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SYNTHESIS OF MACROCYCLIC LIGANDS CONTAINING THE INDOLE RING SYSTEM

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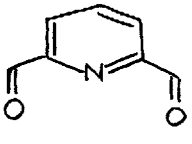
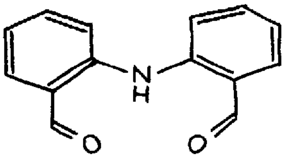
Summary: 2,7-Diformyl-3-methyl-4,6-dimethoxyindole (6) has been synthesized and converted by metal template reactions into the macrocyclic complexes (10-12).

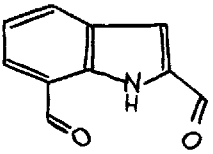
Numerous macrocyclic metal complexes have been prepared using the metal template condensation of pyridine -2,6-dicarbonyl compounds [1,2](1) and more recently 2,2′ -iminobisbenzaldehyde (2)[3] with various primary diamines in the presence of suitable metal salts. These structural moieties (1) and (2) respectively offer the incorporation of two five-membered or two six-membered chelate rings into the resulting complexes: furthermore, in the case of dialdehyde (2), deprotonation occurs. The similar incorporation of a 2,7-diformyl indole (3) would be expected to give rise to a combination of five and six-membered chelate rings, again with deprotonation occurring. The indole ring system (3) would also offer a certain rigidity not available in structure (2).



(1)



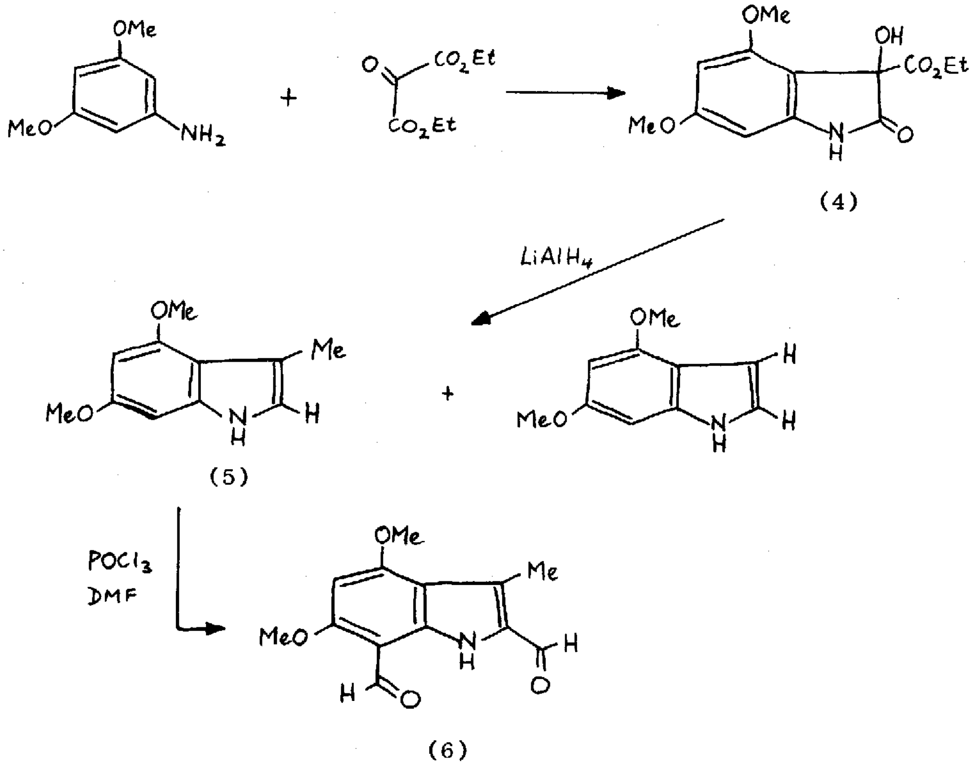
(2)



(3)

We now report the synthesis of 2,7-diformyl-3-methyl-4,6-dimethoxyindole (6) and a selection of macrocyclic metal complexes derived from it. This work forms part of a general investigation of the coordination of indoles within the framework of multidentate ligand systems. The diformyl indole (6) was chosen because it should be obtainable by direct formylation of 3-methyl-4,6-dimethoxyindole (5), the methyl group serving to block the 3-position and also to activate the 2-position, and the methoxy groups providing activation at the 7-position.

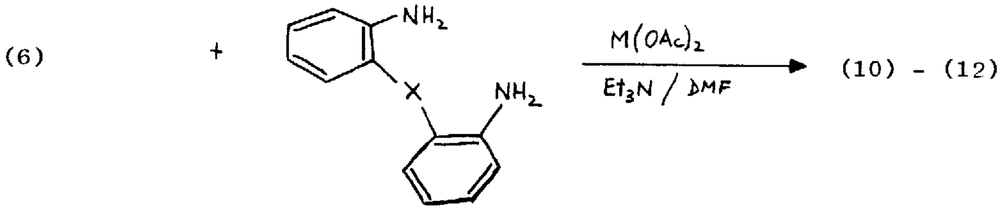
The synthetic route to (6) is outlined in Scheme I.



(Scheme I)

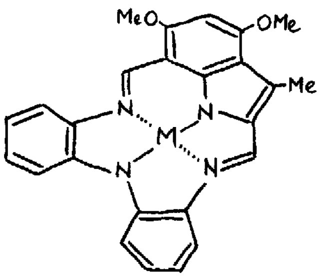
The known oxindole (4)[4], obtained in 85% yield from 3,5-dimethoxyaniline and diethyl mesoxalate, was reduced with excess lithium aluminium hydride in dioxan to afford, after chromatographic separation on silicic acid, the 3-methyl indole (5) in 51% yield [m.p. 73-74°; $C_{11}H_{13}NO_2$; m/e 191 (100); ν_{max} 3400, 1615, 1585cm^{-1}; δ 2.42, s (C-Me); 3.77 and 3.84, each s (OMe); 6.2-6.7, m (H2,H5,H7); 7.7, bs (NH)] and 4,6-dimethoxyindole [4] in 24% yield. Treatment of indole (5) with a little more than two equivalents of phosphorus oxychloride in dimethylformamide (DMF) afforded an 84% yield of the diformyl indole (6) [m.p. 206-207°; $C_{13}H_{13}NO_4$; m/e 247(100); ν max 3440,1680, 1580 cm^{-1}; δ 2.70, s(C-Me); 4.00 and 4.04, each s (OMe); 6.10, s (H5); 9.95 and 10.35, each s (CHO)] .

Reaction of the indole dialdehyde (6) with 2,2′ -diaminodiphenylamine (7)[3], 2-amino-N-(2′-aminophenyl)benzamide (8)[3] or 2′-aminobenzoyl-2-aminobenzamide (9)[3], in the presence of nickel (II) or copper (II) acetates, in DMF containing triethylamine gave the macrocyclic complexes (10), (11) and (12)(M=Ni,Cu) respectively in yields of 31-65% (Scheme 2).

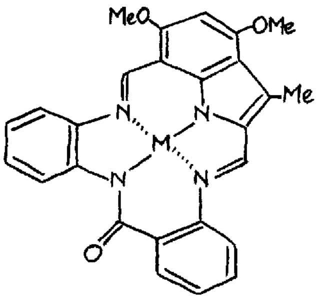


(7) X = NH
(8) X = NHCO
(9) X = CONHCO

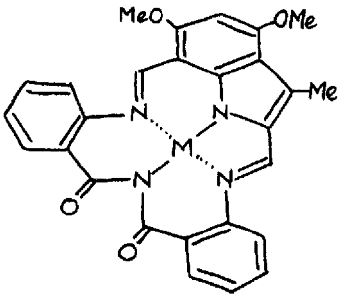
(Scheme 2)



(10)



(11)



(12)

The nickel (II) complexes were reddish-brown and the copper (II) complexes were brown. The infrared spectra of all complexes showed the presence of bands at 1580-1590 cm^{-1}, attributable to imine stretching modes, and the absence of aldehyde absorption bands. Two isomeric structures are possible for complexes (11), but that with a 5,6,5,6 arrangement of chelate rings is preferred over that with an alternative 5,5,6,6 combination for geometrical reasons and in the light of earlier observations[5]. X-ray crystal structure determination has not been possible so far.

The above route to the diformyl indole (6) can easily be adapted to provide other 3-substituted analogs capable of conferring different properties on the resulting macrocyclic ligands. In general, indoles are more amenable to chemical transformation than are pyridine compounds and it is surprising that they have not previously been incorporated into macrocyclic compounds[6]. Compound (6) would also provide a simple entry point into indole-containing macrocycles of the crown ether type.

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