# Multidentate Chelating Agents: Macrocyclic Azaethers

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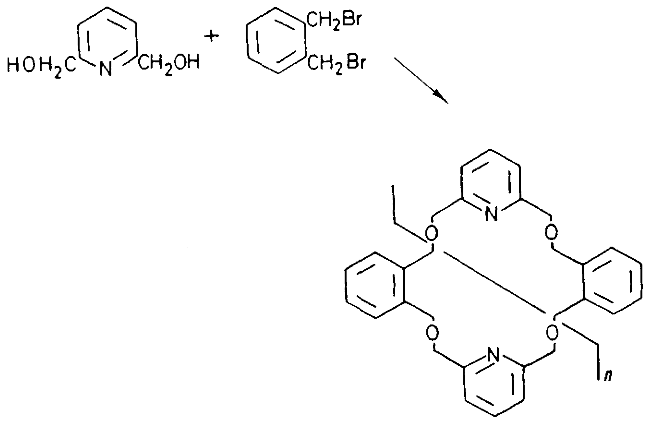
*Summary* The synthesis of the macrocyclic azaether (**1**) and larger pyridine containing macrocycles by cyclocondensation is described.

In view of recent interest[1] in the design and synthesis of specific ligands which form weak metal complexes, we describe the first synthesis of 22-, 33-, 44-, and 55-membered macrocyclic azaethers possessing the 2,6-pyridine unit. 2,6-Di(hydroxymethyl)pyridine, prepared by sodium borohydride reduction of methyl pyridine-2,6-dicarboxylate,[2] in dimethoxyethane (DME) was treated with sodium hydride, followed by dropwise addition of a DME solution of αα′-dibromo-*o*-xylene. The mixture was stirred for a further 1 h at room temperature, heated under reflux for

24 h, cooled, decomposed with ice, and extracted with chloroform giving upon concentration a mixture of macrocycles. Preparative thick-layer chromatography [2 mm, Brinkmann-PF, ethyl acetate–cyclohexane (1 : 1)] afforded (40%) the crystalline 22-membered macrocycle (**1**),† m.p. 142—143°; $M^+$ (25 eV) 482 ($C_{30}H_{30}N_2O_4$); $\lambda_{max}$ ($CHCl_3$) 265 ($\epsilon$ 8800); $\delta$ ($CDCl_3$) 4·53 (s, ArC$H_2$O), 4·59 (s, pyC$H_2$O), and 7·10—7·75 (m, ArH and pyH); molecular weight (osmotic pressure) 480 av. (calc. 482); NaSCN complex: m.p. 195—196° (decomp.). A slower moving fraction contained (9%) the crystalline 33-membered macrocycle (**2**),† m.p. 129—130°; $\lambda_{max}$ ($CHCl_3$) 265 ($\epsilon$ 13,400); molecular weight (osmotic pressure) 688 av. (calc. 723). The n.m.r. spectra of (**2**) and (**1**) were superimposable.



(1) $n$ = 1 (3) $n$ = 3
(2) $n$ = 2 (4) $n$ = 4

The larger 44-membered azaether (**3**) [m.p. 108—109°; $\lambda_{max}$ ($CHCl_3$) 266 ($\epsilon$ 17,680); n.m.r. identical to (**1**)] and the 55-membered macrocycle (**4**) [m.p. 104—105°; $\lambda_{max}$ ($CHCl_3$) 265 ($\epsilon$ 22,400); n.m.r. identical to (**1**)] were isolated and tentatively assigned; however, total proof of structure was hampered by insufficient samples. The "monomeric" unit possessing the 11-membered ring was not detected either under these reaction conditions or when high-dilution procedures, as described by Vogtle,[3] were used.

Co-ordination template effects[4] can be demonstrated to be operative in the synthesis of these heteromacrocycles since in the absence of a metal ion, isolation of linear polymers resulted when an organic base, such as triton B or tetra-n-butylammonium hydroxide, was used. The 2,6-di-(hydroxymethyl)pyridine probably reacts with sodium hydride to form an initial tridentate chelate, which subsequently undergoes Williamson etherification forming the macrocycle (**1**) as either a bis-tridentate or hexadentate chelate.

We acknowledge the support of Public Health Service grant from the National Institute of Neurological Diseases and Stroke, The Petroleum Research Fund, administered by the American Chemical Society, and the Research Corporation.

(*Received*, 23*rd August* 1973; *Com.* 1209.)

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† Satisfactory analytical data were obtained for these new compounds.

[1] D. St. C. Black and A. J. Hartshore, *Coord. Chem. Rev.*, 1973, **9**, 219 and refs. therein.

[2] T. Shimamoto, M. Ishikawa, H. Ishikawa, and M. Inone, Jap. P. 8620/1967; *Chem. Abs.*, 1968, **68**, 2815x.

[3] F. Vogtle, *Chem. and Ind.*, 1972, 346.

[4] D. H. Busch, *Rec. Chem. Progr.*, 1964, **25**, 107; *Helv. Chim. Acta, Fasciculus extraordinarius Alfred Werner*, 1967, 174; L. F. Lindoy and D. H. Busch, *Prep. Inorg. React.*, 1971, **6**, 7.