Synthesis of a New Class of Indole-containing Macrocycles

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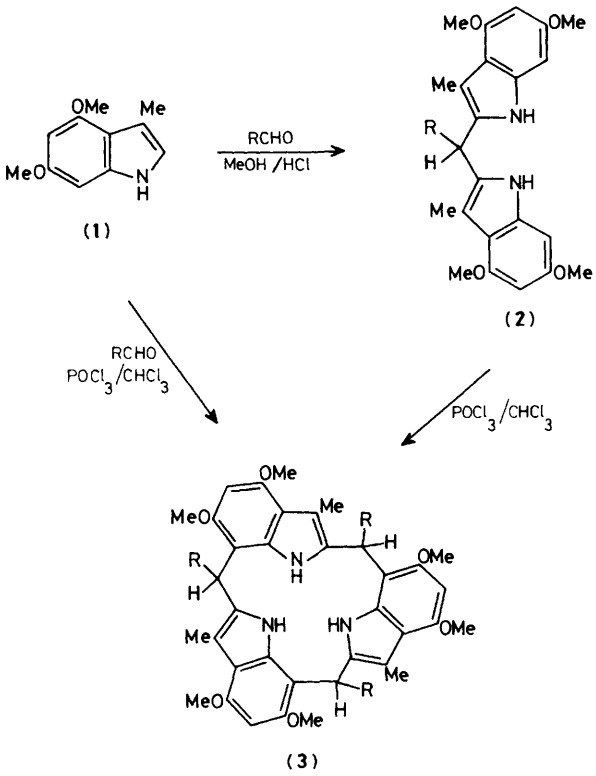
4,6-Dimethoxy-3-methylindole can be converted by treatment with aryl aldehydes and phosphoryl chloride in chloroform into macrocyclic tri-indolyl methanes, with the indole rings linked at C-2 and C-7.

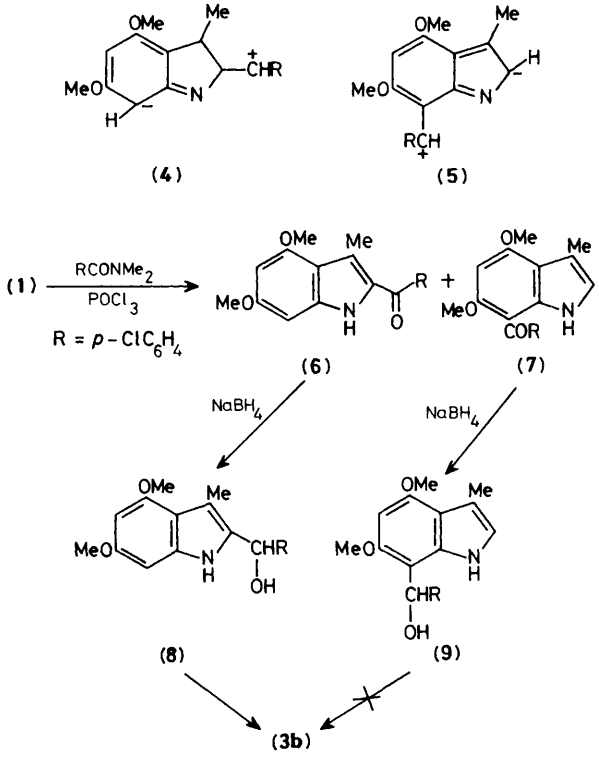
We have previously shown that 4,6-dimethoxy-3-methylindole (**1**) undergoes formylation at C-2 and C-7.[1] We now report that this bifunctional indole (**1**) undergoes addition to a range of aryl aldehydes in methanolic hydrochloric acid to give high yields (79—87%) of the 2,2′-di-indolylmethanes (**2**), showing regioselectivity of addition at C-2 rather than C-7 (Scheme 1).† In contrast, treatment of the indole (**1**) with the same aryl aldehydes and phosphoryl chloride in refluxing chloroform gave the macrocyclic tri-indolylmethanes (**3**) in variable yields [(**3a**), 12%; (**3b**), 83%; (**3c**), 10%; (**3d**), 81%] (Scheme 1). The macrocylic compounds (**3**) could also be formed in similar yields from the di-indolylmethanes (**2**) on treatment with phosphoryl chloride in refluxing chloroform, presumably as a result of the reversal of the process of formation of compounds (**2**) from indole (**1**). An *X*-ray crystal structure determination for compound (**3a**) is consistent with the 2,7′-linkage in the macrocycles (**3**). The rather buckled structure shows a central 15-membered ring containing the three indole nitrogen atoms.

† All new compounds gave spectroscopic and microanalytical data in accord with assigned structures. Data are quoted for the high-yielding compound (**3b**), the ketone (**6**), and the key intermediate (**8**). For (**3b**); 83% yield; m.p. 289—290 °C; ^{1}H n.m.r. (500 MHz, $CDCl_3$), δ 2.07, 2.12, 2.53 (each 3H, s, CH_3), 3.71, 3.72, 3.91, 3.93, 3.94, 4.05 (each 3H, s, OCH_3), 5.98, 6.00 (each 1H, s, CH), 6.20 (2H, d, *J* 8.8 Hz, ArH), 6.24 (1H, s, ArH), 6.30 (2H, s, ArH), 6.38 (2H, d, *J* 8.3 Hz, ArH), 6.66 (1H, s, CH), 6.71 (2H, d, *J* 8.3 Hz, ArH), 6.74, 6.76 (each 1H, s, NH), 6.81 (2H, d, *J* 8.6 Hz, ArH), 6.91 (2H, d, *J* 8.4 Hz, ArH), 7.09 (2H, d, *J* 8.4 Hz, ArH), 7.52 (1H, s, NH); m.s., *m/z* 939 (M^+, 86.8% for ^{35}Cl). For (**6**); 68% yield; m.p. 220 °C; ^{1}H n.m.r. (500 MHz, $CDCl_3$), δ 2.34 (3H, s, CH_3), 3.83, 3.84 (each 3H, s, OCH_3), 6.11, 6.35 (each 1H, d, *J* 1.7 Hz, ArH), 7.45, 7.67 (each 2H, d, *J* 8.4 Hz, ArH), 8.8 (1H, br.s, NH); m.s., *m/z* 329 (M^+, 100%). For (**8**); 100% yield; m.p. 133 °C; ^{1}H n.m.r. [500 MHz, $(CD_3)_2SO$], δ 2.34 (3H, s, CH_3), 3.69, 3.77 (each 3H, s, OCH_3), 5.85 (1H, br.s, CH) 5.90 (H, br.s, OH), 6.01, 6.36 (each 1H, d, *J* 2.0 Hz, ArH), 7.30, 7.36 (each 2H, d, *J* 8.4 Hz, ArH), 10.31 (1H, br.s, NH); m.s., *m/z* 331 (M^+, 17.4% for ^{35}Cl).



a; R = Ph
b; R = *p*-ClC_6H_4
c; R = *o*-ClC_6H_4
d; R = *p*-BrC_6H_4

Scheme 1



Scheme 2

Two phenyl groups lie on one side of the average plane of the macrocycle and one on the other.‡

The formation of macrocycles (**3**) from indole (**1**) could in principle take place by trimerization of either of the zwitterionic intermediates (**4**) or (**5**). Such intermediates were therefore generated independently *via* the sequence shown in Scheme 2. The modified Vilsmeier reaction of indole (**1**) gave a mixture of the 2- and 7-substituted aryl ketones (**6**) and (**7**). After separation, these were reduced to the corresponding alcohols (**8**) and (**9**). Treatment of the alcohol (**8**) with phosphoryl chloride in chloroform at room temperature yielded the macrocycle (**3b**) in 81% yield. In contrast, similar treatment of the alcohol (**9**) yielded no macrocycle but only the di-indolylmethane (**2b**). Thus the intermediate (**4**) is implicated in the trimerization process.

The above reaction represents a significant extension to the range of acid-catalysed additions of aldehydes or ketones to bifunctional electron-rich systems such as furans,[2] pyrroles,[3] and resorcinol,[4] in which macrocycle formation is controlled by the geometry of the system.

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‡ Full details will be published elsewhere.

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