Characterization of a Product Derived from the 1-Methyl-4-phenyl-2,3-dihydropyridinium Ion, a Metabolite of the Nigrostriatal Toxin 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

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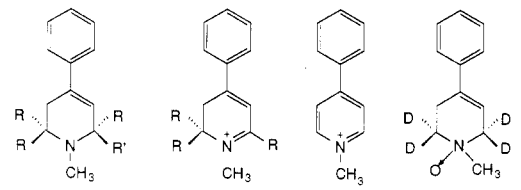
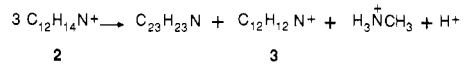
When incubated in aqueous pH 7.4 buffer, 1-methyl-4-phenyl-2,3-dihydropyridinium ($MPDP^+$) perchlorate is transformed to a product ($C_{23}H_{23}N$) by a pathway that involves a net two-electron reductive dimerization reaction combined with a deamination step. Analysis of the ^1H and ^{13}C NMR spectra of this product together with the ^1H NMR spectra of the $C_{23}H_{22}DN$ and $C_{23}H_{16}D_7N$ products obtained from the corresponding reaction of $MPDP^+$ in D_2O and the reaction starting with $MPDP^+$-*2,2,6-d*$_3$, respectively, has led us to propose the structure of this product as 2-methyl-5-methylene-4a,6-diphenyl-2,3,4,4a,5,8-hexahydroisoquinoline. A rational pathway to this compound involves initial Diels–Alder dimerization followed by a ring opening carbon–nitrogen bond cleavage step to generate the partially reduced isoquinoline ring system. Elimination of methylamine forms the terminal olefin while a hydride transfer reaction, which is coupled to the oxidation of 1 mol of $MPDP^+$ (as the corresponding free base) to the pyridinium species, generates the final product.

Introduction

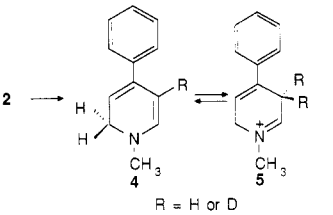
The tertiary allylamine 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, **1**) is biotransformed in a reaction catalyzed by monoamine oxidase B (MAO-B) to species that cause the selective degeneration of nigrostriatal neurons, giving rise to a Parkinsonian syndrome in man and nonhuman primates.[1] The two-electron oxidation product formed in this reaction, the 1-methyl-4-phenyl-2,3-dihydropyridinium ion $MPDP^+$ (**2**), undergoes spontaneous disproportionation to yield the corresponding pyridinium species MPP^+ (**3**), the putative ultimate neurotoxin,[2] and MPTP.[3] Furthermore, $MPDP^+$ undergoes a spontaneous reaction in pH 7.4 buffer that leads to the formation of methylamine via an unknown route.[4]



In an effort to characterize further the chemical breakdown products of this MAO-B-generated metabolite, we have examined extracts of aqueous $MPDP^+$ incubation mixtures by HPLC and have observed in addition to the disproportionation reaction, which accounts for about 75% of the starting material, the time-dependent formation of a product with relatively nonpolar chromatographic characteristics. The diode array UV spectrum of this product (λ_{max} 242 nm) was essentially identical with that of MPTP (λ_{max} 243 nm).[5] High-resolution EI mass spectral analysis established its empirical formula as $C_{23}H_{23}N$. The only significant fragment ion observed in the spectrum (*m/z* 234) corresponds to the loss of a phenyl radical. Assuming that the product is derived from $MPDP^+$, this empirical formula requires a sequence of reactions that includes (a) dimerization, (b) deamination, and (c) a two-electron reduction. If the reducing equivalents are derived from the oxidation of $MPDP^+$ to MPP^+, the net transformation may be expressed as shown below:



The corresponding product obtained when this reaction was run in D_2O was shown by CIMS to contain one deuterium atom. This result was taken as evidence that one of the reactants leading to product formation was the free base derived from $MPDP^+$, namely 1-methyl-4-phenyl-1,2-dihydropyridine (**4**), since we had shown previously that the MPP^+ formed from a disproportionation reaction between $MPDP^+$ and **4** in D_2O contains one deuterium atom at the β-position.[6] Since the MPTP formed in this reaction contains no deuterium, we have proposed that the reaction pathway leading to this exchange involves the irreversible formation of the free base **4** followed by the rapid and reversible deuteration at the C-5 position of **4** to yield the conjugate acid **5** as illustrated.



Additional information on what appeared to be an unusual reaction product was sought via the corresponding reaction with 1-methyl-4-phenyl-2,3-dihydropyridinium-*2,2,6-d*$_3$ perchlorate (**2-*d*$_3$**). The synthesis of this deuterated analogue of $MPDP^+$ was achieved by the condensation of formaldehyde-d_2 with α-methylstyrene (**6**) and methylamine,[7] which gave MPTP-*2,2,6,6-d*$_4$ (**1-*d*$_4$**) in 45%

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(1) Chiba, K.; Castagnoli, N., Jr.; Trevor, A. J. *Biochem. Biophys. Res. Commun.* **1984**, *36*, 250. Markey, S. P.; Johannessen, J. N.; Chiueh, C. C.; Burns, R. S.; Herkenham, M. A. *Nature* **1984**, *311*, 464. Langston, J. W.; Irwin, I.; Langston, E. B.; Forno, L. S. *Neurosci. Lett.* **1984**, *48*, 87.
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(3) Chiba, K.; Peterson, L. A.; Castagnoli, K. P.; Trevor, A. J.; Castagnoli, N., Jr. *Drug. Metab. Dispos.* **1985**, *13*, 342.
(4) Castagnoli, N., Jr.; Sparatore, A.; Ottoboni, S.; Leung, L.; Trevor, A. *Int. Congr. Ser.-Excerpta. Med.* **1987**, *750*, 875.
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(6) Peterson, L. A.; Caldera, P. S.; Trevor, A.; Chiba, K.; Castagnoli, N., Jr. *J. Med. Chem.* **1985**, *28*, 1432.

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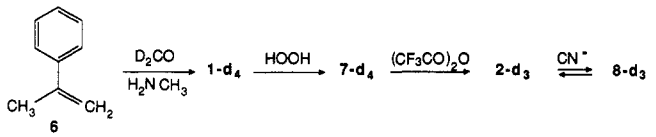
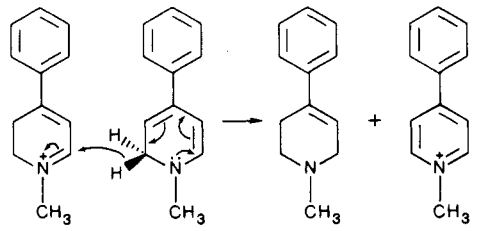
Table I. NMR Data

proton	δ (ppm)	coupling constants, Hz			with MPDP+-d_3	δ ^{13}C	structural unit
H_e(eq)	2.01 (ddd)	ef	eh	eq	H		
		14.5	6.8	2.5		36.86	
H_f(ax)	2.50 (ddd)	fe	fg	fh	H		
		14.5	9.0	2.8			
H_g(ax)	2.72 (ddd)	gh	gf	ge	D		
		11.0	9.0	2.8		47.07	
H_h(eq)	2.78 (m)		not resolved		D		
CH_3	2.64 (s)				H	42.99	$RRNCH_3$
H_a(ax)	2.80 (dd)	ab	ac		D		
		21.0	5.0				
H_b(eq)	3.05 (m)	ba	bc	bd	D	30.65	
		21.0	~2	<2			
H_c	5.52 (t)		not resolved		exchanges	~128	
H_i	5.05 (s)				D	112.25	
H_j	5.38 (s)				D		
H_d	6.10 (d)		ab		D	135.39	
			<2				

yield. Oxidation of **1-d_4** with hydrogen peroxide followed by treatment of the resulting *N*-oxide **7-d_4** with trifluoroacetic anhydride yielded the desired dihydropyridinium compound, which was purified as its α-cyano adduct **8-d_3**.[3] The crystalline perchlorate salt of **2-d_3** was obtained by treatment of **8-d_3** with methanolic perchloric acid.



Incubation of **2-d_3** in pH 7.4 buffer yielded the corresponding deuterium-labeled dimeric species, which was shown by CIMS to contain seven deuterium atoms, i.e. to have the empirical formula $C_{23}H_{16}D_7N$. This result was consistent with the proposed hydride (deuteride) transfer reaction as the two-electron reductive step required by the reaction stoichiometry. The disproportionation of MPDP+ occurs by an analogous hydride transfer reaction as shown below.[6]



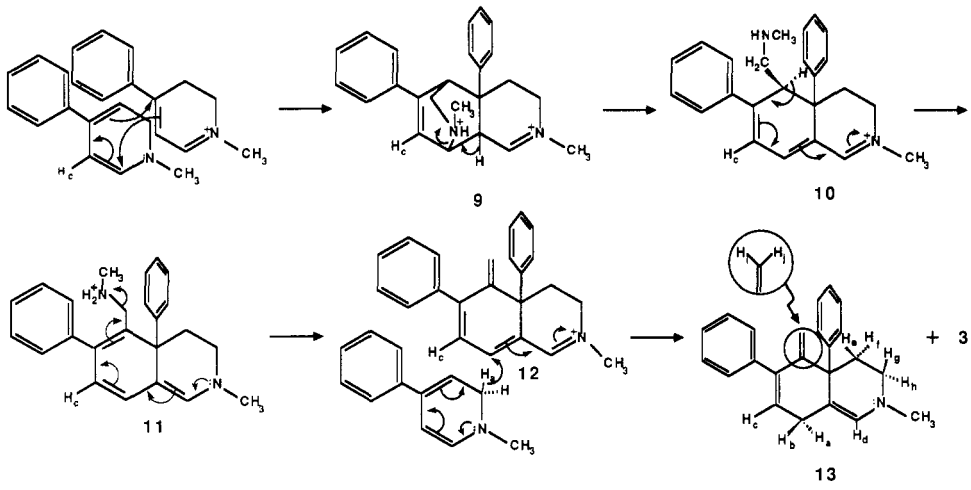
A preparative-scale reaction was run, and the resulting product was purified by silica gel column chromatography. This sample was analyzed by both ^{1}H and ^{13}C NMR spectroscopy. The results obtained from a series of NMR experiments (two dimensional ^{1}H–^{13}C correlation spectroscopy, ^{1}H decoupling experiments, and one-dimensional ^{1}H NOE and relaxation measurements) and from comparison of the original ^{1}H NMR spectrum with the corresponding spectra obtained with the monodeutero and heptadeutero products allowed us to deduce the following structural conclusions (see Table I): (a) Proton decoupling experiments, ^{1}H NOE measurements, and determination of proton relaxation rates led to the identification of four methylene groups in the molecule, one of which is a terminal olefin (H_i, H_j). The latter assignment was substantiated further in the two dimensional ^{1}H–^{13}C correlated spectrum. (b) The coupling pattern of the signals due to the protons of one of the remaining three methylene groups (H_a and H_b) was consistent with the presence of a single vicinal proton, which was assigned to the exchangeable olefinic proton (H_c) identified in the spectrum of the product obtained in the D_2O reaction. (c) The signals due to the two remaining methylene group protons (H_e, H_f and H_g, H_h) have been attributed to an isolated ethylene unit in part as a consequence of information obtained from double resonance experiments and coupling patterns (Table I) and in part from the spectrum obtained with the heptadeuterated product in which the signals for H_e and H_f appear as a geminal AB quartet. (d) The downfield chemical shift of the signal for the remaining olefinic proton (H_d) and its attachment to C_d (δ 135.39 ppm) allowed us to attribute this signal to an enamine proton. Furthermore, the signal for H_d displayed only long-range coupling (<2 Hz), consistent with the absence of vicinal protons. (e) Protons H_e and H_f are likely to be derived from the C_3 methylene group of MPDP+ since these two protons are retained in the product derived from MPDP+-d_3.

Chemical shift and two dimensional ^{13}C–^{1}H correlation data led to the identification in the ^{13}C NMR spectrum of signals for three protonated sp^2 hybridized carbon atoms (C_{ij}, C_c, and C_d) and four protonated sp^3 hybridized carbon atoms (C_{ab}, C_{ef}, CH_3, and C_{gh}). The remaining signals for the 10 protonated aromatic carbon atoms are present in the region 126–129 ppm as four two-carbon resonances (ortho and meta carbon atoms) and two one-carbon resonances (para carbon atoms). Signals for the tertiary carbon atoms were not identified because of their long relaxation times and absence of nuclear Overhauser enhancement. The product has a hydrogen deficiency of 13 units, and therefore we have concluded that it must contain two rings in addition to the phenyl rings since the two phenyl groups and the three double bonds identified from the NMR data account for a hydrogen deficiency of 11 units.

Of the several structures that have been considered for this molecule, we propose the partially reduced isoquinoline system shown in **13**. All of the structural elements identified by analysis of the NMR spectra are present in **13**. Furthermore, the formation of this compound may be rationalized in terms of a Diels–Alder

(7) Schmidle, C. J.; Mansfield, R. C. *J. Am. Chem. Soc.* **1956**, *78*, 425.

Scheme I



condensation between the dihydropyridinium species **2** and the corresponding free base **4** to generate following protonation intermediate **9**. Ring opening of **9** yields the partially reduced isoquinolinium species **10** which rearranges to **11**. Deamination of **11** provides the highly conjugated intermediate **12**, bearing the terminal olefin. Finally hydride-mediated reduction of **12** yields the final product **13** (Scheme I). The proton that undergoes exchange in D_2O (H_c) and the proton that is introduced in the proposed hydride transfer reaction (H_a) have been identified in these structures. Their positions in the final product are fully consistent with the spectroscopic data.

Both MPTP and $MPDP^+$ have been shown to be time- and concentration-dependent inactivators of MAO-B.[8] Furthermore, the catalytic process involves the transient formation of a yellow intermediate.[9] The possible in vivo formation of an intermediate such as **12** from the MAO-B-catalyzed oxidation of MPTP and its role in the inactivation of the enzyme and the nigrostriatal toxicity of MPTP currently are under investigation.

Experimental Section

Synthetic reactions were carried out under a nitrogen atmosphere. NMR spectra were recorded on a GE 500-MHz instrument linked to a Nicolet 1280 computer. Typically 16–32 scans were acquired with a spectral width of 6000 Hz using a 90° pulse. NOE experiments were conducted with use of a 3-s persaturation pulse. Chemical shifts are reported in parts per million (ppm) relative to Me_4Si as an internal standard, and spin multiplicities are given as s (singlet), d (doublet), t (triplet), or m (multiplet). The ^{13}C–^1H correlated spectrum was obtained by observation of the ^{13}C resonances at 125.7 MHz. Sample concentration was 7 mM in CD_2Cl_2, and TMS was used as an internal standard. The spectral width in the ^{13}C dimension was 37 000 Hz and 6000 Hz in the ^1H dimension. A total of 512 data sets were obtained, consisting of 128 scans with 4K data points each.

High-resolution EI mass spectra were obtained on an AEI MS 50S and low-resolution CI spectra on an AEI MS 902S with isobutane (0.7 Torr) as reagent gas. HPLC analysis of the $MPDP^+$-derived dimer was performed on a Beckman Model 114M chromatograph equipped with a Rheodyne 7125 injection valve and a ChemcoPak Chemocosorb cyano column (4.6 mm × 15 cm). The mobile phase (1.5 mL/min) was hexane–2-propanol (95:5), and the eluent was monitored at 280 nm. A Hewlett-Packard Model 1040A diode array detector was used to obtain on-line UV spectra. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley, CA. MPTP hydrochloride was obtained from Research Biochemicals, Inc. (Wayland, MA) while $MPDP^+$ perchlorate[3] and MPP^+ iodide[10] were prepared as described previously.

2-Methyl-5-methylene-4a,6-diphenyl-2,3,4,4a,5,8-hexahydroisoquinoline (13). $MPDP^+$ perchlorate (100 mg, 0.37 mmol)[3,11] was stirred in 70 mL 0.1 M potassium phosphate buffer (pH 7.4) at 37 °C for 2 h. The reaction mixture was extracted with 2 × 25 mL of ether, the combined extracts were dried (Na_2SO_4), and the solvent was removed. The residue in 2 mL of ethyl acetate was chromatographed with ethyl acetate on a 1.6 cm × 16 cm column packed with silica gel (Merck, Grade 60, 60 Å). Fractions between 200 and 300 mL were collected, combined, and evaporated to dryness to yield 5 mg (0.016 mmol, 8% based on moles of $MPDP^+$ consumed in product formation) of a yellow oil: NMR, see Table I; HREIMS calcd for $C_{23}H_{23}N$ 313.1830, found 313.1823. The product isolated from the corresponding reaction carried out in D_2O provided a compound, which gave a parent ion under CIMS conditions at m/z 315 (MH^+) and a ^1H NMR spectrum similar to that described above except that the signal at δ 5.52 was absent and the coupling pattern of H_a was simplified. The product isolated from the corresponding reaction in which $MPDP^+$-*2,2,6-d*$_3$ served as the starting material displayed a protonated molecular ion at m/z 320 and the following ^1H NMR spectrum: δ ($CDCl_3$) 2.01 (d, J = 14.5 Hz, 1 H, H_e), 2.50 (d, J = 14.5 Hz, 1 H, H_f), 2.64 (s, 3 H, CH_3), 5.52 (s, 1 H, H_c), and 7.2–7.6 (m, 5 H, Ar H).

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-*2,2,6,6-d*$_4$ (MPTP-*d*$_4$, 1-*d*$_4$) Hydrochloride. This product was synthesized according to the literature description for the d_0 compound[7] in 45% yield from paraformaldehyde-d_2 (3.5 g, 10.9 mmol), methylamine hydrochloride (4.0 g, 5.9 mmol), and α-methylstyrene (7.1 g, 6.0 mmol): mp 247–248 °C (lit.[7] mp 247–248 °C); ^1H NMR (D_2O) δ 2.85 [m, 2 H, C(3)-H], 2.96 (s, 3 H, CH_3), 6.21 [s, 1 H, C(5)-H], and 7.35–7.55 (m, 5 H, Ar H). Anal. Calcd for $C_{12}H_{11}D_4N$·HCl: C, 67.43; H, 7.55; N, 6.55. Found: C, 67.27; H, 7.29; N, 6.43.

1-Methyl-4-phenyl-2,3-dihydropyridinium-*2,2,6-d*$_3$ ($MPDP^+$-*d*$_3$, 2-*d*$_3$) Perchlorate. A mixture of MPTP-d_4 free base (4.15 g, 23.4 mmol) and 7 mL of 30% H_2O_2 in 40 mL of a 1:1 mixture of CH_2Cl_2–EtOH was heated under reflux for 18 h. Pd/C (25 mg) was added to the cooled reaction mixture, which then was heated under reflux for an additional 3 h. The cooled reaction mixture was filtered through Celite, and the solvents were completely removed under vacuum to yield 3.85 g (19.4 mmol, 85%) of crude *N*-oxide d_4 (**7-*d*$_4$**). This product in 100 mL of CH_2Cl_2 was treated dropwise at room temperature with trifluoroacetic anhydride (7.4 g, 40 mmol). After 40 min an addi-

(8) Singer, T. P.; Salach, J. I.; Crabtree, D. *Biochem. Biophys. Res. Commun.* **1985**, *127*, 707.
(9) Singer, T. P.; Salach, J. I.; Castagnoli, N., Jr.; Trevor, A. *Biochem. J.* **1986**, *235*, 785.
(10) Wu, E. Y.; Chiba, K.; Trevor, A. J.; Castagnoli, N., Jr. *Life Sci.* **1986**, *39*, 1695.
(11) Grierson, D. S.; Harris, M.; Husson, H.-P. *J. Am. Chem. Soc.* **1980**, *102*, 1064.

tional 1.2 g of trifluoroacetic anhydride was added. Following an additional 15 min of stirring, the reaction mixture was concentrated to about 2 mL, and a solution of NaCN (1.5 g, 30 mmol in 50 mL H_2O) was added followed by trifluoroacetic acid to pH 4. After the mixture was stirred at room temperature for 20 min, the pH was adjusted to 8 and the α-cyano adduct 8-d_3 was extracted with 3 × 60 mL of CH_2Cl_2. The combined extracts were washed with H_2O, dried ($MgSO_4$), and filtered through neutral alumina. The residue in 30 mL of MeOH was cooled in an ice bath and treated dropwise with 1.5 mL (22 mmol) of 70% $HClO_4$. After the mixture stood overnight, 1.56 g (6 mmol, 24%) of pure $MPDP^+$-d_3 was obtained: mp 119–120 °C (lit.[3] mp for the d_0 compound 119–120 °C); UV (MeOH) λ_{max} 345 nm (ε 19 000); ^1H NMR (CD_3CN) δ 3.21 (s, 2 H, CH_2), 3.62 (s, 3 H, CH_3), 6.89 [s, 1 H, C(5)-H]; and 7.57 (m, 5 H, Ar H). Anal. Calcd for $C_{12}H_{11}D_3NClO_4$: C, 52.47; H, 5.14; N, 5.1. Found: C, 52.09; H, 5.04; N, 5.07.

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Registry No. 1-d_4, 118459-65-7; 1-d_4·HCl, 118459-68-0; 2·perchlorate, 97467-07-7; 2-d_3·perchlorate, 118473-79-3; 7-d_4, 118459-66-8; 8-d_3, 118459-67-9; 13, 118459-64-6.

Molecular Structure of a Chiral 3,5-Bridged Pyridine and the Effect of Structure on Circular Dichroic Spectra

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The crystal structure of the 3,5-bridged chiral macrocyclic pyridine (4*S*,14*S*)-4,14-di(2-propyl)-6,9,12-trioxa-3,15,19-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,5,13,16-tetrone (**5a**) has been determined by crystallographic means. Each unit cell contains two nonequivalent molecules. In each molecule the amide groups are twisted out-of-plane in a conrotatory fashion righ-handedly with respect to the molecular C_2 axis viewed along the line from C4 to N1 of the pyridine ring. This twist allows avoidance of potential interaction between the amide nitrogen bonded protons and that bonded to C4 of the pyridine ring. The macrocyclic framework is inherently dissymmetric as a result of this helical twist. This is reflected in the circular dichroism spectrum of **5a**, which has two strongly negative effects in the 200–400-nm region, at 218 nm, [θ] −58 800 and 273 nm, [θ] −45 600. Very similar CD effects are found for analogues of **5a** with at the chiral atoms at the 4,14-positions, methyl groups (**6a**), *tert*-butyl groups (**6b**), and proline (**7**). Comparisons are also made with compounds (**8b**) derived (in thought) from **5a** by transposition of the macrocyclic bridge from the 3,5- to the 2,6-positions. Compound **8a** is analogous to **8b** save that it is a benzene rather than a pyridine derivative. Several nonmacrocyclic analogues of **5a** have also been examined as well as the thioamide derivative of **5a** (compound **9**) for which a synthesis has been developed. The longer wavelength CD effect in **5a** is assigned to the *pyridine* n–π* transition and the shorter wavelength effect to π–π* transitions. Attempts to correlate the absolute signs with a recently postulated model fail. A method for synthesis of the unnatural amino acids, (*S*)-(+)-2-amino-3,3-dimethylbutanoic acid (**13**), in enantiomerically pure form is described as well as an NMR method for the determination of the enantiomeric purity of samples of **13**.

In the presence of an electrophile like Mg^{2+} macrocycles **1** transfer hydride at room temperature with excellent enantioselectivity to the *re* face of activated ketone **2** as shown in Scheme I.[1] In this sense they are NADH mimics. Groups other than hydride may also be transferred.[2] The effect of variation in the amino acids incorporated, an example being L-valine in **1** as illustrated, and of bridge length and composition (a diethylene glycol unit for the case of **1**) has been investigated systematically.[1] Further development of these macrocyclic systems has been hampered by the fact that all attempts to determine crystal structures have failed. The information forthcoming from crystallographic studies is virtually indispensable for understanding the stereochemical intricacies of the complexes formed as well as spectroscopic details. Although the structure of **1** or a related 1,4-dihydropyridine still has not been obtained, we have now solved the structure of bridged *pyridine* **5a**.[3] This structure provides considerable insight

(1) See, for example: Talma, A. G.; Jouin, P.; De Vries, J. G.; Troostwijk, C. B.; Werumeus Buning, G. H.; Waninge, J. K.; Visscher, J.; Kellogg, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 3981.

(2) (a) Mashraqui, S. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1983**, *105*, 7792. (b) Van Keulen, B. J.; Kellogg, R. M. *J. Am. Chem. Soc.* **1984**, *106*, 6029.

(3) Several structures of other 1,4-dihydropyridines have been obtained, however. In general, the 1,4-dihydropyridine ring is either planar or adopts a shallow boat conformation: (a) Van der Veen, R. H.; Kellogg, R. M.; Vos, A.; Van Bergen, T. J. *J. Chem. Soc., Chem. Commun.* **1978**, 923. (b) Karle, I. L. *Acta Crystallogr.* **1961**, *14*, 497. (c) Krajewski, J.; Urbanczyk-Lipkowska, Z.; Gluzinski, P. *Cryst. Struct. Commun.* **1977**, *6*, 787. (d) Krajewski, J.; Urbanczyk-Lipowska, Z. *Acta Crystallogr.* **1977**, *B33*, 2967. (e) Hempel, A.; Gupta, M. P. *Acta Crystallogr.* **1978**, *B34*, 3815. (f) Triggle, A. M.; Shefter, E.; Triggle, D. J. *J. Med. Chem.* **1980**, *23*, 1442. (g) See also: Hays, G. R.; Huis, R.; Coleman, B.; Clague, D.; Verhoeven, J.; Rob, F. *J. Am. Chem. Soc.* **1981**, *103*, 5140.

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