 (1H, s), 4.35 (1H, d, *J*=12 Hz), 4.28 (1H, d, *J*=14 Hz), 3.77 (1H, d, *J*=14 Hz), 3.66 (1H, d, *J*=12 Hz), and 0.70 (6H, s). Found: C, 57.92; H, 6.78; N, 4.42; S, 20.57%. Calcd for $C_{15}H_{21}NO_2S_2$: C, 57.85; H, 6.80; N, 4.50; S, 20.59%.

*(−)-14-Hydroxy-15-hydroxyiminomethyl-5,5-dimethyl-2,8-dithia[9](2,5)pyridinophane (**12a**).* To a solution of **4a** (1.22 g) in ethanol (60 ml) was immediately added solid hydroxylamine hydrochloride (0.38 g) and sodium acetate trihydrate (1.0 g). The mixture was stirred overnight at room temperature, concentrated to dryness, and extracted with chloroform–water. After being washed with aqueous sodium hydrogencarbonate and with water, the organic layer was dried ($MgSO_4$), concentrated, and chromatographed. Elution with chloroform afforded 1.01 g (79%) of **12a**: mp 218—219 °C; $[\alpha]_D^{23}$ −363° (*c* 0.204, $CHCl_3$); UV_{max} (MeCN) 330 (ε 4.6×10^3), 260 (ε 9.9×10^3), and 215 nm (ε 18.9×10^3); IR (KBr) 3400 (OH) and 1660 cm^{-1} (CH=N); ^1H NMR (CD_3SOCD_3) δ=12.28 (1H, s), 10.99 (1H, s), 8.73 (1H, s), 8.06 (1H, s), 4.28 (1H, d, *J*=12 Hz), 4.22 (1H, d, *J*=12 Hz), 3.77 (1H, d, *J*=13 Hz), 3.58 (1H, d, *J*=12 Hz), and 0.65 (6H, s). Found: C, 55.02; H, 6.80; N, 8.51; S, 19.54%. Calcd for $C_{15}H_{22}N_2O_2S_2$: C, 55.19; H, 6.79; N, 8.58; S, 19.64%.

*(±)-14-Hydroxy-15-hydroxyiminomethyl-5,5-dimethyl-2,8-dithia[9](2,5)pyridinophane (**12**).* Racemic isomer (**4**) was treated as described in the treatment of **4a**, yielding **12** in 93% yield: mp 205—206 °C. Found: C, 55.05; H, 6.79; N, 8.40; S, 19.58%. Calcd for $C_{15}H_{22}N_2O_2S_2$: C, 55.19; H, 6.79; N, 8.58; S, 19.64%.

*(−)-15-Aminomethyl-14-hydroxy-5,5-dimethyl-2,8-dithia[9]-(2,5)pyridinophane (**5a**).* Dry THF (15 ml) was added all at once to a stirred mixture of sulfur (675 mg) and sodium tetrahydroborate (264 mg) under nitrogen atmosphere and stirred for 1 h at room temperature. A solution of **12a** (1.13 g) in dry THF (30 ml) was added to the mixture over a period of 20 min at room temperature with stirring and refluxed for 6 h. After removal of the solvent, the residue was dissolved in hot chloroform–methanol and extracted with dilute hydrochloric acid. The aqueous layer was treated with charcoal, made basic with solid sodium hydrogencarbonate, and extracted with chloroform. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed. Elution with chloroform–methanol (9:1 v/v) gave 617 mg (57%) of **5a**: mp 174—175 °C dec; $[\alpha]_D^{25}$ −262° (*c* 0.409, $CHCl_3$); ORD: λ_{max} 314 ([α] $-1.32°\times10^4$), 285 ([α] $+1.58°\times10^4$), 247 ([α] $-5.0°\times10^2$), and 220 nm ([α] $+4.8°\times10^4$) (*c* 6.4×10^{-5} M, MeCN, 21 °C); CD: λ_{max} 300 ($\Delta\varepsilon$ −22.3), 260 ($\Delta\varepsilon$ +1.65), and 239 nm ($\Delta\varepsilon$ −19.3) (*c* 6.4×10^{-5} M, MeCN, 21 °C); UV_{max} (MeCN) 299 (ε 5.7×10^3) and 214 nm (ε 14×10^3); IR (KBr) 3350, 3200, and 3150 cm^{-1} (NH_2, OH); ^1H NMR (CD_3SOCD_3) δ=7.79 (1H, s), 5.99 (2H, s), 4.18 (2H, s), 4.15 (1H, d, *J*=11 Hz), 3.78 (1H, d, *J*=13 Hz), 3.70 (1H, d, *J*=13 Hz), 3.45 (1H, d, *J*=11 Hz), and 0.64 (6H, s). Found: C, 57.45; H, 7.79; N, 8.79; S, 20.57%. Calcd for $C_{15}H_{24}N_2OS_2$: C, 57.65; H, 7.74; N, 8.96; S, 20.52%.

*(±)-15-Aminomethyl-14-hydroxy-5,5-dimethyl-2,8-dithia[9]-(2,5)pyridinophane (**5**).* The racemate (**12**) was treated as described in the preparation of **5a**, affording **5** in 59% yield: mp 154—155 °C dec. Found: C, 57.37; H, 7.74; N, 8.80; S, 20.43%. Calcd for $C_{15}H_{24}N_2OS_2$: C, 57.65; H, 7.74; N, 8.96; S, 20.52%.

*Optical Resolution of **5**.* *(−)-Enantiomer of **5** (**5a**)*: A solution of (−)-(*R,R*)-dibenzoyltartaric acid (1.59 g) in ethanol (15 ml) was added to a hot solution of **5** (1.31 g) in ethanol (100 ml), concentrated to *ca.* 30 ml, and cooled in an ice bath. The precipitates were collected and stirred with a mixture of chloroform and saturated sodium hydrogencarbonate solution at room temperature for 1 h. The organic layer was washed with water, dried ($MgSO_4$), and concentrated to dryness, giving crude **5a**. Two more treatments of the crude **5a** with (−)-dibenzoyltartaric acid and sodium hydrogencarbonate, successively yielded 295 mg (45% based on half of **5**) of **5a**: mp 174—175 °C dec; $[\alpha]_D^{21}$ −262° (*c* 0.327, $CHCl_3$).

*(−)-Dibenzoyltartarate of **5a** (**13a**)*: Mp >280 °C; $[\alpha]_D^{22}$ −186° (*c* 0.273, DMF). Found: C, 59.18; H, 5.70; N, 4.14; S, 9.52%. Calcd for $C_{33}H_{38}N_2O_9S_2$: C, 59.09; H, 5.71; N, 4.18; S, 9.56%.

*(+)-Enantiomer of **5** (**5b**)*: By the use of (+)-(*S,S*)-dibenzoyltartaric acid instead of (−)-optical isomer, **5b** was obtained in 43% yield (based on half of **5**): mp 174—175 °C dec; $[\alpha]_D^{21}$ +262° (*c* 0.330, $CHCl_3$). Found: C, 57.37; H, 7.74; N, 8.78; S, 20.46%. Calcd for $C_{15}H_{24}N_2O_2S_2$: C, 57.65; H, 7.74; N, 8.96; S, 20.52%.

*(+)-Dibenzoyltartarate of **5b** (**13b**)*: Mp >280 °C; $[\alpha]_D^{21}$ +187° (*c* 0.330, DMF). Found: C, 59.19; H, 5.65; N, 4.10; S, 9.55%. Calcd for $C_{33}H_{38}N_2O_9S_2$: C, 59.09; H, 5.71; N, 4.18; S, 9.56%.

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