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Functionalized Dithia(2,5)pyridinophanes as Vitamin B_6 Analogues. Synthesis, Properties, and Catalytic Activity for Racemization Reaction

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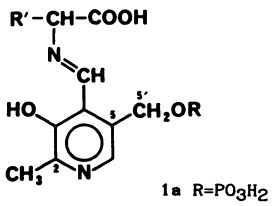
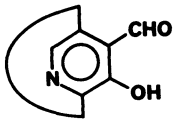
Exploration of synthetic routes to achieve designed vitamin B_6 models on the structural basis of functionalized dithia(2,5)pyridinophanes from pyridoxine hydrochloride was undertaken and the catalyst potency for a racemization reaction was examined in comparison with that of pyridoxal. By the reaction of 3,4′-*O*-isopropylidenepyridoxine 2′,5′-dichloride with α,ω-dithiols, dithia(2,5)pyridinophanes were synthesized in good yields. For dithia[3]paracyclo[3](2,5)pyridinophanes, juncture sulfur atoms were extruded photochemically, whereas 2,(n+3)-dithia[m](2,5)pyridinophanes incompletely extruded sulfur atoms under various conditions. Because of instability and low preparative yield of 15-hydroxy-16-formyl[2]paracyclo[2](2,5)pyridinophane, dithia-containing phanes, (n+9)-hydroxy-(n+10)-formyl-2,(n+3)-dithia[m](2,5)pyridinophanes [**26a** (n=4), **26b** (n=6), **26c** (n=8); m=n+4], 17-hydroxy-18-formyl-2,11-dithia[3]paracyclo[3](2,5)pyridinophane (**27**), and an acyclic congener for **26a**, 5′-deoxy-2′,5′-bis(ethylthio)pyridoxal (**28**), were eventually prepared in high yields by use of manganese dioxide in the presence of a primary amine. It was found on the basis of ^{1}H-NMR spectral analyses that the rotations of pyridine rings in some molecules, **26a**, **26b**, and **27** with ring sizes equal to or less than fourteen were restricted. The racemization potency of **26a—c**, **27**, and **28** for sodium hydrogen L-glutamate demonstrated that these are 1.4- to 1.7-fold more potent than pyridoxal itself under certain conditions (pH 10.0, 25±0.5 °C) until *ca.* 80% completion of the racemization reaction. **26a** was found to be quite stable (no decomposition), but the others, **26b**, **26c**, and **28**, indicated 14, 8, and 12% decomposition, respectively. **27** was so unstable that a 63% decomposition was marked at the time of 56% completion of the racemization reacion.

Racemization, transamination, decarboxylation, replacement, condensation, and elimination of amino acids (depending on the system requirements in the biological systems) are mediated by coenzyme B_6 through a common intermediate, the Schiff base (**1a**).[1] Various chemical model systems for this coenzyme have been devised so far to elucidate the coenzyme function. It is convinced that (a) **1b** mimics all types of reactions *via* **1a**,[2-7] (b) 3-hydroxy-4-pyridinecarbaldehyde[8] and salicylaldehydes[9] may be pyridoxal substitutes, and (c) most of the nonenzymic reactions are catalyzed by metal ions[3c,4,9] and imidazole,[8] or in a cationic micelle without metal ions.[10] The distinct difference between the enzymic and nonenzymic reactions investigated so far is that the former proceeds in a stereospecific manner regarding amino acids (assisted by the protein backbone of the enzyme)[1b-f] and that a stereospecific catalyst is lacking in the latter.[11]



1a R=PO_3H_2
b R=H



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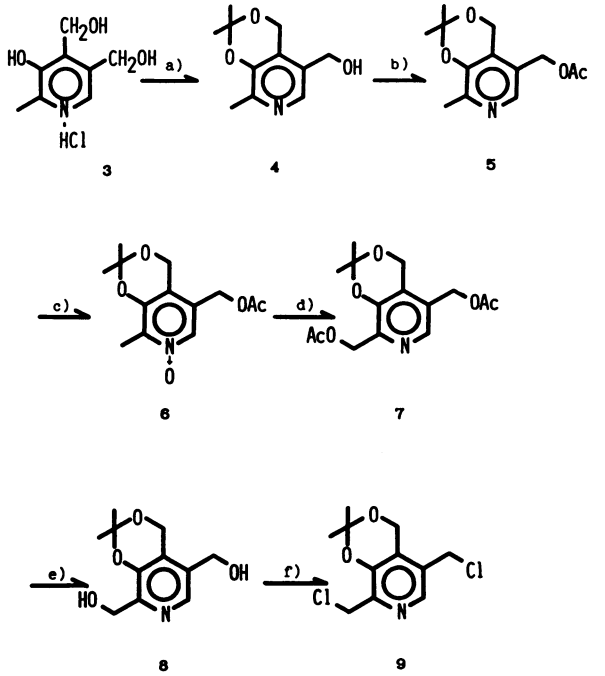
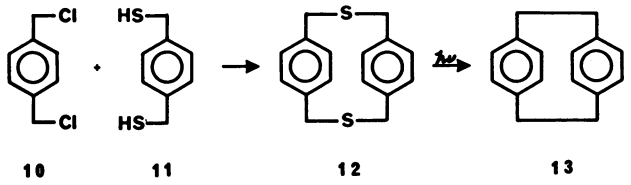
Along the line of our continuing interest in chemical congeners to B_6-coenzymes,[9c,12] we started to construct functionalized dithia(2,5)pyridinophanes **2** nearly a decade ago, which were expected to function as a stereospecific vitamin B_6-like catalyst through a mechanism. This includes a bridged chain with a specified length to provide a restricted rotation of the molecule (inducing planar chirality) and functional groups to act in the same way that the catalytic sites of vitamin B_6 do in biological systems. Through a series of experiments since then, this type of molecular design has been found to be very promising regarding alternative enantioselective catalysts. Evidence has been produced in successful studies concerning the optical resolution,[13a-d] the stereoselective racemization of α-amino acids,[13a] enantioselective transamination to α-keto acids,[13e-g] and the stereospecific α-deuteration of α-amino acids.[13h] The present report deals with a synthetic elaboration regarding the exploration of prototypes of pyridoxal-like (dithia)(2,5)pyridinophanes (which are routinely employed now). Also, the properties of the pyridinophanes have been scrutinized and an examination of catalytic activities for the racemization reaction of L-glutamate in terms of racemate catalysts (including the details of preliminary reports)[13a,i,j] was carried out.

Results and Discussion

Synthesis. Syntheses of the target molecules, **21**, **26**, and **27**, were achieved through sequences of



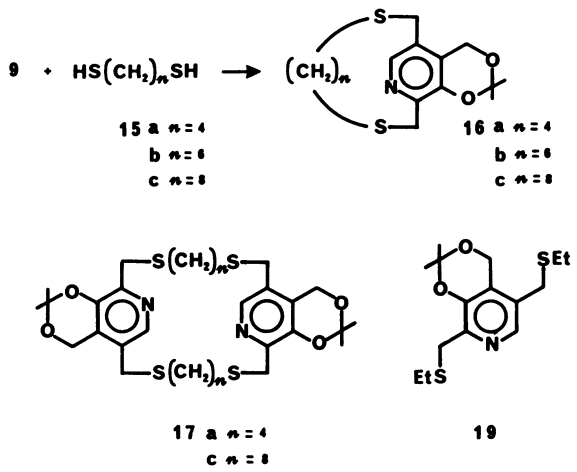
Scheme 1. Modification of C_2- and C_5-Positions of Pyridoxine; (a) i) acetone/HCl, ii) $NaHCO_3$ (Yield of **4**, 95%). (b) Ac_2O–Pyridine (**5**, 93%). (c) *m*-CPBA (**6**, 98%). (d) Ac_2O at 80—90 °C. (e) i) $NaOCH_3$/MeOH, ii) CO_2 (**8**, 83%). (f) i) $SOCl_2$, ii) $NaHCO_3$ (**9**, 98%).



Scheme 2. Preliminary Attempts of Coupling and Photochemical Extrusion of Sulfur Atoms.

reactions which will be described in the following order; (1) modification of the C_2- and C_5-positions of pyridoxine (Scheme 1), (2) the coupling reaction of the modified pyridoxine with α,ω-dithiol (Scheme 3), taking into account preliminary attempts (Scheme 2), (3) the photochemical extrusion of sulfur atoms from the coupling product (Scheme 4) and (4) oxidation with manganese dioxide (Scheme 5).

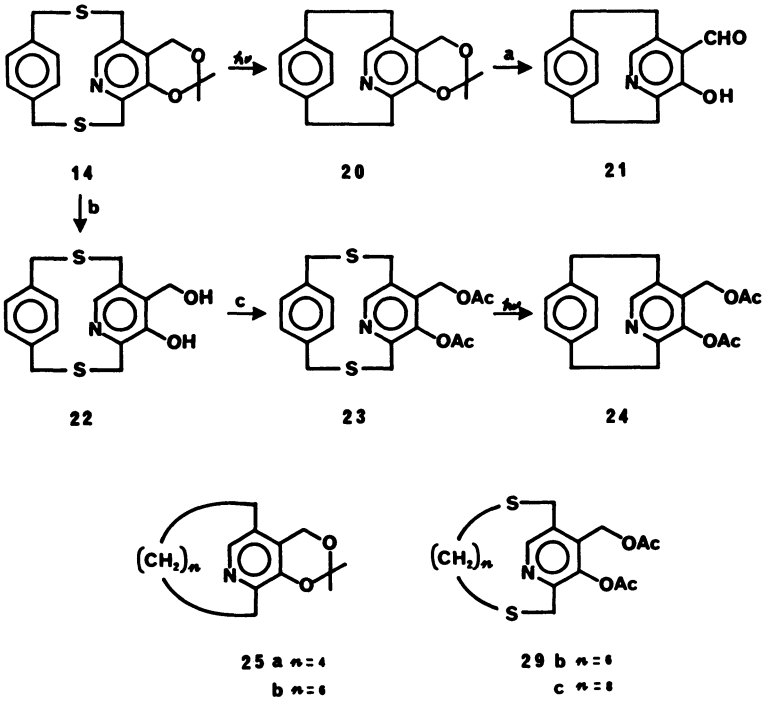
Modification of the C_2- and C_5-positions of pyridoxine to give the first stable key intermediate (**8**) was attained by a different route from that reported.[14] Pyridoxine hydrochloride (**3**) was treated with dry acetone–hydrogen chloride followed by neutralization with sodium hydrogencarbonate to yield 3,4′-*O*-isopropylidenepyridoxine (**4**)[15] which was converted by acetylation to 5′-acetyl-3,4′-*O*-isopropylidenepyridoxine (**5**) (Scheme 1). Oxidation of **5** with *m*-chloroperbenzoic acid (*m*-CPBA) gave the corresponding *N*-oxide (**6**) in high yield. This was rearranged in a mixture of chloroform and acetic anhydride to 2′-acetoxy-5′-acetyl-3,4′-*O*-isopropylidenepyridoxine (**7**). A hydrolysis of **7** with sodium methoxide in methanol was accomplished to afford a key intermediate, 2′-hydroxy-3,4′-*O*-isopropylidenepyridoxine (**8**)[14] in 70% total yield based on **3**. Another key intermediate **9** was quantitatively obtained by the direct chlorination of **8** with thionyl chloride, after several unsatisfactory attempts with triphenylphosphine–carbon tetrachloride[16] or with thionyl chloride–pyridine. Unfortunately, however, **9** was relatively unstable ($t_{1/2}$ *ca.* 1 d), and, thus, the next coupling reaction had to be executed soon after its preparation.



Scheme 3. The Coupling Reaction of the Modified Pyridoxine with α,ω-Dithiol.

In order to prepare bridged compounds connected by heteroatoms from **8** or **9** in good yield, several attempts using *p*-xylene derivatives as model compounds were performed (Scheme 2). The coupling trial employing **8** and α,α'-dichloro-*p*-xylene (**10**) mediated by sodium hydride as a base trigger in dioxane was quite unsuccessful under any condition. Then, in an effort to seek out the appropriate counterparts for the bridge resulted in finding efficient conditions to couple *p*-xylene-α,α'-dithiol (**11**)[17] with **10**. A mixture of **10** and **11** in ethanol was added to sodium ethylate in an ethanol solution (highly diluted).[18] The resulting 2,11-dithia[3.3]-paracyclophane (**12**)[19] had a sulfur atom juncture which may benefit the preparation of [2.2]paracyclophane (**13**) through a photochemical extrusion of the sulfur atoms.[20] Practically, **12** was photochemically desulfurized to **13** by triethyl phosphite in benzene with a high-pressure mercury lamp in 55% yield.

These perspectives through model reactions were put into practice by use of the dichlorides, **9** and **11**, which were successfully coupled to afford 17,18′-*O*-isopropylidene-17-hydroxy-18-hydroxymethyl-2,11-di-



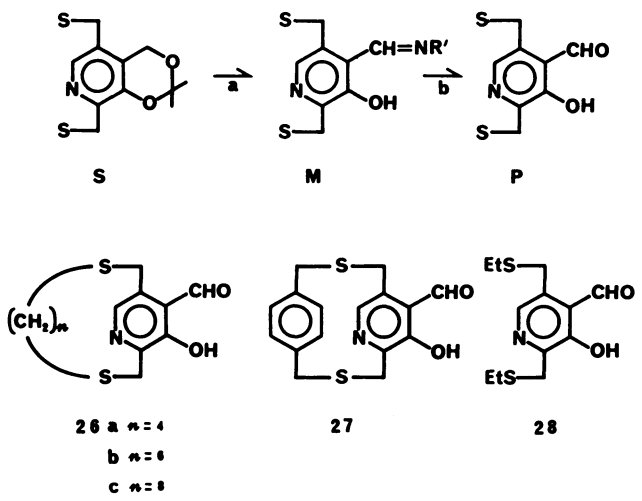
Scheme 4. Photochemical Extrusion of Sulfur Atoms from the Coupling Product; **a** $(C_6H_5)_3C^+BF_4^-$. **b** H_3O^+. **c** Ac_2O–pyridine.

thia[3]paracyclo[3](2,5)pyridinophane (**14**) by a high-dilution method. Likewise, **9** was condensed with α,ω-alkanedithiol (**15**) to give 2,(n+3)-dithia[m](2,5)-pyridinophane (n=4, 6, 8; m=n+4) (**16**) in fairly good yields, with the concomitant formation of the corresponding dimer **17**. The susceptibility of a reactive intermediate **9** to a nucleophilic attack was further exemplified in a condensation with ethanethiol (**18**) to yield 5′-deoxy-2′,5′-bis(ethylthio)-3,4′-*O*-isopropylidenepyridoxine (**19**) (95% based on **8**). This can be a reference open-chain compound relevant to **16a** for a comparison of the catalytic potency.

A photochemical extrusion of the juncture sulfur atoms from **14** yielded **20** (83%) under conditions similar to those aforementioned for **12**. The acetate derivative (**23**) which was obtained through the hydrolysis of **14** was likewise desulfurized to **24** (59%, based on **23**) (Scheme 4). However, this extrusion method regarding the sulfur atom was not satisfactorily applicable to cyclophanes, **16a** and **16b**, and their acetate derivatives **29b,c** (see Experimental). In addition, although the sulfur-extruded cyclophane (**20**) was directly oxidized to the corresponding aldehyde (**21**) by means of a reagent, triphenylmethylium tetrafluoroborate,[21] we had to abandon this type of paracyclophane as a target molecule because of the low yield of **21** (only 7%, based on **20**) and with an unexpected instability ($t_{1/2}$ *ca.* 15d). Therefore, we had to change our tentative target toward direct functionalization as embodied in pyridoxal without desulfurization and with the alternative oxidation method.

Manganese dioxide seemed promising as an alternative oxidant since numerous examples exemplified so far had shown the practical usefulness of this oxidant for the oxidation of α,β-unsaturated alcohols,[22] including pyridoxine derivatives.[23] Therefore, newly prepared active manganese dioxide[24] was applied to the oxidation of the acid-hydrolyzed products of the isopropylidene derivatives (**16b** and **16c**) which are potentially pyridoxine-like. Unfortunately, however, the product yields of **26b** and **26c** remained less than 18 and 16%, respectively. The reason for such low yields might be due to an inadequate preparation of the active manganese dioxide and/or chosen reaction conditions referring to those reported, and/or due to the substrate selectivity of manganese dioxide. A number of trials were carried out which resulted in the conclusion that all these possible causes operated together. The requisite construction of the tentative target encouraged us to develop a new preparative oxidation system.

Recently, we have reported that pyridoxine is oxidized in practical synthetic yield with commercially available manganese dioxide in the presence of a primary amine. We proposed that the oxidation proceeds on the amine-manganese dioxide complex[25] through a probable bimolecular oxidation mechanism.[26,27] The product prepared through the amine-mediated oxidation is the corresponding Schiff base



Scheme 5. Oxidation, Mediated by Primary Amine, with Commercial Manganese Dioxide; **a** i) H_3O^+, ii) $MnO_2/R'-NH_2$. **b** H_3O^+.

Table 1. Effect of amine on MnO_2 oxidation of **16b,c**

Amine[a]	Yield/% of M[b] 16b	16c	Yield/% of P[b] 16b	16c
—	—	—	18(39)[c]	16(71)
$ArNH_2$	49(1.3)	38(1)	—	—
DAPA	—	—	71(1)	51(2)

a) $ArNH_2$; *p*-phenetidine hydrochloride, DAPA; 3-(dimethylamino)propylamine. b) Based on **S**. c) Reaction time (h) is shown in parentheses.

of the pyridoxal. In addition, we have found that Schiff bases prepared from amines with strong basicity can transfer the methylene moiety to amines with relatively weaker basicity.[25] The trend of this transimination is, in principle, compatible to those found by Jencks[28a] and Leussing.[28b] The "basicity-dependent transimination" has been successfully applied to the direct *in situ* resolution of phanes in the treatment of a Schiff base prepared from phane and 3-(dimethylamino)propylamine (DAPA) with an amino sugar.[13a]

These findings made it possible to overcome synthetic problems in the oxidation of the present compounds. The pertinent results are given in Table 1, in which the same remarkable trend as found regarding the oxidation of pyridoxine[25] (that the product yields are increased 4—5 fold in the presence of a primary amine) is substantiated. Likewise, strained compounds like **14** and **16a** and an unstrained molecule **19** (*vide infra*) (**S**) were satisfactorily oxidized (Scheme 5) to corresponding pyridoxal-type compounds (**P**), **26a—c**, **27**, and **28**, by use of DAPA as a coexisting amine (Table 2). It is noteworthy that the juncture sulfur atoms were unaffected during the oxidation process.

Table 2. Synthesis of pyridoxal analogues from the corresponding acetals according to Scheme 5 by use of DAPA as a primary amine

S	Time[a]/h	P	Yield/%[b]
16a	1.5	**26a**	42
16b	1	**26b**	71
16c	2	**26c**	51
14	3	**27**	41
19	1.2	**28**	78

a) Reaction time for conversion of **S** to **M**. b) Based on **S**.

Properties. It is of special interest to scan the properties in the light of the determination of the possible upper-limit length for the restricted rotation depending on the length of the bridged chain and of the general catalytic activity of such modified pyridoxal compounds with heteraphane structures.

In contrast to carba(2,5)pyridinophanes,[29] dithia-(2,5)pyridinophanes offer certain advantages for ^{1}H-NMR spectral studies regarding the restricted rotation as well as the sulfur analogues of metacyclophane.[30] The incorporation of a sulfur atom into the β-position of the benzene ring not only simplified the methylene signals at the α-position by eliminating the complex spin-spin coupling with the other methylene groups, but also shifted them to a sufficiently lower field, allowing them to be observed separately from the other methylene signals.[30] Therefore, the existence of a restricted rotation can be simply judged from an observation of whether or not the proton signal of the α-methylene group of the pyridine ring is split into an AB quartet.

The chemical shifts and coupling constants of the focused α-methylene, formyl, and hydroxyl protons for the final products, **26a—c** and **27**, are summarized in Table 3, and refer to the related simpler compounds, **12**, **13**, and **28**. Chemical shifts of the signals with AB spin systems in Table 3 were adjusted, according to the general method of NMR analysis,[31] based on those observed on the spectral chart. Additionally, signal assignments were elaborated on the basis of numerous reference compounds synthesized through the present study. In Fig. 1, the representative spectral aspect of the methylene proton signals contiguous to heteroatoms and to the pyridine ring is illustrated for the isopropylidene derivatives, **14** and **16a—c**.

The appearance of the spin-spin couplings of the α-methylene protons of **26a,b**, and **27** split into AB quartets is a measure of the restricted rotation of the bridge chain due to an unsymmetrical magnetic field effect on those nuclei. As for the chemical shifts of formyl and hydroxyl protons, it was indicated that the greater conformational strain becomes, the more

Table 3. ^{1}H NMR data referred to methylene, formyl and hydroxyl protons[a)]

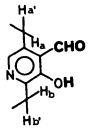


Table 3. ^{1}H NMR data referred to methylene, formyl and hydroxyl protons[a)]

Compd	Size	Ha-C-Ha'		Hb-C-Hb'		CHO	OH	Jaa'	Jbb'
12	14	3.82				—	—	—	—
13	12	3.10				—	—	—	—
26a	12	3.68	4.21	3.72	4.27	10.41	11.68	12.3	13.5
26b	14	3.76	4.17	3.78	4.20	10.56	11.68	12.8	14.0
26c	16	3.90		3.99		10.63	11.63	—	—
27	14	3.76	4.26	3.81	4.21	10.43	11.43	14.3	15.8
28		3.90		3.92		10.50	11.53	—	—

a) Measured in $CDCl_3$ at 24°C; δ in ppm and J in Hz.

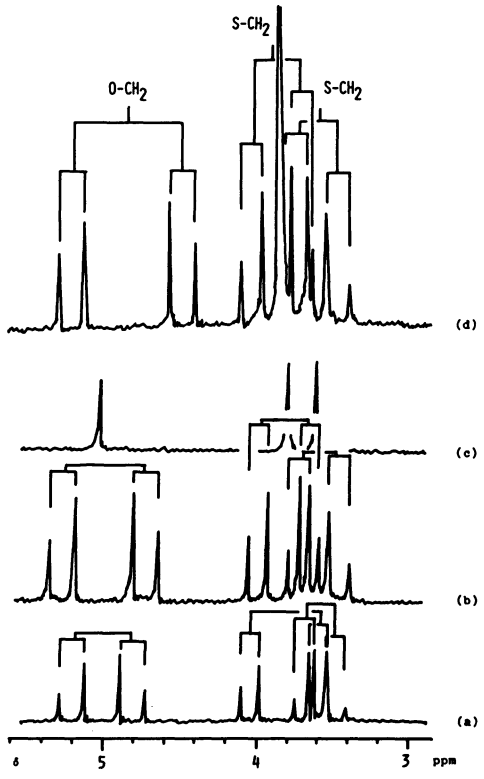


Fig. 1. ^{1}H NMR Spectra of the Methylene Protons between Hetero (O or S) Atoms and the Pyridine Ring; (a) for **16a** (n=4, 12-membered ring), (b) for **16b** (n=6, 14-membered ring), (c) for **16c** (n=8, 16-membered ring), and (d) for **14** (14-membered ring).

an upper-field shift is induced for the formyl proton of **26a—c**, but the hydroxyl protons behave independently. The α-methylene protons of the isopropylidene derivatives **14** and **16a—c** (Fig. 1) appear in a separate range, which benefits an ^{1}H-NMR analysis. The same tendency as that of the pyridoxal-type compounds **26a—c** and **27** is observable at a glance.

Table 4. The UV-VIS spectral data in ethanol; λ_{max} in nm (ε in $M^{-1}cm^{-1}$)

26a	**26b**	**26c**	**27**
207 (15000)	206.5 (16100)	208 (14100)	206.5 (19000)
227 (11500) sh	221.5 (13000) sh	223 (10400) sh	241 (8300) sh
247 (8700)	244 (8300) sh	300 (3900)	295 (2100) sh
313 (2800)	301.5 (3100)	348 (2100)	380 (2100)
364 (3800)	361.5 (3700)		

The investigation of the temperature dependence of the spin-spin interaction is a subject related to the practical optical resolution of enantiomers. For this purpose, the ^{1}H-NMR spectra of **14**, **16a,b**, and **26b** were recorded in $CDBr_3$ at 10 °C intervals up to 120 °C while monitoring the AB quartets as markers. Within the temperature range examined, all the AB quartets of the α-methylene protons remained uncolapsed together with unchanged chemical shift differences while participating in the spin-spin interaction. Thus, the conformation of the compounds with the AB quartet signals is found to be fairly rigid and the energy barrier for free rotation is estimated to be more than 15 kcal† mol^{-1}.[30] This suggests that these compounds could be resolved into each enantiomer by appropriate means. A congener of **26** has actually been resolved with an amino sugar.[13a,d]

The UV-VIS spectra of **26a—c** and **27** in ethanol are characterized by a ring strain (Table 4) as well as ^{1}H-NMR spectra. The absorption maxima appear-

† 1 cal_{th}=4.184 J.

Table 5. Racemization potency of pyridinophanes and related compounds for sodium hydrogen L-glutamate (pH 10.0 at 25±0.5 °C)

Catalyst	React. time /h	Final % racemi. completn	Time for 50% completn/h	$k_{obsd} \times 10^4$ min^{-1}	Catalyst dec/%
Pyridoxal	188	84	56	2.09	6.6 (288) [a]
26a	88	80	36	3.19	0 (325)
26b	96	65	37	3.13	14 (307)
26c	188	83	40	2.93	8 (305)
27	96	56	78	1.48	42 (243)
28	96	78	32	(3.58) [b]	12 (305)

a) λ_{max} used for O.D. change measurement. b) Estimated values, based on the plot.

ing at the longest wavelength show distinct red shifts with an augmentation of the extinction coefficient when the ring strain is increased. The red shifts are directly related to the sterically induced nonplanarity of the pyridine ring.[32] The tendency to increase the extinction coefficient with a shortening of the length of the carbon chain, may reflect the increment of the electron density around the formyl chromophore, which, in turn, may positively enforce the catalytic potency of these model compounds.

Catalytic Potency. The catalytic activities of the synthesized pyridinophanes, **26a—c** and **27**, were examined by a measure of the racemization ability for sodium hydrogen L-glutamate as a representative amino acid (chosen for its large rotatory power as in previous work).[9] These were referred to the less modified derivative **28** and pyridoxal as a standard reference. The reaction conditions were set, taking into account the catalyst solubility and those reported[9] (see Experimental). The analyzed results are collected in Table 5 and as a relative measure of catalytic activity, the times for 50% racemization completion are also listed. In addition, the evaluated apparent rate constants for **26b** and **28** are shown on the basis of less-scattered values of k_{obsd} (see Experimental). The results clearly reveal that **26a** is the best catalyst among those investigated. This showed superior properties to those of pyridoxal, with respect to catalytic activity (1.5 fold more active) and to stability (no decomposition) in contrast to an open-chain congener **28**. This compound is highly strained, as shown in ^{1}H-NMR and UV-VIS spectra and, thus, is a promising enantioselective catalyst. Structurally, the same is embodied in **26b** and **27**, but **27** is less active than pyridoxal and outstandingly labile, on one hand. On the other hand, **26b** might have a complex reaction mechanism (suggested by an observation of a nonlinear optical rotation change with considerable catalyst instability). It is of interest to note that less-strained or unstrained compounds, **26c** and **28**, are even more active than pyridoxal with a comparable decomposition each other.

In conclusion, the present results demonstrate that (a) the bridging between C_2- and C_5-positions by suitable chains afforded many advantages over natural vitamin B_6, especially, with respect to catalyst stability and catalytic effectiveness, (b) the π-donor-acceptor interaction between the bridged chain and the pyridine ring decreases the catalytic activity and catalyst stability, and (c) the torsion of the pyridine ring working as an electron sink has no effect on rate enhancement. It would be of interest to extend the present investigation to the construction of better model compounds which might intramolecularly provide suitable groups to efficiently affect the proton abstraction-addition process on the α-carbon of α-amino acid in a transition state.

Experimental

Apparatus. The IR spectra were obtained with a Shimadzu IR-27 spectrophotometer, the UV-VIS measurements (λ_{max}) with a Hitachi 124 spectrophotometer, ^{1}H-NMR spectra with a Varian HA-100D instrument, using TMS as an internal standard, and the optical-rotation measurements with a Perkin-Elmer 241MC polarimeter. The mass spectra (MS) and the exact mass measurements were obtained with a Japan Electron Optics Lab. Model JMS-OISG instrument. The melting points were recorded with a micro-melting apparatus, Yanagimoto Seisakusho, ser. No. 2647. The photochemical reaction was carried out with a high-pressure mercury lamp, UVL-100p (100 W), Rikoh Kagaku Co., Ltd. The elemental analyses were performed by the staff of the Organic Microanalysis Lab. in this Institute.

Materials. Pyridoxine hydrochloride, *m*-chloroperbenzoic acid, thionyl chloride, α,α'-dichloro-*p*-xylene (**10**), triphenylmethylium tetrafluoroborate, triethyl phosphite, 3-(dimethylamino)propylamine (DAPA), α,ω-alkanedithiols (**15a—c**) and ethanethiol were obtained commercially. The preparation of *p*-xylene-α,α'-dithiol (**11**) was performed according to a reported method;[17] 90% yield, colorless crystals, mp 42—44 °C (lit,[33] 46—47 °C). Pyridoxine was prepared by neutralization of the corresponding commercial hydrochloride with sodium hydrogencarbonate followed by azeotropic distillation of water with 1-propanol and by trituration into pyridine. For a separation of the products using column chromatography, Merck Art 7734 (E. Merck,

Darmstadt) silicagel was used. For the detection of the product and for monitoring the reaction by thin-layer chromatography (TLC), a Wakogel B-5 FM (Wako Pure Chem. Ind.) was employed. The following solvent systems were used for column chromatography and TLC unless otherwise stated; benzene:acetone=10:1 v/v (solvent BA1), 9:1 v/v (solvent BA2), 5:1 v/v (solvent BA3), 4:1 v/v (solvent BA4), 5:2 v/v (solvent BA5); chloroform:methanol=95:5 v/v (solvent CM1), 9:1 v/v (solvent CM2). Chemical shift (δ) and coupling constants (J) in ^{1}H-NMR spectrum (in $CDCl_3$) are shown in ppm and Hz, respectively.

Synthesis of 8 from 3 (Scheme 1). The acetonation of pyridoxine hydrochloride (**3**) was achieved by a method reported by Korytnyk and Ikawa[34] in 92% yield. The subsequent treatment of a suspended mixture of 55.1 g of 3,4′-*O*-isopropylidenepyridoxine hydrochloride, colorless crystals, mp 216—217 °C (dec) (lit,[15] 210—212 °C (dec). 217—218 °C (dec)[35]), in water with sodium hydrogencarbonate yielded 45.1 g (96%) of HCl free **4**, mp 118—120 °C (lit, 111—112 °C,[15] 113—115 °C,[35] 108—109 °C[36]), which, in turn, was acetylated by acetic anhydride–pyridine (1:1 v/v) at ambient temperature to give 5′-acetyl-3,4′-*O*-isopropylidenepyridoxine (**5**) in 93% yield, after a usual work-up; colorless liquid, R_f 0.5 (solvent BA3), IR (neat) $\nu_{C=O}$ 1740 cm^{-1}. The corresponding *N*-oxide (**6**) was obtained in 98% yield upon treatment of **5** with a slight molar excess of *m*-chloroperbenzoic acid in chloroform at ambient temperature. This was followed by neutralization with sodium acetate; colorless crystals, recryst, from diisopropyl ether, R_f 0.2 (benzene:acetone 2:1 v/v). In the mixed solution of chloroform and acetic anhydride (4:1 v/v) at *ca.* 50 °C, **6** was rearranged to 2′-acetoxy-5′-acetyl-3,4′-*O*-isopropylidenepyridoxine (**7**), R_f 0.8 (solvent CM1), in 98% yield with column chromatographic separation; colorless viscous liquid (R_f 0.5; chloroform:acetone 93:7 v/v), IR (neat) $\nu_{C=O}$ 1740 and ν_{st} 1420, 1380, 1365, 1220, 1060, 1025, and 855 cm^{-1}. At this stage, it was noted that the lower the reaction temperature was upon mixing an organic solvent such as $CHCl_3$, the better was the product yield and the darkening was less. The hydrolysis of **7** (3.05 g) with sodium (0.6 g) in methanol (40 ml) was followed by neutralization with solid carbon dioxide, then by the evaporation of the solvent and, subsequently, by filtration of the acetone solution, yielded 1.8 g (83%) of 2′-hydroxy-3,4′-*O*-isopropylidenepyridoxine (**8**), R_f 0.3 (solvent CM1); recryst. from acetone–diisopropyl ether, colorless needles, mp 119—122 °C (lit,[15] 110 °C); λ_{max} (EtOH) 281.5 nm; IR (KBr) ν_{OH} 3430, ν_{st} 1420, 1385, 1375, 1290, 1060, 1020, 1010, 900, 860, and 790 cm^{-1}.

Chlorination of 8. Chlorination with triphenylphosphine–carbon tetrachloride[16a] or DMF[16b] was unsuccessful. Then, several trials employing thionyl chloride–pyridine, changing the mole ratio 1:1 to 1:12, suggested that the greater the ratio becomes, the less the product yield of 5′-deoxy-2′,5′-dichloro-3,4′-*O*-isopropylidenepyridoxine (**9**). The reaction was monitored by TLC (R_f of **9**, 0.7 (solvent BA3)). Thus, it was eventually found that when 10—12 ml of thionyl chloride (cooled to 0 °C) was added all at once to 4.5 g of **8** (while being magnetically stirred in an iced-water bath). Stirring was continued for 30 min. The system was then equipped with a drying tube containing anhydrous calcium chloride and any excess of thionyl chloride was removed under reduced pressure. The mixture was neutralized by the addition of sodium hydrogencarbonate solution until no more carbon dioxide was generated and then extracted with ether. After a usual work-up, **9** was obtained in 91% yield (4.78 g) as yellow crystals; mp 89—91 °C. IR (KBr) ν_{st} 1415, 1385, 1380, 1305, 1280, 1250, 1205, 1135, 1060, 855, 760, and 715 cm^{-1}. On a smaller scale, the product yield became quantitative, by supressing decomposition during the work-up. However, **9** seemed to be not so stable that the next reaction was executed immediately after the preparation of **9**.

Attempts of Coupling and Photochemical Extrusion of Sulfur Atom (Scheme 2). Since the condensation of diol (**8**) with α,α'-dichloro-*p*-xylene (**10**) mediated by sodium hydride was unsuccessful in dioxane under any condition, the coupling of **10** with *p*-xylene-α,α'-dithiol (**11**) was examined under basic conditions. After 1.7 g (0.01 mol) of hot **10** in 20 ml of ethanol was rapidly added to a sodium ethylate solution prepared by 0.5 g (0.02 mol) of sodium in 50 ml of ethanol, containing 1.7 g (0.01 mol) of **11** the mixture was warmed for 3 h with stirring and precipitated a white solid (2.6 g) which was not the intended product. After it was filtered off, the filtrate contained a small amount of 2,11-dithia[3.3]paracyclophane (**12**), detected on TLC (R_f 0.6, benzene:cyclohexane 3:2 v/v). Thus, a 16-fold dilution[18] of the above reaction was carried out at ambient temperature to give 0.6 g (22%) of **12**, after chromatography with benzene; recryst. from benzene, mp 236.5—237.5 °C. Calcd for $C_{16}H_{16}S_2$: C, 70.54; H, 5.92; S, 23.54%. Found: C, 70.53; H, 5.70; S, 23.42%. MS *m/z* 272 (M^+) (base peak). ^{1}H-NMR ($CDCl_3$) δ=6.86 (8H, aromatic protons) and 3.82 (8H, $-CH_2-$). IR (KBr) ν_{S-CH} 1423; ν_{st} 1105, 850, 806, 758, 715, and 536 cm^{-1}. λ_{max} (EtOH) 255.5 nm.

According to a reported method,[20] a solution of 0.19 g of **12** and 20 ml of triethyl phosphite in 35 ml of benzene was irradiated using a high-pressure mercury lamp for 6 h while bubbling dry nitrogen gas. After the evaporation of the solvents *in vacuo*, the residue was recrystallized from ethanol to yield 80 mg (55%) of [2.2]paracyclophane (**13**) as colorless fine needles; mp 218—220 °C (lit,[37] 285—287 °C); MS *m/z* 208 (M^+) and 104 (base peak); λ_{max} (EtOH) 225 nm; R_f 0.8 (benzene:cyclohexane 3:2 v/v).

Coupling 9 with α,ω-Dithiols (Scheme 2). In a typical procedure, a mixture of 0.37 g (1.4 mol) of dichloride (**9**) and 0.3 g (1.76 mol) of dithiol (**11**) in 100 ml of ethanol was added (dropwise) over a period of 2.5 h to a 300-ml ethanol solution containing 0.1 g (4 mmol) of sodium in an ice-water bath while bubbling dry nitrogen gas. The mixture was then stirred overnight. After evaporating the ethanol, the residue was triturated with benzene and filtered. The filtrate was chromatographed on a silica-gel column eluted with benzene–acetone (7:2 v/v) then (5:2 v/v) to give 17-hydroxy-18-hydroxymethyl-17,18′-*O*-isopropylidene-2,11-dithia[3]paracyclo[3](2,5)pyridinophane (**14**) as colorless crystals; mp 194—196 °C. Calcd for $C_{19}H_{21}O_2S_2N$: C, 63.48; H, 5.89; S, 17.84; N, 3.90%. Found: C, 63.36; H, 5.92; S, 17.63; N, 3.75%. IR (KBr) ν_{st} 1423, 1406, 1383, 1372, 1295, 1244, 1200, 1135, 1059, 1049, 860, 725, and 543 cm^{-1}. λ_{max} (EtOH) (relative O.D. to the maximum absorption) 258—268 (broad, 0.95), 271.5 (0.97), 281 (1.0), and 306.5 (0.84) nm. ^{1}H-NMR ($CDCl_3$) δ=1.55 and 1.75 (3H each, s,

$C(CH_3)_2$) 3.51 and 3.75 (1H each, AB-q, J=14.9, -CH_2-S), 3.75, and 4.05 (1H each, AB-q, J=14.0, -CH_2-S), 4.53 and 5.24 (1H each, AB-q, J=16.5, -CH_2-O), 3.88 (4H, broad s, -SCH_2-C_6H_4-CH_2S), 6.95 (2H, broad d, J=8.0, Ar-H), 7.10 (2H, broad d, J=8.0, Ar-H), and 7.14 (1H, s, Ar_{py}-H). The spectral aspect of the methylene groups is depicted in Fig. 1. MS, metastable peaks appeared at m/z 138.2 for the fragmentation of m/z 197 to m/z 165 and at m/z 113.1 for m/z 166 to m/z 137.

The dropwise addition (3.5 h) of 1.9 g (7.3 mmol) of **9** and 0.82 g (6.6 mmol) of 1,4-butanedithiol (**15a**) in 100 ml of benzene to 400 ml of an ethanol solution containing 0.4 g (14 mmol) of sodium yielded 0.57 g (27% based on **8**) of **16a** and 0.68 g (19%, based on **8**) of the dimer of **16a**, (**17a**), after a similar work-up to the above was eluted with the solvent BA1 for column chromatography.

13-Hydroxy-14-hydroxymethyl-13,14′-*O*-isopropylidene-2,7-dithia[8](2,5)pyridinophane (**16a**); recryst. from diisopropyl ether as colorless crystals; mp 144.5—145.5 °C. R_f 0.55 (solvent BA1). Calcd for $C_{15}H_{21}O_2NS_2$: C, 57.84; H, 6.80; N, 4.50; S, 20.59%. Found: C, 57.59; H, 6.53; N, 4.50; S, 20.62%. IR (KBr) ν_{st} 1408, 1375, 1354, 1295, 1275, 1255, 1235, 1210, 1145, 1130, 1118, 1060, 1050, 855, 780, 730, 685, 665, and 565 cm^{-1}. λ_{max} (EtOH) (M^{-1} cm^{-1}); 211.5 (18900), 235sh (8100), and 303 (7700) nm. ^{1}H-NMR ($CDCl_3$); δ=1.61 (6H, s, $C(CH_3)_2$), 0.6—1.4 (4H, m, -CH_2-), 1.8—2.7 (4H, m, -CH_2-), 3.51 and 3.68 (1H each, AB-q, J=13.0, -CH_2S), 3.62 and 4.05 (1H each, AB-q, J=12.5, -CH_2S), 4.85 and 5.21 (1H each, AB-q, J=16.5, -CH_2O), and 7.81 (1H, s, Ar-H). The spectral aspect of the methylene signals is shown in Fig. 1. MS; m/z 311 (M+).

The corresponding dimer (**17a**), recryst. from benzene (minor) and diisopropyl ether (major); mp 149.5—150.5 °C. R_f 0.3 (solvent BA1). Calcd for $C_{30}H_{42}O_4N_2S_4$: C, 57.84; H, 6.80; N, 4.50; S, 20.59%. Found: C, 58.12; H, 6.68; N, 4.49; S, 20.59%. IR (KBr) ν_{st} 1410, 1375, 1293, 1250, 1200, 1135, 1063, 1050, and 845 cm^{-1}. λ_{max} (EtOH) (M^{-1} cm^{-1}), 209 (34200), 227.5sh (19000), and 290 (17200) nm. ^{1}H-NMR ($CDCl_3$) δ=1.55 (12H, s, -$C(CH_3)_2$), 1.4—1.6 (8H, m, -CH_2-), 2.2—2.6 (8H, m, -CH_2-), 3.51 (4H, s, -CH_2S), 3.75 (4H. s, -CH_2S), 4.95 (4H. s, -CH_2O), and 7.88 (2H, s, Ar-H). No signal shift or intensity change was observed until −30 °C in $CDCl_3$. MS: m/z 622 (M^+).

In a similar way, the reaction of 1.325 g (4.8 mmol) of 9 and 0.66 g (4.5 mmol) of 1,6-hexanedithiol (**15b**) in 100 ml of benzene with 400 ml of an ethanol solution containing two molar equiv. of sodium yielded 1.37 g (91%, based on **8**) of 2,9-dithia[10](2,5)pyridinophane (**16b**). This was isolated by silica-gel chromatography eluted with a solvent (BA1) as colorless crystals; R_f 0.5 (solvent BA1). mp 168—170 °C. Calcd for $C_{17}H_{25}O_2NS_2$: C, 60.14; H, 7.42; N, 4.13; S, 18.89%. Found: C, 59.88; H, 7.32; N, 3.86; S, 18.90%. IR (KBr) ν_{st} 1413, 1385, 1377, 1297, 1262, 1242, 1202, 1135, 1065, 1045, and 853 cm^{-1}. λ_{max} (EtOH) (M^{-1} cm^{-1}); 208 (19200), 228sh (8800), and 293 (8300) nm. ^{1}H-NMR ($CDCl_3$) δ=1.57 and 1.63 (3H each, s, -$C(CH_3)_2$), 0.4—1.4 (8H, m, -CH_2-), 1.8—2.7 (4H, m, -CH_2-), 3.50 and 3.73 (1H each, AB-q, J=13.5, -CH_2S), 3.66 and 4.04 (1H each, AB-q, J=12.5, -CH_2S), 4.77 and 5.29 (1H each, AB-q, J=16.5, -CH_2O), and 7.85 (1H, s, Ar-H). The spectral aspect of the methylene signals is depicted in Fig. 1.

Likewise, the reaction of 1.17 g (4.5 mmol) of **9** and 0.8 g (4.8 mmol) of 1,8-octanedithiol (**15c**) in 100 ml of benzene with 400 ml of an ethanol solution containing 0.21 g. (8.96 mmol) of sodium yielded 1.27 g (78%, based on **8**) of 2,11-dithia[12](2,5)pyridinophane (**16c**), 0.26 g (8%, based on **8**) of the dimer of **16c**, **17c** (as colorless crystals), and a pale-yellow viscous liquid. They were isolated by silica-gel column chromatography eluted with a solvent (BA1).

16c showed R_f 0.4 (solvent BA1); mp 68.5—70 °C. Calcd for $C_{19}H_{29}O_2NS_2$: C, 62.09; H, 7.95; N, 3.81; S, 17.44%. Found: C, 62.08; H, 7.82; N, 3.82; S, 17.48%. IR (neat) ν_{st} 1410, 1385, 1875, 1296, 1275, 1240, 1200, 1140, 1062, 1049, and 860 cm^{-1}. λ_{max} (EtOH) (M^{-1} cm^{-1}); 208.5 (18800), 226sh (9700), and 292 (8400) nm. ^{1}H-NMR ($CDCl_3$) δ=1.57 (6H, s, -$C(CH_3)_2$), 0.95—1.5 (12H, m, -$(CH_2)_6$-), 2.40 (2H, t, J=6.5, CH_2-CH_2S), 2.60 (2H, t, J=6.5, CH_2-CH_2S), 3.59 (2H, s, Ar-CH_2S), 3.78 (2H, s, Ar-CH_2S), 5.01 (2H, s, CH_2O), and 7.92 (1H. s, Ar-H). The spectral aspect of the methylene signals is depicted in Fig. 1.

17c revealed R_f 0.25 (solvent BA1); Calcd for $C_{38}H_{58}O_4N_2S_4$: C, 62.09; H, 7.95; N, 3.81; S, 17.44%. Found: C, 62.80; H, 7.93; N, 3.62; S, 16.36%. IR (neat) ν_{st} 1410, 1385, 1375, 1295, 1275, 1240, 1200, 1138, 1062, 1047, and 856 cm^{-1}. λ_{max} (EtOH) (M^{-1} cm^{-1}); 208.5 (33700), 224.5sh (18400), and 291 (16000) nm. ^{1}H-NMR ($CDCl_3$) δ=1.56 (12H, s, $C(CH_3)_2$), 1.0—1.6 (24H, m, -$(CH_2)_6$-), 2.38 (4H, t, J=7.0, CH_2-CH_2S), 2.52 (4H, t, J=7.0, CH_2-CH_2S), 3.56 (4H, s, Ar-CH_2S), 3.79 (4H, s, Ar-CH_2S), 4.98 (4H, s, Ar-CH_2O), and 7.89 (2H, s. Ar-H).

In a similar treatment of the dichloride (**9**), prepared from 1.0 g (4.45 mmol) of **8**, and 0.9 g (8.9 mmol) of ethanethiol (**18**) in 50 ml of benzene with 200 ml of ethanol solution containing 0.21 g (8.9 mmol) of sodium for 1 h, 5′-deoxy-2′,5′-bis(ethylthio)-3,4′-*O*-isopropylidenepyridoxine (**19**) was prepared in 95% (1.35 g) yield, based on **8**; R_f 0.75 (solvent BA2), as a pale-yellow viscous liquid. Calcd for $C_{15}H_{23}O_2NS_2$: C, 57.47; H, 7.40; N, 4.47; S, 20.45%. Found: C, 57.44; H, 7.33; N, 4.47 S, 20.14%. IR (neat) ν_{st} 1410, 1380, 1370, 1292, 1270, 1236, 1197, 1135, 1055, and 852 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ=1.22 (3H, t, J=7.3, SCH_2CH_3), 1.25 (3H, t. J=7.3, SCH_2CH_3), 1.54 (6H, s, $C(CH_3)_2$), 2.45 (2H. q, J=7.3, SCH_2CH_3), 2.57 (2H, q, J=7.3, SCH_2CH_3), 3.55 (2H, s, Ar-CH_2S), 3.79 (2H, s, Ar-CH_2), 4.95 (2H, s, Ar-CH_2O), and 7.89 (1H, s, Ar-H).

Photochemical Extrusion of Juncture Sulfur Atoms (Scheme 4). The irradiation of 1.93 g (5.37 mmol) of **14** in a mixture of 350 ml of triethyl phosphite and 150 ml of benzene in an inlet-jacket with a high-pressure mercury lamp at tap-water temperature for 17 h (bubbling dry nitrogen gas throughout) yielded 1.31 g (83%, based on **14**) of [2]paracyclo[2](2,5)pyridinophane (**20**). This was isolated upon evaporation of solvents from the reaction mixture, silica-gel column chromatography eluted with a solvent (BA2). This resulted in a pale-yellow liquid; R_f 0.35 (solvent BA5). MS m/z 295 (M^+) and base peaks at m/z 155 and 182. Exact mass measurement; Calcd for $C_{19}H_{21}O_2N$, 295.157; Found 295.151. IR (neat) ν_{st} 1407, 1383, 1372, 1281, 1242, 1200, 1137, 1058, 1043, 1024, and 858 cm^{-1}. λ_{max} (EtOH) (O.D.); 252sh (0.884); 280sh (0.411), 290 (0.525), and 313.5 (0.515) nm. ^{1}H-NMR ($CDCl_3$) δ=1.32 and 1.68 (3H each, s, $C(CH_3)_2$), 3.00 (center) (8H, AA′BB′-m, Ar-CH_2-CH_2-Ar), 4.43 and 4.62 (1H each AB-q, J=16.0, Ar-CH_2O), 6.74 (center) (4H, AA′BB′-m, Ar-H),

and 7.39 (1H, s, Ar_{py}-H).

To obtain 17-acetoxy-18-acetoxymethyl-2,11-dithia[3]-paracyclo[3](2,5)pyridinophane (**23**), 0.5 g (1.39 mmol) of **14** was heated at 50 °C for 30 min with 24 ml of 2M-HCl(1 M=1mol dm^{-3}), followed by neutralization by the addition of sodium hydrogencarbonate after cooling. The precipitate (**22**) was collected by filtration, washed several times with water and dried *in vacuo* over Drierite. The solid was treated with 10 ml of acetic anhydride in 30 ml of pyridine at the ambient temperature for 30 min, followed by evaporation under reduced pressure. After silica-gel chromatography eluted with benzene–acetone (85:15 v/v), the result was 0.45 g (80%, based on **14**) of **23**, as colorless viscous liquid which, then, became crystals by scrubbing; mp 115—116 °C, R_f 0.8 (solvent BA5). Calcd for $C_{20}H_{21}O_4S_2N$: C, 59.53; H, 5.25; N, 3.47; S, 15.89%. Found: C, 59.65; H, 5.29; N, 3.44; S, 15.71%. IR (neat) $\nu_{C=O}$ 1765 and 1740, ν_{st} 1425, 1407, 1370, 1220, 1185, 1027, and 680 cm^{-1}. λ_{max} (EtOH) (M^{-1} cm^{-1}); 207.5 (17800), 215sh (16400), 234sh (8100), 275 (3700), and 297.5sh (2200) nm. ^{1}H-NMR ($CDCl_3$) δ=1.95 (3H, s, $COCH_3$), 2.37 (3H, s, Ar-$OCOCH_3$), 3.81 and 4.09 (1H each, AB-q, J=16.1, Ar_{py}-CH_2-S), 3.83 (2H, s, Ar_{py}-CH_2S), 3.85 (2H, s, Ar-CH_2S), 3.89 (2H, s, Ar-CH_2S), 5.06 and 5.34 (1H each, AB-q, J=12.5, -CH_2O), 7.65 (1H, s, Ar_{py}-H), 6.93 (2H, broad d, J=8.0, Ar-H), and 7.07 (2H, broad d, Ar-H).

23 (0.4 g) in 250 ml of triethyl phosphite was irradiated at tap-water temperature (*ca.* 20 °C) for 9.5 h with a high-pressure mercury lamp. Dry nitrogen was bubbled throughout. After the removal of the solvent *in vacuo*, the residue was chromatographed on a silica-gel column eluted with a solvent (BA5) to give 0.2 g (59%, based on **23**) of 15-acetoxy-16-acetoxymethyl[2]paracyclo[2](2,5)pyridinophane (**24**) as colorless viscous liquid. MS; m/z 339 (M^+) and a base peak at m/z 155. Exact mass measurement; Calcd for $C_{20}H_{21}O_4N$, 339.147. Found, 339.151. IR (neat) $\nu_{C=O}$ 1765 and 1743, ν_{st} 1370, 1226, 1182, 1025, 970, 795, and 720 cm^{-1} λ_{max} (EtOH) (O. D.); 222 (2.73), 287 (0.437), and 307 (0.263) nm. ^{1}H-NMR ($CDCl_3$) δ=1.95 (3H s, $COCH_3$), 2.32 (3H, s, Ar-$OCOCH_3$), 3.09 (center) (8H, AA'BB'-m, -CH_2-CH_2-), 4.83 and 4.91 (1H each, AB-q, J=12.0, CH_2O), 6.71 (center) (4H, AA'BB'-m, Ar-H), and 7.75 (1H, s, Ar_{py}-H).

Photochemical reactions of **16a** (0.2 g) or **16b** (0.5 g) in a solution comprised of 50 ml of benzene and 200 ml of triethyl phosphite at *ca.* 20 °C (by circulating tap-water) under a nitrogen atmosphere for 4 h or 16 h, respectively, resulted in a slight disappearance of the starting materials (R_f 0.55 and 0.5, respectively) on TLC (solvent BA1). However, sulfur-extruded products are unisolable as a result of careful silica-gel chromatography. Then, both isopropylidene-cyclophanes (**16b,c**) were converted to the corresponding acetates **29b,c** in order to examine any alternative possibility regarding the photochemical extrusion of a sulfur atom.

16b (1.6 g, 4.7 mmol) was subjected to the same sequence of procedures as those for the preparation of **23** from **14** to yield 1.8 g (99%, based on **16b**) of 15-acetoxy-16-acetoxymethyl-2,9-dithia[10](2,5)pyridinophane (**29b**) as colorless crystals. These were recryst. from diisopropyl ether after a chromatographic separation by silica gel; R_f 0.6 (solvent BA1), mp 121—122 °C. Calcd for $C_{18}H_{25}O_4NS_2$: C, 56.37; H, 6.57; N, 3.65; S, 16.72%. Found: C, 56.43; H, 6.54; N, 3.55; S, 16.72%. IR (KBr) $\nu_{C=O}$ 1770 and 1745, ν_{st} 1440, 1405, 1377, 1362, 1301, 1215, 1178, 1153, 1055, 1034, 1010, and 830 cm^{-1}. λ_{max} (EtOH) (M^{-1} cm^{-1}); 205.5 (14400), 221sh (10300), 240sh (5400), and 285 (6100) nm. ^{1}H-NMR ($CDCl_3$) δ=0.4—1.4 (8H, m, -(CH_2)$_4$-), 1.8—2.7 (4H, m, -CH_2CH_2S), 2.03 (3H, s, CH_2OCOCH_3), 2.40 (3H, s, Ar-$OCOCH_3$), 3.79 and 4.11 (1H each, AB-q, J=14.0, Ar-CH_2S), 3.82 (2H, s, Ar-H), 5.22 and 5.41 (1H each, AB-q, J=13.0, Ar-CH_2O), and 8.22 (1H, s, Ar-H).

29b (1.0 g) was irradiated in a solution comprising 50 ml of benzene and 200 ml of triethyl phosphite for 9 h. Dry nitrogen was bubbled throughout. However, the obtained product still included one sulfur atom. 0.15 g of **29b** was recovered by silica-gel chromatography.

16c (0.75 g, 2 mmol) was acetylated by a sequence of procedures similar to those for **23** from **14** to afford 0.79 g (94%, based on **16c**) of 17-acetoxy-18-acetoxymethyl-2,11-dithia[12](2,5)pyridinophane (**29c**) as a pale-yellow viscous liquid. This was isolated by silica-gel column chromatography eluted with a solvent (BA1) (R_f 0.5). Calcd for $C_{20}H_{29}O_4NS_2$: C, 58.37; H, 7.10; N, 3.40%. Found: C, 58.88; H, 6.77; N, 3.41%. IR (neat) $\nu_{C=O}$ 1775 and 1745, ν_{st} 1370, 1220, 1180, and 1028 cm^{-1}. λ_{max} (EtOH) (O.D.); 220sh (0.642), 241sh (0.30), and 283.5 (0.374) nm. ^{1}H-NMR ($CDCl_3$) δ=0.8—1.5 (12H, m, -(CH_2)$_6$-), 2.01 (3H, s, CH_2OCOCH_3), 2.37 (2H, t, J=6.5, CH_2CH_2S), 2.50 (2H, t, J=6.5 CH_2CH_2S), 2.38 (3H, s, Ar-$OCOCH_3$), 3.76 (2H, s, Ar-CH_2S), 3.90 (2H, s, Ar-CH_4S), 5.27 (2H, s, Ar-CH_2O), and 8.33 (1H, s, Ar-H).

29c (0.55 g, 1.3 mmol) in 200 ml of triethyl phosphite was irradiated for 28 h and monitored by TLC. After a work-up followed by a careful silica-gel chromatography eluted with the solvent BA1 (R_f 0.5). gave 80 mg (16%) of a product (R_f 0.45) with a concomitant recovery of the starting material **29c** (50 mg). The product showed MS, m/z 379 (M^+). Exact mass measurement; Calcd for $C_{20}H_{29}O_4NS$, 379.181. Found, 379.188. IR (neat) $\nu_{C=O}$ 1775 and 1750, ν_{st} 1224, 1188, and 930 cm^{-1}. λ_{max} (EtOH) (O.D.); 238sh (0.4) and 277 (0.52) nm. These spectral data suggest that only one sulfur atom is extruded from the starting diacetate **29c**.

Attempts at the oxidation of **20** with triphenylmethylium tetrafluoroborate was carried out as follows:[21] a mixture of 0.95 g (1.2 mmol) of **20** and 3.2 g (3 mol equiv) of triphenylmethylium tetrafluoroborate in 100 ml of dichloromethane was stirred at the ambient temperature under a nitrogen atmosphere for 18 h. This was followed by hydrolysis with a saturated sodium hydrogencarbonate solution. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered through Celite (No. 545) and evaporated to dryness. The residue was chromatographed on a silica-gel column eluted with the solvent BA3 to yield 60 mg (7.4% based on **20**) of 15-hydroxy-16-formyl[2]paracyclo[2](2,5)pyridinophane (**21**) as yellow liquid; R_f 0.9 (benzene–acetone 3:2 v/v) and 0.8 (chloroform). MS; m/z 253 (M^+), 237 (M^+—16), and 225 (M^+—28) and base peaks at m/z 91 and 77. Exact mass measurement; Calcd for $C_{16}H_{15}O_2N$, 253.110. Found, 253.114. ^{1}H-NMR ($CDCl_3$) δ=9.94 (1H, s, CHO).

Oxidation with (Active) Manganese Dioxide (Scheme 5). General Procedure Prior to Oxidation. All the

pyridoxine-type cyclophanediols and related compounds were prepared from corresponding isopropylidene derivatives using acid hydrolysis as follows; the isopropylidene derivatives were heated at *ca.* 70 °C for 1—2 h with 2M-HCl (*ca.* 30 ml/g of the acetal) while being magnetically stirred. The reaction mixture, in which mostly diol hydrochloride was crystallized out as a white solid when the hydrolysis came closer to the terminal point (monitored by TLC), was neutralized with sodium hydrogencarbonate after cooling, followed by the evaporation of any water. The residue was triturated with ethanol and/or pyridine and filtered through Celite (No. 545). The filtrate was evaporated to dryness under reduced pressure to give a colorless solid which was subjected to manganese dioxide oxidation in the presence or absence of amine.

i) *Direct Oxidation with Active Manganese Dioxide.* Newly prepared active manganese dioxide (MnO_2*) (according to the method described by Attenburrow *et al.*)[24] was employed.

When the hydrolyzed product of **16b** (0.4 g, 1.18 mmol) was refluxed with MnO_2* (2.0 g) in chloroform (50 ml) for 23 h, followed by filtration through Celite (No. 545) on 3G sintered-glass filter, washed several times with hot ethanol and pyridine, the combined filtrate was evaporated to dryness and then chromatographed on a silica-gel column eluted with the solvent BA3 to yield 50 mg (14%, based on **16b**) of 16-formyl-15-hydroxy-2,9-dithia[10](2,5)pyridinophane (**26b**) with concomitant recovery of 40 mg (11%) of the starting diol. Obtained **26b** was recrystallized from acetone; R_f 0.75 (solvent BA5), mp 128—130 °C. Calcd for $C_{14}H_{19}O_2NS_2$: C, 56.53; H, 6.44; N, 4.71; S, 21.56%. Found: C, 56.64 H, 6.42; N, 4.39; S, 21.32%. IR (neat) $\nu_{C=O}$ 1653, ν_{st} 2930, 1375, 1295, 1240, 1195, 964, 728, 697, and 670 cm^{-1}. The UV-VIS data are shown in Table 4. ^{1}H-NMR data except for those listed in Table 3; 0.2—1.65 (8H, m, $-(C\underline{H}_2)_4-$), 1.95—2.75 (4H, m, $-CH_2C\underline{H}_2S$), and 7.95 (1H, s, Ar-$\underline{H}$).

When a mixture of the hydrolyzed product from **16b** (0.4 g, 1.18 mmol) and MnO_2* (1.6 g) in benzene (50 ml) was refluxed with an azeotropic removal of the resulting water using Dean-Stark apparatus for 39 h, followed by filtration and washing as mentioned above, **26b** was obtained by silica-gel chromatography in 18% (50 mg) yield, based on **16b**. with a recovery of 70 mg (20%) of the diol.

After the diol obtained from the hydrolysis of **16c** (0.43 g) was oxidized with MnO_2* (1.5 g) in a mixed solvent of pyridine (5 ml) and chloroform (50 ml) and refluxed for 71 h, the reaction mixture was treated as mentioned above and chromatographed on a silica-gel column eluted with the solvent BA2 to yield 60 mg (16%, based on **16c**) of 18-formyl-17-hydroxy-2,11-dithia[12](2,5)pyridinophane (**26c**) as a pale-yellow liquid. This was crystallized spontanously at the ambient temperature; R_f 0.65 (solvent BA2), mp 68.0—69.5 °C. Calcd for $C_{16}H_{23}O_2NS_2$: C, 59.04; H, 7.12; N, 4.30; S, 19.70%. Found: C, 59.05; H, 7.12; N, 3.90; S, 19.67%. IR (neat) $\nu_{C=O}$ 1655, ν_{st} 2930, 1380, 1248, 1234, and 870 cm^{-1}. The UV-VIS data are listed in Table 4. ^{1}H-NMR data except for those shown in Table 3 are 0.8—1.7 (12H, m, $-C\underline{H}_2)_6-$), 2.40 (2H, t, J=7.5, $CH_2C\underline{H}_2S$), and 8.04 (1H, s, Ar-$\underline{H}$).

ii) *MnO_2* Oxidation in the Presence of* p-*Phenetidine Hydrochloride.* After the diol prepared by the hydrolysis of **16b** (0.3 g, 0.88 mmol) was refluxed with *p*-phenetidine hydrochloride ($ArNH_2$) (0.3 g, 1.6 mmol) and MnO_2* (1.5 g) in a mixed solvent of pyridine (10 ml) and chloroform (40 ml) for 64 h, filtered cooled, through Celite (No. 545) mounted on a 3G sintered-glass filter (the filtrate was evaporated), the residue was chromatographed on a silica-gel column eluted with a solvent BA3 to give 160 mg (39%, based on **16b**) of the Schiff base (**30b**). It comprised **26b** and $ArNH_2$ as red brown crystals, recryst. from benzene-diisopropyl ether; R_f 0.65 (solvent BA3), mp 173—174 °C. Calcd for $C_{22}H_{28}O_2N_2S_2$: C, 63.43; H, 6.77; N, 6.72; S, 15.39%. Found: C, 63.43 H, 6.74; N, 6.66; S, 15.20%. IR (KBr) $\nu_{C=N}$ 1615, ν_{st} 2920, 1510, 1390, 1305, 1292, 1250, 1043, and 836 cm^{-1}. λ_{max} (EtOH) (M^{-1} cm^{-1}); 204 (16200), 228 (15800), 295 (4200), 340sh (10900), 361 (13200), 373 (13300), and 390sh (11000) nm. ^{1}H-NMR ($CDCl_3$) δ=0.55—1.4 (8H, m, $-(C\underline{H}_2)_4-$), 1.45 (3H t, J=6.95, $-CH_2C\underline{H}_3$), 2.0—2.7 (4H, m, $CH_2C\underline{H}_2S$), 3.80 and 4.25 (1H each, AB-q, J=12.78, Ar_{py}-$C\underline{H}_2S$), 3.82 and 4.04 (1H each, AB-q, J=14.03, Ar-$C\underline{H}_2S$), 4.10 (2H, q, J=6.95, $OC\underline{H}_2CH_3$), 6.99 (2H, d, J=8.9, Ar-$\underline{H}$), 7.40 (2H, d, J=8.9, Ar-$\underline{H}$), 7.88 (1H, s, Ar_{py}-$\underline{H}$), and 14.45 (1H, s, -O$\underline{H}$).

Diol (0.05 g, 0.167 mmol), prepared by the hydrolysis of **16b**, was oxidized with MnO_2* (0.5 g) in the presence of $ArNH_2$ (0.1 g, 0.53 mmol) in a mixed solvent of pyridine (5 ml) and benzene (20 ml) while removing the resulting water (using a the Dean-Stark tube), and gave **30b** (70 mg, 99% yield based on the diol).

Diol (**22**) (0.1 g, 0.313 mmol), prepared by the hydrolysis of **14**, was oxidized with MnO_2* (0.7 g) in the presence of $ArNH_2$ (0.1 g, 0.53 mmol) in benzene (30 ml), refluxed for 12 h while removing the resulting water (using a Dean-Stark tube). The residue, after a work-up as mentioned above, was chromatographed on a silica-gel column eluted with a solvent (BA3) to give 55 mg (40%, based on **22**) of the Schiff base (**31**) composed of **27** and $ArNH_2$, as yellow-red fine needles, recryst. from benzene-diisopropyl ether; R_f 0.6 (solvent BA3), mp 243.5—244.5 °C (dec). Calcd for $C_{24}H_{24}O_2N_2S_2$: C, 66.03; H, 5.54; N, 6.42; S, 14.69%. Found: C, 66.11; H, 5.59; N, 6.27; S, 14.63%. IR (KBr) $\nu_{C=N}$ 1615, ν_{st} 1510, 1390, 1300, 1255, and 820 cm^{-1}. λ_{max} (EtOH) (O.D.); 240sh (0.597), 295sh (0.205), 350sh (0.497), 364 (0.525), and 400sh (0.330) nm. ^{1}H-NMR ($CDCl_3$) δ=1.46 (3H, t, J=7.1, $OCH_2C\underline{H}_3$), 3.91 (2H, s, Ar-$C\underline{H}_2S$), 4.97 (2H, s, Ar-$C\underline{H}_2S$), 4.12 (2H, q, J=7.1, $OC\underline{H}_2CH_3$), 3.85 and 4.08 (1H each, AB-q, J=14.56, Ar_{py}-$C\underline{H}_2S$), 3.78 and 4.35 (1H each, AB-q, J=14.0, Ar_{py}-$C\underline{H}_2S$), 6.86—7.46 (8H, m, Ar-$\underline{H}$), 7.36 (1H, s, Ar_{py}-$\underline{H}$), 9.04 (1H, s, -C$\underline{H}$=N), and 14.13 (1H, s, -O$\underline{H}$).

iii) *Oxidation with Commercial MnO_2 in the Presence of Amines.* The hydrolysis of each acetal was performed under the conditions mentioned above. The oxidation was carried out under the similar conditions to those described in a previous report,[25] unless otherwise noted. When $ArNH_2$ was used as a coexisting amine, the product was isolated in the form of the corresponding Schiff base (**M** in Scheme 5) by means of silica-gel chromatography. When 3-(dimethylamino)propylamine (DAPA) was employed as a coexistent amine, the resulting Schiff base (**M** in Scheme 5) was hydrolyzed with 0.3 M-HCl, monitored by TLC, followed by extraction with benzene-ethyl acetate. It was then isolated in the form of the corresponding pyridoxal-

type compound (**P** in Scheme 5) by means of silica-gel chromatography.

Diol (**22**), prepared by the hydrolysis of **14** (0.85 g, 2.36 mmol), was oxidized for 3 h with commercial MnO_2[38] (5 g) in the presence of DAPA (1.5 ml) in a mixed solvent of benzene (50 ml) and pyridine (20 ml). This was followed by filtration through Celite (No. 545), washing with hot pyridine, and evaporation of the filtrate. The residue was hydrolyzed with 0.3 M-HCl (40 ml) in benzene–ethyl acetate (1:1 v/v) (20 ml) for 40 min, carefully monitored by TLC (solvent BA2, R_f 0.4 for **27**, and solvent CM2, R_f 0.4 for the Schiff base **M**). The organic layer was separated and passed through a short column to remove the amine and residual water eluted with a solvent (BA2). The eluate was further chromatographed on a silica-gel column to yield 0.31 g (41%, based on **14**) of 18-formyl-17-hydroxy-2,11-dithia-[3]paracyclo[3](2,5)pyridinophane (**27**) as pale-yellow crystals; mp 218—219 °C (start browning near at 204 °C and then decomposed). Calcd for $C_{16}H_{15}O_2NS_2$: C, 60.54; H, 4.76; N, 4.41; S, 20.20%. Found: C, 60.43; H, 4.82; N, 4.39; S, 20.12%. IR (KBr) $\nu_{C=O}$ 1645, ν_{st} 1423, 1410, 1377, 1250, 970, and 723 cm^{-1}. The UV-VIS data are listed in Table 4. ^{1}H-NMR data except for those collected in Table 3 are 3.84 (2H, s, Ar-C$\underline{H}_2$S), 6.84—7.16 (4H, m, Ar-$\underline{H}$), and 7.42 (1H, s, Ar_{py}-$\underline{H}$).

Diol, prepared by the hydrolysis of **16a** (1.1 g, 3.54 mmol), was oxidized with MnO_2 (7.0 g) in the presence of DAPA in a mixed solvent of benzene (50 ml) and pyridine (20 ml) for 1.5 h, followed by filtration, washing with hot pyridine, and an evaporation of the filtrate. The residue in the benzene–ethyl acetate (1:1 v/v) (20 ml) was hydrolyzed with 0.3 M-HCl (60 ml), carefully monitored by TLC (solvent BA2, R_f 0.6 for **26a** and solvent CM2, R_f 0.4 for the Schiff base **M**). The organic layer was treated using the method mentioned above and by a chromatographic separation with silica gel eluted with a solvent (BA4), 0.4 g (42%, based on **16a**) of 14-formyl-13-hydroxy-2,7-dithia-[8](2,5)pyridinophane (**26a**) was obtained as pale-yellow crystals. These were spontaneously crystallized; mp 118—119.5 °C. Calcd for $C_{12}H_{15}O_2NS_2$: C, 53.51; H, 5.61; N, 5.20; S, 23.80%. Found: C, 53.74; H, 5.64; N, 5.03; S, 23.37%. IR (neat) $\nu_{C=O}$ 1655, ν_{st} 1385, 1297, 1240, 1223, 1110, 967, 755, 695, and 675 cm^{-1}. The UV-VIS data are listed in Table 4. ^{1}H-NMR data except for those listed in Table 3; 0.7—1.4 (4H, m, -(C$\underline{H}_2$)$_2$-), 1.6—2.8 (4H, m, SC$\underline{H}_2$C$\underline{H}_2$), and 7.87 (1H, s, Ar_{py}-$\underline{H}$).

Diol, prepared by the hydrolysis of **16b** (1.09 g, 3.22 mmol), in the mixed solvent of benzene (50 ml) and pyridine (20 ml) was oxidized with MnO_2 (7.0 g) in the presence of DAPA (2 ml) for 1 h. This was followed by the hydrolysis of the Schiff base (**M**) with 0.3 M-HCl and a similar work-up to that described above. This yielded 0.68 g (71%, based on **16b**) of **26b**; physical data and elemental analyses are described in section i) of this section.

Diol, propared by the hydrolysis of **16c** (1.14 g, 3.1 mmol), in the mixed olvent of benzene (50 ml) and pyridine (18 ml) was oxidized with MnO_2 (3.5 g) in the presence of DAPA (1.0 ml) for 2 h. This was followed by a similar work-up to that described above and yielded 0.48 g (51%, based on **16c**) of **26c**; physical data and elemental analyses are described in section i) of this section.

Diol, prepared by the hydrolysis of **16c** (0.27 g, 0.825 mmol), in benzene (30 ml), was oxidized with MnO_2 (0.72 g) in the presence of $ArNH_2$ (0.31 g, 1.65 mmol) for 1 h. This produced 0.14 g (38%, based on **16c**) of a Schiff base (**M**) composed of **26c** and $ArNH_2$. This was chromatographically isolated with eluting a solvent (BA3); R_f 0.7 (solvent BA3).

The oxidation of the diol, prepared by the hydrolysis of **16b** (1.33 g, 4.48 mmol), in benzene (100 ml) with MnO_2 (4.6 g) in the presence of $ArNH_2$ (1.7 g, 8.89 mmol) yielded 0.9 g (49%, based on **16b**) of the Schiff base (**M**) comprising **26b** and $ArNH_2$; physical data and elemental analyses are described in section ii) of this section.

The oxidation of the diol, prepared by the hydrolysis of **19** (1.26 g, 4 mmol), with MnO_2 (7 g) in the presence of DAPA (2 ml) in the mixed solvent of benzene (50 ml) and pyridine (20 ml) for 1.2 h, followed by the hydrolysis of the Schiff base (**M**) with 0.3 M-HCl and a similar work-up to that described for the preparation of **26a**. This yielded 0.85 g (78%, based on **19**) of 5′-deoxy-2′,5′-bis(ethylthio)pyridoxal (**28**), as yellow viscous liquid, after chromatography; R_f 0.8 (solvent BA2). Calcd for $C_{12}H_{17}O_2NS_2$: C, 53.11; H, 6.31; N, 5.16; S, 23.63%. Found: C, 53.22; H, 6.24; N, 5.14; S, 23.23%. ^{1}H-NMR ($CDCl_3$) δ=1.25 (6H, t, J=7.5, $SCH_2C\underline{H}_3$), 2.51 (2H, q, J=7.5, $SC\underline{H}_2CH_3$), 2.60 (2H, q, J=7.5, $SC\underline{H}_2CH_3$), 3.90 (2H, s, Ar_{py}-C$\underline{H}_2$S), 3.92 (2H, s, Ar_{py}-C$\underline{H}_2$S), 7.98 (1H, s, Ar_{py}-$\underline{H}$), 10.50 (1H, s, -C$\underline{H}$O), and 11.53 (1H, s, -O$\underline{H}$). IR (neat) $\nu_{C=O}$ 1655, ν_{st} 1380, 1243, and 968 cm^{-1}.

Racemization Reaction. A 0.03 M-borate buffer (pH 10.0) was prapared as follows; 5.73 g (15 mmol) of sodium borate·10H_2O was dissolved in 300 ml of water. A part (60 ml) of the solution was made to be pH 10.0 by adding *ca.* 35 ml of a 0.1 M-NaOH solution and allowed to stand overnight. Then, the pH was readjusted to be 10.0 by adding a 0.1 M-NaOH solution (to become 100 ml).

Sodium hydrogen L-glutamate (18.7 g, 0.1 mol) and 0.5 g (2 mmol) of copper(II) sulfate·5H_2O was mixed in a small amount of water. Then 2 M-NaOH was added to produce a pH of 10. This was then allowed to stand overnight. Then, total volume of the solution was made to be 100 ml by the addition of water and 2 M-NaOH (readjusting the pH to 10.0).

A catalyst solution was prepared as follows; 0.5 mmol of a catalyst was dissolved into a 0.03 M-borate buffer (50 ml) and the pH was readjusted to be 10.0 by adding 2 M-NaOH. Then, the mixture was made to be 100 ml by the addition of *ca.* 50 ml of ethanol.

In a thermostated water bath at 25±0.5 °C, a 2 ml aliquot of an amino acid solution containing copper(II) sulfate (a.a. 1 M, Cu^{+2}, 2×10^{-2} M, pH 10 (NaOH), 25 °C) and a 5 ml aliquot of a catalyst solution (5×10^{-3} M, pH 10 (0.03 M borate buffer), 25 °C) was withdrawn from each stock solution using a pipet. These were mixed in a test tube equipped with a glass stopper and sealed (final molar ratio; a.a.:Cu^{+2}:catalyst=80:1.6:1). The degree of the optical rotation (α_t) was recorded in a standard cell with sodium D-line (589 nm) when the racemization reaction was terminated (every 8 h by the addition of 6 M-HCl all at once). In cases where we found precipitate in a terminated solution, it was filtered through Celite (No. 545) mounted on a 3G4 sintered-glass filter. The filtrate was used for an optical-rotation measurement. The measurement of α_t

continued until the racemization yield (calculated using 100 $(\alpha_0-\alpha_t)/\alpha_0$) became 56—84% (in ten to seventeen aliquots). α_0 is the average magnitude of the initial and the final optical rotation of the amino acid solution in the absence of catalyst. This showed almost no observable difference. The apparent rate constants (k_{obsd}) were calculated (using $2.30(\log \alpha_0-\log \alpha_t)/60t$). It was assumed that the reaction obeys first-order kinetics. The catalyst stability (decomposition percent) was checked by measuring the optical-density change at several specific absorption maxima for a 25-fold diluted aliquot of the reaction mixture terminated by the addition of 6 M-HCl (in the range of 210—450 nm).

In the case of pyridoxal, a plot of $(\log \alpha_0-\log \alpha_t)$ *vs.* time was linearly correlated for 56 h (50% racemization completion). Then the slope was decreased slowly with a linear correlation for 188 h (84% completion, 6.6% decomposition of catalyst at 288 nm). In the case of **27**, the same plot showed a linear relationship for up to 64 h (43% completion) and then leveled off (linearly) for 96 h (56% completion, 42 and 63% decomposition at 243 and 396 nm, respectively). The same plot for **26** was linearly correlated perfectly through measurements lasting 96 h (80% completion, zero percent decomposition at 325 nm). However, **26c** showed the same propensity as that of pyridoxal with a linear relation for 56 h (62% completion). Then it showed a decreased slope until an elapsed time of 188 h (83% completion, 8% decomposition at 305 nm). Additionally, the same plot of **26b** and **28** partly showed a linear correlation (but totally nonlinear) until 96 h (70 and 76% completion respectively, 14 and 26% decomposition at 307 and 385 nm for **26b**, and 12% decomposition at 304.5 nm for **28**, respectively). The reaction of **26c**, **27**, and **28** proceeded with the formation of a preciptate which could be dissolved by the final addition of 6 M-HCl.

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References

1) a) E. E. Snell and S. J. DiMari, "The Enzyme," 3rd ed, ed by P. D. Boyer, Academic Press, New York (1970), Vol. 2, pp. 335; b) E. A. Boeker and E. E. Snell, *ibid.*, 3rd ed, (1972), Vol. 6, pp. 217; c) E. Adams, *ibid.*, 3rd ed, (1972), Vol. 6, pp. 479; d) L. Davis and D. E. Metzler, *ibid.*, 3rd ed, (1972), Vol. 7, pp. 33; e) A. E. Braunstein, *ibid.*, 3rd ed, (1973), Vol. 9, pp. 379; f) C. Walsh, *Ann. Rev. Biochem.*, **47**, 881 (1978).

2) J. Olivard, D. E. Metzler, and E. E. Snell, *J. Biol. Chem.*, **199**, 669 (1952).

3) a) E. E. Snell and W. T. Jenkins, *J. Cell. Comp. Physiol.*, **54**, Suppl., 1, 161 (1959); b) E. E. Snell, *J. Am. Chem. Soc.*, **67**, 194 (1945); c) D. E. Metzler and E. E. Snell, *ibid.*, **74**, 979 (1952); d) D. E. Metzler, M. Ikawa, and E. E. Snell, *ibid.*, **76**, 648, (1954); e) J. B. Longenecker, M. Ikawa, and E. E. Snell, *J. Biol. Chem.*, **226**, 663 (1957).

4) J. B. Longenecker and E. E. Snell. *J. Am. Chem. Soc.*, **79**, 142 (1957).

5) D. E. Metzler and E. E. Snell, *J. Biol. Chem.*, **198**, 353 (1952).

6) D. E. Metzler, J. B. Longenecker, and E. E. Snell, *J. Am. Chem. Soc.*, **75**, 2786 (1953) and **76**, 639 (1954).

7) a) G. D. Kalyankar and E. E. Snell, *Biochemistry*, **1**, 594 (1962); b) E. Werle and W. Koch, *Biochem. Z.*, **1949**, 319; c) J. W. Thanassi and J. S. Fruton, *Biochemistry*, **1**, 975 (1962).

8) a) T. C. Bruice and R. M. Topping, *J. Am. Chem. Soc.*, **85**, 1480 and 1488 (1963); b) T. C. French, D. C. Auld, and T. C. Bruice, *Biochemistry*, **4**, 77 (1965); c) J. W. Thanassi, A. B. Butler, and T. C. Bruice, *ibid.*, **4**, 1465 (1965); d) D. S. Auld and T. C. Bruice, *J. Am. Chem. Soc.*, **89**, 2083, 2090, and 2098 (1967).

9) a) K. Ohno. I. Sasaji, and M. Hara, Japan Kokai Pat., 295110 (1961); b) S. Yoshikawa, K. Kuga, Y. Ueda, M. Goto, and H. Sugiyama, *Kogyo Kagaku Zasshi*, **70**, 105 (1967); c) M. Ando and S. Emoto, *Bull. Chem. Soc. Jpn.*, **42**, 2624 (1969).

10) H. Kondo, J. Kikuchi, and J. Sunamoto, *Tetrahedron Lett.*, **24**, 2403 (1983).

11) a) Incidental induced stereoselective transamination, owing to diastereoisomeric chelate complex of **1b**, is reported; J. B. Longenecker and E. E. Snell, *Proc. Nat. Acad. Sci. U. S. A.*, **42**, 221 (1956); b) After this work had been completed, publication has been retarded by special reasons. In the meantime, several interesting articles related to stereoselective catalyst based on the independent design of vitamin B_6 derivatives have been reported; S. C. Zimmerman and R. Breslow, *J. Am. Chem. Soc.*, **106**, 1490 (1984) and references cited therein.

12) M. Iwata and S. Emoto, *Bull. Chem. Soc. Jpn.*, **47**, 1687 (1974) and **49**, 1163 (1976).

13) a) H. Kuzuhara, M. Iwata, and S. Emoto, *J. Am. Chem. Soc.*, **99**, 4173 (1977); b) T. Sakurai, H. Kuzuhara, and S. Emoto, *Acta Crystallogr. Sec. B*, **35**, 2984 (1979); c) M. Ando, Y. Tachibana, and H. Kuzuhara, *Bull. Chem. Soc. Jpn.*, **55**, 829 (1982); d) Y. Tachibana, T. Komatsu, M. Ando, and H. Kuzuhara, *ibid.*, **57**, 237 (1984); e) H. Kuzuhara, T. Komatsu, and S. Emoto, *Tetrahedron Lett.*, **1978**, 3563; f) Y. Tachibana, M. Ando, and H. Kuzuhara, *Chem. Lett.*, **1982**, 1765 and 1769; g) *idem, Bull. Chem. Soc. Jpn.*, **56**, 2263 (1983); h) *ibid.*, **56**, 3652 (1983); i) M. Iwata, H. Kuzuhara, and S. Emoto, *Chem. Lett.*, **1976**, 983; j) M. Iwata and H. Kuzuhara, *ibid.*, **1981**, 5.

14) W. Korytnyk, S. C. Srivastava, N. Angelino, P. G. G. Potti, and B. Paul, *J. Med. Chem.*, **16**, 1096 (1973).

15) W. Korytnyk and W. Wiedeman, *J. Chem. Soc.*, **1962**, 2531.

16) a) J. M. Downie, J. B. Holms, and J. B. Lee, *Chem. Ind. (London)*, **1966**, 900; b) J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **37**, 2289 (1972).

17) C. F. Horn, F. Hostettler, and N. R. Eldred, U. S. Pat., 2696387 (1961); *Chem. Abstr.*, **55**, P 27218d (1961).

18) R. H. Michell, T. Ohtsubo, and V. Boekelheide, *Tetrahedron Lett.*, **1975**, 219.

19) See for nomenclature: F. Voegtle and P. Neumann, *Tetrahedron Lett.*, **1969**, 5329; *Tetrahedron*, **26**, 5847 (1970).

20) a) Boeckelheide, I. D. Reingold, and M. Tuttle, *J. Chem. Soc., Chem. Commun.*, **1973**, 406; b) J. Bruhin and W. Jenny, *Tetrahedron Lett.*, **1973**, 1215.

21) D. H. R. Barton, P. D. Magnus, G. Smith, G.

Streckert, and D. Zurr, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 542.

22) A. J. Fatiadi, *Synthesis*, **1976**, 65 and 133 and references cited therein.

23) a) D. Heyl, *J. Am. Chem. Soc.*, **70**, 3434 (1948); b) A. N. Wilson and S. A. Harris, *ibid.*, **73**, 4693 (1951).

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

25) M. Iwata, *Bull. Chem. Soc. Jpn.*, **54**, 2835 (1981).

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

27) a) H. Kwart and T. J. George, *J. Org. Chem.*, **44**, 162 (1979); b) I. M. Goldman, *ibid.*, **34**, 3289 (1969); c) T. K. Hall and P. R. Story, *J. Am. Chem. Soc.*, **89**, 6759 (1967).

28) a) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 826 (1962); b) S.-H. Weng and D. L. Leussing, *ibid.*, **105**, 4082 (1983).

29) H. Gerlach and E. Huber, *Helv. Chim. Acta*, **51**, 2027 (1968).

30) T. Sato, M. Wakabayashi, M. Kainosho, and K. Hata, *Tetrahedron Lett.*, **1968**, 4185.

31) W. J. Emseley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, London (1965), pp. 310.

32) N. L. Allinger, L. A. Freiberg, R. B. Hermann, and M. A. Miller, *J. Am. Chem. Soc.*, **85**, 1171 (1963).

33) A. Koetz, *Ber.*, **33**, 729 (1900).

34) W. Korytnyk and M. Ikawa, "Methods in Enzymology," ed by D. B. MaCormick and L. D. Wright, (1970), Vol. 18 part A, pp. 527.

35) A. Cohen and E. G. Hughes, *J. Chem. Soc.*, **1952**, 4383.

36) J. Baddiley and A. P. Mathias, *J. Chem. Soc.*, **1952**, 2583.

37) D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, **73**, 5691 (1951).

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