The 1-Methylene Derivatives of [7](2,6)Pyridinophane. Preparative and Conformational Studies

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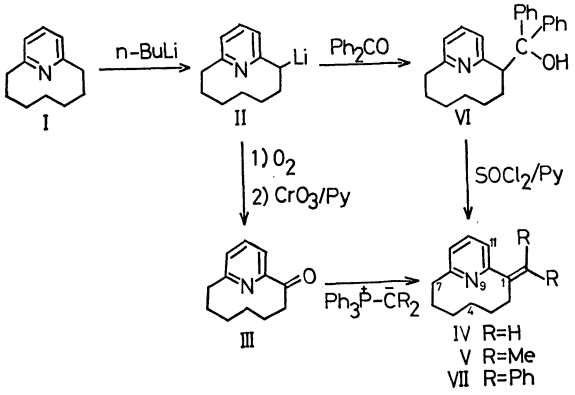
The 1-*exo*-methylene derivatives (IV, V and VII) of [7](2,6)pyridinophane (I) are synthesized by Wittig's reaction of [7](2,6)pyridinophan-1-one (III) or by the dehydration of the corresponding carbinol (VI). The C-4 protons are all shielded magnetically to varying extents, depending on their respective 1-substituents. The shielding effect is ascribed to the anisotropy of the pyridine ring. The signals of the C-4 protons are temperature-dependent, and the energy barriers for the conformational changes are estimated to be 8.7 for III, 9.1 for IV, 9.1 for V and 9.8 kcal/mol for VII.

Dynamic NMR spectrometry has revealed the conformational details of [7](2,6)pyridinophane (I), particularly the flipping of the heptamethylene chain.[1,2] The present report will describe the synthesis of several 1-π derivatives (IV, V, and VII) of I and the conformational changes induced by the incorporation of a trigonal (sp^2) carbon on C-1.

The Synthesis of 1-Methylene[7](2,6)pyridinophanes. The treatment of [7](2,6)pyridinophane (I) with *n*-butyllithium gave an orange-red solution of 1-lithio-[7](2,6)pyridinophane (II), which afforded [7](2,6)-pyridinophan-1-one (III) upon quenching with oxygen and subsequent Cornforth oxidation.[1] The reaction of III with methylenetriphenylphosphorane yielded 1-methylene[7](2,6)pyridinophane (IV), which exhibited IR bands characteristic of an *exo*-methylene double bond at 1633 and 894 cm^{-1}. A similar Wittig reaction of III with isopropylidenetriphenylphosphorane gave 1-isopropylidene[7](2,6)pyridinophane (V). The IR absorptions characteristic of an isopropylidene group appeared at 1642, 1373, and 1365 cm^{-1}. The reaction of the 1-lithio derivative (II) with benzophenone afforded 1-(α-hydroxybenzhydryl)[7](2,6)pyridinophane (VI). 1-Diphenylmethylene[7](2,6)pyridinophane (VII) was obtained by the dehydration of VI with thionyl chloride in pyridine. All the new compounds gave elemental analyses and spectral data consistent with the assigned structures.



Dynamic NMR Spectrometry and Conformational Changes of 1-Oxo- and 1-exo-Methylene[7](2,6)pyridinophanes. The NMR spectra of IV, V, and VII at room temperature are shown in Fig. 1. The C-4 protons are magnetically shielded to various extents, depending on their 1-substituents (Table 1).[3] The chemical shift of the C-4 protons of IV (δ 0.92 ppm) is comparable to the value of 1-ketone III (δ 1.07 ppm),[1] and the stereochemical requirements of the oxo and methylene groups are similar to each other. The conjugation of the pyridine ring of IV with the 1-*exo*-methylene group should favor such an extreme conformer as VIII, in which one of the C-4 protons, H_x, is above, but slightly out of the center of the pyridine ring as

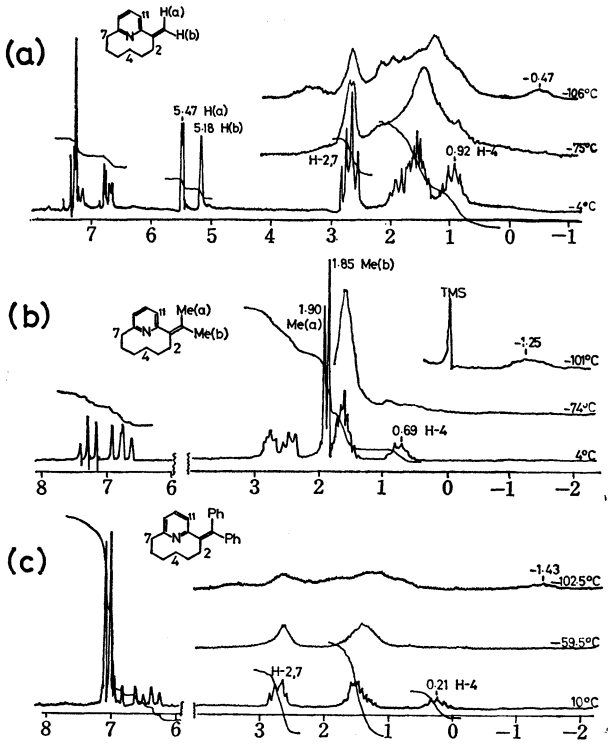


Fig. 1. Dynamic NMR spectra of IV (a), V (b) and VII (c); 60 MHz in $CFCl_3$, TMS as an internal standard.

1) a) S. Fujita and H. Nozaki, This Bulletin, **44**, 2827 (1971). b) H. Nozaki, S. Fujita, and T. Mori, *ibid.*, **42**, 1163 (1969).

2) a) H. Nozaki, T. Koyama, T. Mori, and R. Noyori, *Tetrahedron Lett.*, **1968**, 2181; *Tetrahedron*, **25**, 5357 (1969). b) S. Fujita, T. Kawaguti, and H. Nozaki, This Bulletin, **43**, 2596 (1970). c) S. Fujita, T. Kawaguti, and H. Nozaki, *Tetrahedron Lett.*, **1971**, 1119.

3) The shielding effect may be ascribed to the diamagnetic ring current of the pyridine ring and/or to the anisotropy of the nitrogen atom (See Ref. 1).

Table 1. Energy barriers of the flipping of the heptamethylene bridges of 1-π-[7](2,6)-pyridinophanes[a)]

Compound	Observed chemical shift of C-4 proton(s) (temperature)		$\Delta\nu$	T_c	k_c[b)]	$\Delta G^{\neq}{}_c$[c)]
	Average δ ppm (°C)	Fixed δ ppm (°C)	(Hz)	(°C)	sec^{-1}	kcal/mol
III	1.07(0)	−0.15(−109)	146	−84.0	324	8.7
IV	0.92(−4)	−0.47(−106)	167	−75.0	371	9.1
V	0.69(4)	−1.25(−101)	233	−74.0	510	9.1
VII	0.21(10)	−1.43(−102)	197	−59.5	437	9.8
I[d)]	0.22(−10)	−1.40(−111)	194	−75.5	432	9.0

a) Determined in $CFCl_3$ at 60 MHz. See Fig. 1.
b) $k_c=\pi\Delta\nu/\sqrt{2}$ (Ref. 5)
c) $\Delta G^{\neq}{}_c=2.303RT_c$ $(10.319-\log k_c+\log T_c)$ (Ref. 5)
d) Reported in Ref. 1.

compared with the corresponding proton of I.[4)] However, the C-4 protons of VII are more shielded than those of III and IV, and the chemical shift (δ 0.21 ppm) is comparable to that (δ 0.22 ppm) of unsubstituted [7](2,6)pyridinophane (I) itself. In the case of VII, steric hindrance arising from the H-11 of the pyridine ring and the phenyl group should influence the coplanarity of the pyridine and the *exo*-methylene group and consequently, the conformation of the heptamethylene bridge. The chemical shift (δ 0.69 ppm) of V is intermediate between those of IV and VII.

The NMR signals of the heptamethylene chain of IV are temperature-dependent as is illustrated in Fig. 1a. At room temperature, the heptamethylene bridge flips up and down (VIII⇄VIII') and its protons show an average chemical shift. At low temperatures, one of the C-4 protons (δ −0.47 at −106°C) of IV is more shielded than at room temperature. This fact indicates the fixation of the heptamethylene bridge to an extreme conformation such as VIII. The

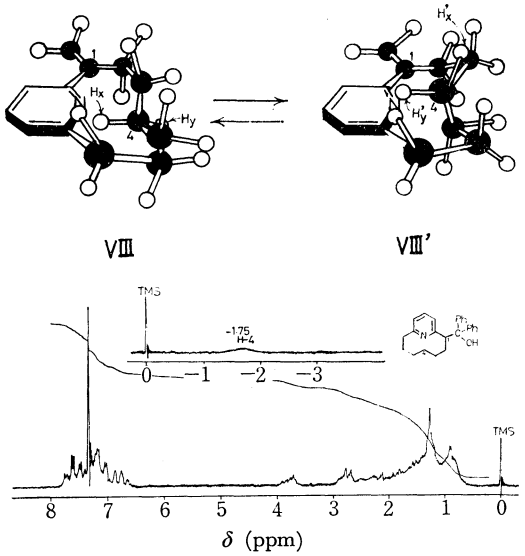


Fig. 2. The NMR spectrum of VI (24°C, 60 MHz in $CDCl_3$).

4) The anisotropy of the pyridine rings should be dependent upon the electron densities of the respective pyridine rings conjugated by π bonds.

bridges of the other 1-π derivatives exhibited similar dynamic NMR spectra (Figs. 1b and 1c).

The estimated energy barriers for the conformational changes of 1-π-[7](2,6)pyridinophanes are shown in Table 1 as well as that of the mother compound (I). The introduction of π-bonds on C-1 reduces the energy barriers for the flipping of the heptamethylene chains, as is exemplified in III. In the *exo*-methylene derivatives, the steric crowding between H-11 and the 1-substituents compensates the above-mentioned reduction by the incorporation of π-bonds on C-1. Thus, the coalescence temperature (T_c) and the $\Delta G^{\neq}{}_c$ values of IV and V are comparable to those of the unsubstituted pyridinophane (I) itself. Moreover, those of VII are much higher and indicate that the steric hindrance becomes dominant. In conclusion, the chemical shifts of the C-4 protons, the coalescence temperature, and the $\Delta G^{\neq}{}_c$ values may be regarded as adequate measures of the relative steric bulkiness of 1-substituents.

The NMR spectrum of the carbinol VI (Fig. 2) is an extreme case as compared with those of other 1-monosubstituted [7](2,6)pyridinophanes.[1)] The one proton on C-4 is highly shielded (δ −1.75 ppm in $CDCl_3$) even at room temperature. In contrast, the two C-4 protons of [7](2,6)pyridinophan-1-ol have been reported to show an average signal at δ −0.08 ppm ($CDCl_3$) at room temperature.[1)] Probably, the bulky 1-substituent ($Ph_2(HO)C$-) prevents the flipping of the heptamethylene chain of VI.

Experimental

The dynamic NMR spectra were determined on a JEOL C-60-H spectrometer at 60 MHz, using fluorotrichloromethane ($CFCl_3$) as the solvent and tetramethylsilane (TMS) as the internal standard unless otherwise stated. The mass spectra were obtained on a Hitachi RMU-6L spectrometer.

1-Methylene[7](2,6)pyridinophane (IV). A solution (1.0 N, 4.0 *ml*) of *n*-butyllithium in *n*-hexane was added at room temperature under a nitrogen atmosphere to a suspension of triphenylmethylphosphonium bromide[6)] (1.29 g,

5) a) G. Binsch, "Topics in Stereochemistry," Vol. 3, ed. by E. L. Eliel and N. L. Allinger, Interscience Publishers, New York (1968), p. 97—192. b) I. C. Calder and P. J. Garratt, *J. Chem. Soc., B*, **1967**, 660.

3.6 mmol) in tetrahydrofuran (15 ml). After stirring under nitrogen for 2 hr, the resulting red solution was added to a solution of III[1] (0.57 g, 3.0 mmol) in tetrahydrofuran (25 ml), after which stirring was continued for 24 hr. The reaction mixture was then poured into water and extracted with ether (200 ml). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. The oily residue was separated by preparative-scale thin layer chromatography (TLC) on silica gel, using *n*-hexane-benzene (1 : 3) as the solvent. The crude product was distilled to give IV (0.15 g, 26%); bp 70°C (bath temperature)/2 mmHg. IR (neat): 3055, 2924, 2840, 1633, 1580, 1461, 894, 838, 821, 799, 745, and 725 cm^{-1}. MS *m/e* (relative abundance): 187 (88), 186 (43), 172 (78), 159 (100), 158 (79), 146 (21), 144 (35), 133 (65), 130 (22), 117 (23), 77 (22), 65 (22), 39 (29). UV $\lambda_{max}^{n\text{-hexane}}$ (log ε): 246 nm (3.94), 277 nm (3.74). The NMR spectrum is shown in Fig. 1a.

Found: C, 83.6; H, 9.4; N, 7.4%. Calcd for $C_{13}H_{17}N$: C, 83.4; H, 9.2; N, 7.5%.

1-Isopropylidene[7](2,6)pyridinophane (V). A red solution of phosphorane, prepared from triphenylisopropylphosphonium bromide[7] (1.39 g, 3.6 mmol) and *n*-butyllithim (1.0 N, 4.5 ml), was added to a solution of III (0.57 g, 3.0 mmol) in tetrahydrofuran (25 ml). After stirring for 24 hr under nitrogen, the white precipitates were filtered off and the filtrate was concentrated. The residual oil was separated by preparative TLC (silica gel, *n*-hexane-benzene (1 : 3)) and distilled to give V (0.21 g, 33%); bp 117—118°C/0.5 mmHg. IR (neat): 3055, 2924, 2840, 1642, 1579, 1455, 1373, 1365, 1190, 1160, 853, 826, 801, 787, 753, and 731 cm^{-1}. MS *m/e* (relative abundance): 215 (100), 214 (63), 200 (62), 187 (85), 186 (88), 174 (20), 172 (48), 161 (34), 158 (27), 144 (30), 131 (24), 130 (21), UV $\lambda_{max}^{n\text{ hexane}}$ (log ε): 250.5 nm (3.92), 274 nm (3.80). The NMR spectrum is shown in Fig. 1b.

Found: C, 83.8; H, 9.9; N, 6.4%. Calcd for $C_{15}H_{21}N$: C, 83.7; H, 9.8; N, 6.5%.

1-(α-Hydroxybenzhydryl)[7](2,6)pyridinophane (VI). A solution (0.90 N, 4.4 ml) of *n*-butyllithium in *n*-hexane was added to solution of I[1] (0.70 g, 4.0 mmol) in tetrahydrofuran (75 ml) at room temperature. After stirring under a nitrogen atmosphere for 30 min, a solution of benzophenone (0.73 g, 4.0 mmol) in tetrahydrofuran (25 ml) was added to the resulting orange-red solution of II. The reaction mixture was stirred for 2 hr and then treated with aqueous ammonium chloride (100 ml), extracted with ether, and dried over sodium sulfate. Concentration and recrystallization gave VI (1.42 g, quantitative); mp 162—163°C (benzene). IR (KBr disk): 3300, 3050, 2960, 2940, 2885, 2810, 1593, 1570, 1495, 1463, 1450, 1412, 1350, 1279, 1174, 1049, 1031, 999, 960, 943, 930, 908, 889, 864, 853, 845, 810, 784, 775, 765, 757, 746, 728, 700, 689, 671, 640, 601 cm^{-1}. The NMR may be found in Fig. 2.

Found: C, 83.9; H, 7.5; N, 4.0%. Calcd for $C_{25}H_{27}NO$: C, 84.0; H, 7.6; N, 3.9%.

1-Diphenylmethylene[7](2,6)pyridinophane (VII). Thionyl chloride (1.0 ml) was added in one portion under nitrogen to a solution of VI (0.17 g, 0.5 mmol) in pyridine (10 ml), and then the solution was heated at 50°C for 5 hr. The reaction mixture was subsequently poured onto ice, extracted with ether, and dried over sodium sulfate. After the removal of the ether, the residual solid was recrystallized from *n*-hexane to afford VI as white crystals (0.14 g, 85%); mp 116—118°C. IR (KBr disk); 3075, 3050, 3015, 2960, 2950, 2910, 2840, 1597, 1582, 1567, 1494, 1454, 1444, 1203, 870, 838, 815, 794, 769, 760, 754, 736, 827, 714, 702, 674, 630, and 602 cm^{-1}. MS *m/e* (relative abundance): 339 (100), 338 (98), 311 (47), 310 (76), 182 (37), 105 (100), 77 (76), 57 (20), 51 (35). UV $\lambda_{max}^{n\text{-hexane}}$ (log ε): 236 nm (4.21), 309.5 nm (4.16). The NMR spectrum is shown in Fig. 1c.

Found: C, 88.3; H, 7.4; N, 4.3%. Calcd for $C_{25}H_{25}N$: C, 88.5; H, 7.4; N, 4.1%.

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6) G. Wittig and U. Schoelkopf, "Organic Synthesis," Vol. 40, p. 66 (1960); N. A. Milas, L. Chiang, C. P. Priesing, A. A. Hyatt, and J. Peter, *J. Amer. Chem. Soc.*, **77**, 4180 (1955).

7) U. H. M. Fagerlund and D. R. Idler, *ibid.*, **79**, 6473 (1957).