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SYNTHESIS OF FUNCTIONALIZED DIAZA(2,5)PYRIDINOPHANES[1)]

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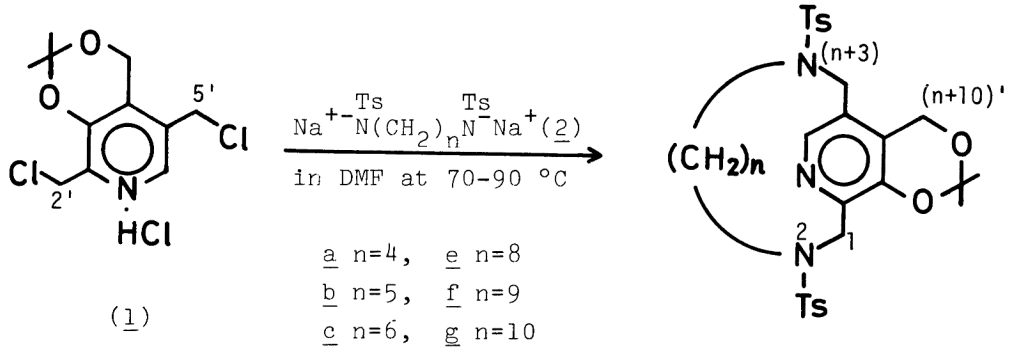
A general synthetic method of N^2,$N^{(n+3)}$-di-*p*-toluenesulfonyl-(n+9)-hydroxy-(n+10)-hydroxymethyl-(n+9),(n+10)'-O-isopropylidene-2,(n+3)-diaza[m](2,5)pyridinophanes [n=5,6,7,8,9,10; m=n+4] was established by the reaction of 5'-deoxy-2',5'-dichloro-3,4'-O-isopropylidenepyridoxine hydrochloride with N,N'-di-*p*-toluenesulfonyl-α,ω-alkanediamine disodium salt in N,N-dimethylformamide at 70-90 °C in fairly good yield depending on the chain length.

Our continued interest pertaining to modelize natural vitamin B_6 activity in the nonenzymic system that both catalysis and stereo-recognition functions are provided in a molecule has been partly achieved by the synthesis of (n+9)-hydroxy-(n+10)-formyl-2,(n+3)-dithia[m](2,5)pyridinophanes [n=4,5,6,8; m=n+4][2)] and its (n+10)-aminomethyl congener.[3)] In these model compounds, the catalytic potency is comparable to that of pyridoxal[2c)] while the recognition potency for substrate stereochemistry remains unsatisfactory as far as we have reported.[2b,3)] The present study is initiated for the synthesis of new model compounds with improved stereo-recognition potency by introduction of nitrogen atoms into the bridged chain, which will provide more flexible molecular design than sulfur atoms, *e.g.* dynamic control of the transition state of catalysis through complexation and immobilization of the coenzyme on polymer support, as was exemplified by cryptands.[4)]

Instead of versatile methods reported so far to synthesize aza(2,5)pyridinophanes,[5)] we gave the first priority to utilization of 5'-deoxy-2',5'-dichloro-3,4'-O-isopropylidenepyridoxine hydrochloride[6)] (1), as a precursor for the catalytic site, which was characterized by feasible synthesis,[2b)] strong electrophilicity as HCl-free form,[2a,b)] and facile conversion to the coenzymic functional groups.[2b,3,7)] As a consequence of many trials using α,ω-alkanediamine as the first choice of the counter-part for further model-building, we eventually found a new generally applicable method to synthesize N^2,$N^{(n+3)}$-di-*p*-toluenesulfonyl-(n+9)-hydroxy-(n+10)-hydroxymethyl-(n+9),(n+10)'-O-isopropylidene-2,(n+3)-diaza[m](2,5)pyridinophanes (3) [n=5,6,7,8,9,10; m=n+4].

In a typical procedure, 3c was prepared as follows; for the preparation of N,N'-di-*p*-toluenesulfonyl-1,6-hexanediamine disodium salt (2c), 0.5 g (1.18 mmol) of N,N'-di-*p*-toluenesulfonyl-1,6-hexanediamine was added to 30 ml of ethanol containing 82 mg (3.56 mg-atom) of metal sodium followed by reflux for an hour and by evaporation of ethanol under reduced pressure. The resulting fine powder, 2c, was mixed with 50 ml of N,N-dimethylformamide (DMF)[8] and stirred, to which 0.352 g (1.18 mmol) of 1 in 20 ml of DMF[9] was, then, added dropwise in the period of 3 h in an oil-bath (*ca.* 90 °C).[10] After cooling, the brown reaction mixture was poured into 700 ml of water for precipitation, which was promoted by addition of *ca.* 10 g of sodium chloride (salting-out effect). The precipitate was collected by filtration followed by silica gel column chromatography (Merck silica gel 60, Art. 7734; eluent benzene-ethyl acetate (4 : 1 v/v)) to give 3c (0.65 g), recryst. from ethanol as colorless crystals. All the spectral[11] and analytical data supported the structure.



(1)

a n=4, e n=8
b n=5, f n=9
c n=6, g n=10
d n=7, Ts = $-SO_2-C_6H_4-p-CH_3$ (3)

The others were prepared likewise and the results obtained are summarized in Table, which demonstrate that yields are fairly dependent on the chain length: 2a (n=4) seems too short to couple 1 to give 3a. Yield culminated in 2c (n=6) and 2d (n=7)(best fit length) followed by decreased gradually as the chain length becomes longer.

The present approach to the synthesis of 3 might provide a new method for the extended diazapyridinophane synthesis in general, because this approach is characterized by that (a) stable hydrochloride of dichloro-pyridine derivatives is used directly, (b) high-dilution preparation, commonly employed in cyclophane syntheses, is not required, and (c) versatile synthesis of 2, containing additional nitrogen atoms in between the methylene groups, is feasible[4] and, thus, desirable molecular design will be made possible.

Table. Preparation of $N^2,N^{(n+3)}$-di-*p*-toluenesulfonyl-(n+9)-hydroxy-(n+10)-hydroxymethyl-(n+9),(n+10)'-O-isopropylidene-2,(n+3)-diaza[m](2,5)pyridinophanes [n=5,6,7,8,9,10; m=n+4]

Compnd	n	Ring size m	Isolated yield/%*	mp/°C
3a	4	8	0	——
3b	5	9	18	245 – 246 (decomp)
3c	6	10	90	224 – 225
3d	7	11	95	224 – 226
3e	8	12	76	208 – 209.5
3f	9	13	60	159 – 160
3g	10	14	43	141 – 143

*not optimized

References

1) Partly reported at the 44th Autumn Annual Meeting of the Chemical Society of Japan, October 13th, 1981; Abstr. No. 2H27.

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3) H. Kuzuhara, T. Komatsu, and S. Emoto, Tetrahedron Lett., 1978, 3563.

4) B. Dietrich, M. W. Hosseini, J. M. Lehn, and R. B. Sessions, J. Am. Chem. Soc., 103, 1282 (1981).

5) G. R. Newkome, J. D. Sauer, J. M. Roper, and D. C. Hager, Chem. Revs., 77, 513 (1977).

6) This salt is directly derived by the reaction of 2'-hydroxy-3,4'-Oisopropylidene-pyridoxine[2b] with thionyl chloride in benzene at ambient temperature; recryst. from acetone, as colorless crystals; mp 143 °C (decomp). Found: C, 44.40; H, 4.66; N, 4.67; Cl, 35.50%. Calcd for $C_{11}H_{14}O_2NCl_3$: C, 44.24; H, 4.73; N, 4.69; Cl, 35.62%. IR (KBr disc) ν 2030, 1950, 1540, 1310, 1285, 1050, 840, and 725 cm^{-1} as strong characteristic absorption bands.

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

8) Solubility of the disodium salt (2) into (hot) ethanol or DMF is independent of the chain length; soluble into both hot solvents, n = 4, 5, 7, 9; insoluble into both hot solvents, n = 6, 8; soluble into hot ethanol but insoluble into hot DMF, n = 10. However, the solubility does not seem to affect the final product yield.

9) The dichloro-pyridine hydrochloride (1) was found to be favorably soluble into DMF.

10) Rapid addition and higher temperature resulted in lower yield of 3c.

11) Of spectral data, ^{1}HNMR spectra were particularly interested in relation to the restricted rotation depending on the chain length in comparison with those of the preceding dithia-congeners.[2a] The significant features and the analysis of ^{1}HNMR will be reported elsewhere in due course of time.

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