CHEMISTRY LETTERS, pp. 983-986, 1976. Published by the Chemical Society of Japan

A PMR STUDY ON THE FIXED CONFORMATION OF FUNCTIONALIZED (2,5)PYRIDINOPHANES(*)

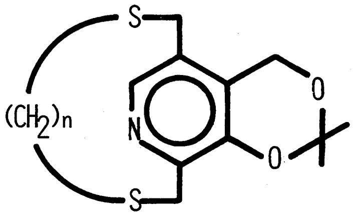
Masaaki IWATA, Hiroyoshi KUZUHARA, and Sakae EMOTO
The Institute of Physical and Chemical Research,
Wako-shi, Saitama 351

The relationship of the hindered rotation with the ring size in phane derivatives of pyridoxine and pyridoxal was investigated with the aid of the appearance of an AB quartet signal in PMR spectra at ambient or elevated temperature, and it was found that phane derivatives with the ring size equal to or less than fourteen members could be optically resolved into enantiomers.

Characteristic features of phanes allow versatile applications of their physical and chemical properties. We designed to convert coenzyme pyridoxal to its phane derivatives with planar chirality and to investigate relative catalytic activities between them. Following the establishment of the general synthetic method of pyridoxal-like phanes from pyridoxine,[1,2] we now wish to describe here the findings concerning the length of the ansa-chain required for creating chiral properties of the heterophanes.

In order to determine the limitation of the ring size in the ristricted inversion, we newly synthesized 2,(n+3)-dithia[m](2,5)pyridinophanes [m = n + 4; I (n=4), yield, 28%, mp 145 °C; II (n=6), 91%, mp 169 °C; III (n=8), 78%, pale yellow syrup], their acetyl-derivatives [IV (n=6), 98%, mp 122 °C; V (n=8), 94%, pale yellow viscous liquid], and their oxidation products [VI (n=4), 48%, yellow viscous liquid; VII (n=6), 71%, mp 129 °C; VIII (n=8), 51%, yellow viscous liquid] by the coupling reaction of 1,n-alkanedithiol (n=4, 6, 8) with 5'-deoxy-2',5'-dichloro-3,4'-*O*-isopropylidenepyridoxine under the same conditions as the previously reported method[1] followed by a sequence of reactions to give their derivatives.[2] IX [19%, mp 150 °C] and X [8%, a pale yellow viscous liquid] were concomitantly obtained in the syntheses of I and III respectively. 2,11-Dithia[3]paracyclo[3](2,5)pyridoxalophane (XV) was synthesized from XI[2] [41%, mp 218-219 °C (deccmp.), yellow crystals]. The structures of these compounds were supported by spectral and analytical data.

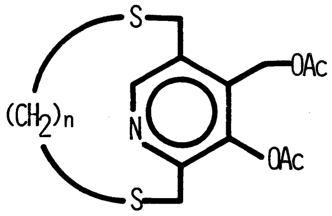
Compared with carba-(2,5)pyridinophanes,[3] these hetera-(2,5)pyridinophanes offered certain advantages for PMR spectral studies. The incorporation of a sulfur atom into the β-position of the pyridine ring not only simplified the methylene signals at its α-position by eliminating the complex spin-spin coupling with the other adjacent methylene groups but also shifted them to a sufficiently lower field to be observable separately from the other methylene signals. Therefore, the existence of enantiomers can be simply deduced on the basis of the knowledge whether or not the PMR signal of the methylene group at the α-position of the pyridine ring is splitted into an AB quartet.



I n = 4

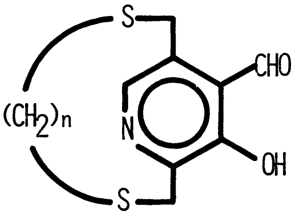
II n = 6

III n = 8



IV n = 6

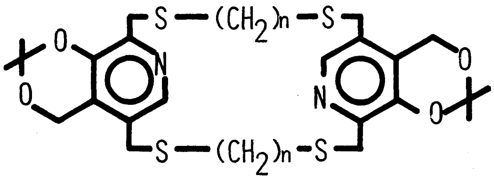
V n = 8



VI n = 4

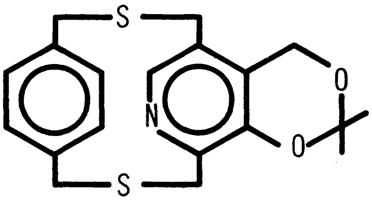
VII n = 6

VIII n = 8

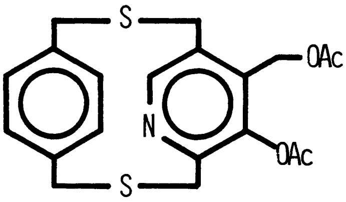


IX n = 4

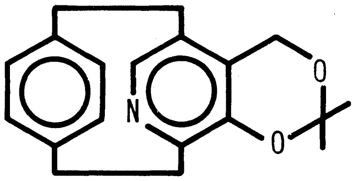
X n = 8



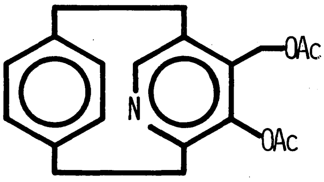
XI



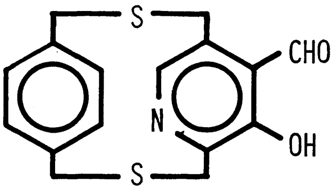
XII



XIII

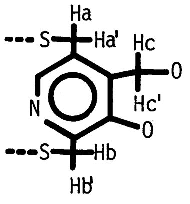


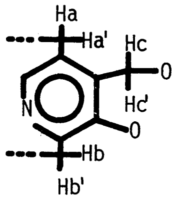
XIV

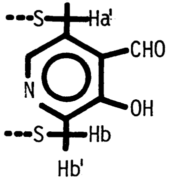


XV

Table 1. PMR Data of the Focused Methylene Groups in (2,5)Pyridinophanes in $CDCl_3$.







Type: S and S-Ac de-S and de-S-Ac S-CHO

at 24 °C δ ppm

Compounds	Structural Type[a)]	Ring size	Chemical shift of methylene group[b)] Ha'-C-Ha	Hb'-C-Hb	Hc'-C-Hc	coupl. const. (Hz) Jaa'	Jbb'	Jcc'
I	S	12	3.51 3.68	3.62 4.05	4.85 5.21	13.0	12.5	16.5
II	S	14	3.50 3.73	3.66 4.04	4.77 5.29	13.5	12.5	16.5
III	S	16	3.59	3.78	5.01	——	——	——
IV	S-Ac	14	3.79 4.11	3.82	5.22 5.41	14.0	——	13.0
V	S-Ac	16	3.76	3.90	5.27	——	——	——
VI	S-CHO	12	3.68 4.21	3.72 4.27	——	12.3	13.5	——
VII	S-CHO	14	3.76 4.17	3.78 4.20	——	12.8	14.0	——
VIII	S-CHO	16	3.90	3.99	——	——	——	——
IX	S	24	3.51	3.75	4.95	——	——	——
X	S	32	3.56	3.79	4.98	——	——	——
XI	S	14	3.51 3.75	3.75 4.05	4.53 5.24	14.9	14.0	16.5
XII	S-Ac	14	3.81 4.09	3.83	5.06 5.34	16.1	——	12.5
XIII	de-S	12	3.00[c)]		4.43 4.62	A_2B_2		16.0
XIV	de-S-Ac	12	3.09[c)]		4.83 4.91	A_2B_2		12.0
XV	S-CHO	14	3.76 4.26	3.81 4.21	——	14.3	15.8	——

[a)] S; the corresponding *O*-isopropylidene derivative, S-Ac; the corresponding *O*-acetyl derivative, de-S; the corresponding desulfurized compound. [b)] All the chemical shift values with geminal proton coupling are the adjusted ones calculated as an AB spin system of geminal protons in the focused methylene group. [c)] the center of the multiplet.

Table 2. Temperature Dependence of the Chemical Shift of the Focused Methylene Groups in $CDBr_3$.

Compounds	Structural Type	Temp. °C	δ ppm Ha'-C-Ha	Hb'-C-Hb	Hc'-C-Hc	J in Hz Jaa'	Jbb'	Jcc'
I	S	24	3.53 3.69	3.58 4.06	4.84 5.16	13.0	12.0	16.0
		90	3.51 3.67	3.59 4.06	4.82 5.16			
II	S	24	3.52 3.74	3.68 3.97	4.77 5.21	14.0	12.5	17.0
		90	3.49 3.70	3.65 3.97	4.74 5.21			
VII	S-CHO	24	3.73 4.14	3.80 4.24	——	13.0	14.5	——
		90	3.70 4.14	3.76 4.21	——			
XI	S	24	3.53 3.77	3.72 4.03	4.51 5.16	15.3	13.6	16.0
		90	3.52 3.74	3.74 4.00	4.50 5.16			

The PMR signals of the methylene groups in $CDCl_3$ recorded at 24 °C on a Varian HA-100D spectrometer are shown in Table 1, which also includes the already reported data of the compounds XI through XIV[1] as references. These data clearly revealed that (2,5)pyridinophanes with the ring size equal to or less than fourteen members existed as stable conformers being independent of kinds of the functional groups and thus could be resolved into optical active species by suitable means.

In relation to our particular interest in the synthesis of planar chiral model compounds with pyridoxal-like activities, it is important to know whether or not the fixed conformation of the pyridinophanes will be maintained even at elevated temperatures.[4] We examined temperature dependence of the PMR signals of the focused methylene groups of compounds I, II, VII, and XI in $CDBr_3$ at 10 °C intavals up to 120 °C. However, none of AB quartets of these compounds collapsed. Representative cases are listed in Table 2.

Although [p](2,5)pyridinophanes have been reported to be optically resolved when p is less than twelve which, in turn, is equal to the sixteen membered ring,[3] it is of interest to be found that the introduction of more than one substituent into the pyridine ring prevents the inversion of the fourteen membered ring containing two sulfur atoms, the ring size of which may be expected to be nearly equal to the eighteen membered ring containing fourteen methylene groups in the ansa-chain because a sulfur atom is known to be nearly equivalent to two carbon atoms in volume.

This study was supported in part by a Grant for Life Science from this Institute.

References and Note

(*) Presented in part at the 34th Spring Annual Meeting of the Japan Chemical Society, Hiratsuka, April 4, 1976; Abstract No. 4A10.

1) M. Iwata, H. Kuzuhara, and S. Emoto, Chem. Lett., to be published.

2) Acetyl derivatives were obtained by the hydrolysis of the corresponding acetonide with 2M-HCl at 70-75 °C for 0.5-3 hr followed by the treatment of the corresponding hydrolyzed product with acetic anhydride-pyridine; the oxidation products were obtained by the treatment of the corresponding hydrolyzed product of acetonide with manganese dioxide in benzene-pyridine in the presence of 3-N',N'-dimethylamino-1-propylamine followed by the hydrolysis of the resulting Schiff base, the novel method of which will be described elsewhere.

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

4) The examination of the catalytic activities of pyridoxal model compounds has been usually run at about 80 °C; for example, M. Ando and S. Emoto, Bull. Chem. Soc. Japan, 42, 2624 (1969).

(Received June 29, 1976)