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Reaction of 4,6-Dimethoxy-3-methylindole with Aromatic Aldehydes: a Simple Synthesis of Calix[3]indoles*†

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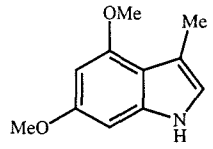
2,7:2,7:2,7-Linked calix[3]indoles (3a–d) have been prepared by the reaction of 4,6-dimethoxy-3-methylindole (1) and benzaldehydes with phosphoryl chloride or by a direct reaction of di(4,6-dimethoxy-3-methylindol-2-yl)phenylmethanes (2a–d) with phosphoryl chloride. An X-ray crystal structure determination of the macrocycle (3d) is reported. 4,6-Dimethoxy-3-methylindolemethanols (9) and (10) were prepared and reacted with phosphoryl chloride to study the mechanism of formation of the macrocycle.

Introduction

Calixarenes,[2] phenol–formaldehyde macrocyclic oligomers, are an important class of compounds having unprecedented properties. These compounds can act as ionophores and adsorbents for heavy metals and can have applications as catalysts, hosts for guest inclusion and in catalysis. Phenols react with formaldehyde under basic conditions to yield calixarenes of different size depending upon the reaction conditions. Resorcinol on the other hand reacts with less reactive aldehydes under acidic conditions to give cyclic tetramers.[3,4] Although the chemistry of these compounds has been very widely studied, reports on the related heterocyclic analogues of calixarenes are rather limited. Furan reacts under acidic conditions with aldehydes or ketones to give cyclic tetramers.[5,6] Thiophen[7,8] and pyrrole[9] undergo similar acid-catalysed reaction with acetone. The reaction of pyrrole with aromatic aldehydes is well known to give tetraarylporphyrins[10] through the rapid oxidation of initially formed tetramers. Hence these compounds are not calixarene-like. A pyridinocalix[4]arene has been reported by Newkome *et al.*[11]



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The basic requirement for the synthesis of calixarenes is that the substrate reacting with the aldehyde or ketone must have two reactive sites for electrophilic substitution. 4,6-Dimethoxylindoles,[12] e.g. (1), belong to a special class of electron-rich indoles which possess this ambident reactivity. These indoles, in addition to undergoing electrophilic substitution at C 7, undergo a facile electrophilic reaction at C 2 or C 3 as well, depending upon the substitution pattern of the indole. For example a Vilsmeier–Haack formylation of 4,6-dimethoxy-3-methylindole gives a mixture of 2-formyl- and 7-formylindoles.[13] As a result of this reactivity it was of interest to investigate the reaction of 4,6-dimethoxy-3-methylindole (1) with aldehydes and ketones. Such reactions would be expected to yield either linear or cyclic oligomers in which indoles would be linked through methylene bridges. The cyclic oligomers, depending upon their size and shape, could show interesting properties. Furthermore, substitution on the indole ring in the macrocycle could be easily manipulated to fine tune the properties of the macrocycles. In this paper we describe the reactions of 4,6-dimethoxy-3-methylindole with substituted benzaldehydes.

Results and Discussion

Synthesis of Macrocyclic Trimers

4,6-Dimethoxy-3-methylindole[13] (1) was prepared in two steps by reaction of 3,5-dimethoxyaniline with diethyl oxomalonate followed by reduction according to the method previously described by us. It became clear from the initial experiments that the base-catalysed method so successfully used in the phenol–formaldehyde synthesis of calixarenes was not the method of choice for indole aldehyde reactions. The indole was found to be generally unreactive under these conditions, but, in

* A preliminary report of some of these results has appeared.[1]
† Dedicated to Professor Stephen Angyal on the occasion of his 80th birthday

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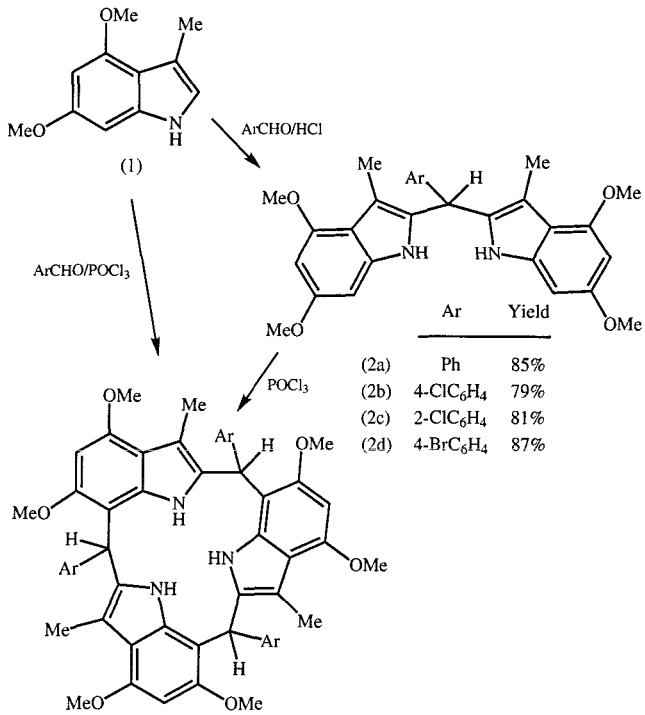
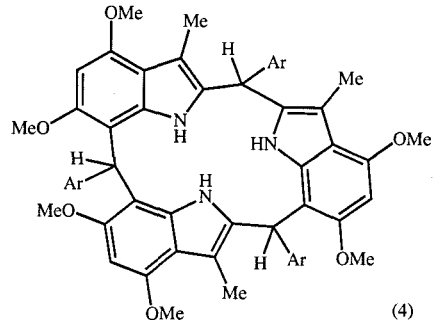
the case of formaldehyde, traces of diindolylmethane were observed. So the main attention was focused on acid- and Lewis acid-catalysed reaction of the indole with aldehydes along the lines of resorcinol–aldehyde chemistry. Reaction of 4,6-dimethoxy-3-methylindole (1) with formaldehyde or benzaldehyde in refluxing ethanol in the presence of concentrated hydrochloric acid produced very complex mixtures of products from which nothing significant could be isolated. Although it has been reported[14] that indole itself reacts with formaldehyde in the presence of sulfuric acid to yield a cyclic tetramer in low yield, the reaction is not reproducible. Skatole on the other hand is known to react with benzaldehydes at room temperature to yield di(indol-2-yl)phenylmethanes[15] in good yield. Reaction of 4,6-dimethoxy-3-methylindole (1) under these conditions led similarly to the formation of di(indol-2-yl)phenylmethanes (2a–d) (Scheme 1). The product precipitated out during the reaction and was identified by spectroscopic data. The ^{1}H n.m.r. spectrum clearly showed the presence of a pair of doublets for H5 and H7 with a coupling constant of 1·8 Hz, indicating that those positions are unsubstituted. The proton H2 of 4,6-dimethoxy-3-methylindole (1) was absent and the methine proton appeared at 5·8 ppm. In this reaction none of the other possible isomers, the 2,7′ or 7,7′, was detected. It is possible that the 2,2′ isomer di(indol-2-yl)phenylmethane is a kinetic product which precipitates out of the reaction mixture, or alternatively that the bulky electrophile favours attack at the less hindered 2-position of the indole.

The reaction of 4,6-dimethoxy-3-methylindole (1) with benzaldehydes in the presence of phosphoryl chloride took another path. Thus refluxing a solution of the indole and substituted benzaldehydes with phosphoryl chloride gave the unusual and novel products (3a–d) which could be purified by column chromatography. Furthermore, these products could be prepared by direct reaction of di(indol-2-yl)phenylmethanes (2a–d) with phosphoryl chloride. The ^{1}H n.m.r. spectrum of the product (3a) showed the presence of three methyl resonances, six methoxy resonances, three H5 resonances and three methine resonances. The mass spectrum clearly showed a molecular ion at m/z 837. The observed spectroscopic data fitted perfectly with an indole arylmethine trimer. However, the mode and nature of the arylmethine link could not be assigned unambiguously from the above data. In a trimer with three indoles and three arylmethines, two different types of linkage are possible, namely 2,7:2,7:2,7 (3) and 2,2:7,2:7,7 (4). In terms of geometry the molecule can have a cone shape or a flattened cone shape with three aryl rings being either axial or equatorial. The possibility of the macrocycle being a cone with three axial or three equatorial phenyl groups was ruled out on the basis of symmetry arguments, because the three indoles were found to show separate sets of n.m.r. signals. An interesting feature of the reaction is that,



Scheme 1



(4)

despite all the different structural possibilities, only one isomer of the macrocycle was detected.

The structure of the product was finally established by single-crystal X-ray crystallography. The crystal structure showed the product (3d) to be a symmetrical 2,7:2,7:2,7-macrocycle with a flattened partial cone structure. This structure clearly shows that, relative to the approximate plane of the ring, one indole NH points up, one down and the third is almost in the plane. The various bond angles (see Fig. 1) defined by C(1A)–C(12B)–C(7B), C(1B)–C(12C)–C(7C) and C(1C)–C(12A)–C(7A) were found to be 112·9(6), 112·2(6) and 114·3(6)° respectively. On the other hand, torsional angles defined by C(2B)–C(1B)–C(12C)–C(7C), C(2A)–C(1A)–C(12B)–C(7B) and C(2C)–C(1C)–C(12A)–C(7A) were 177·0(7),

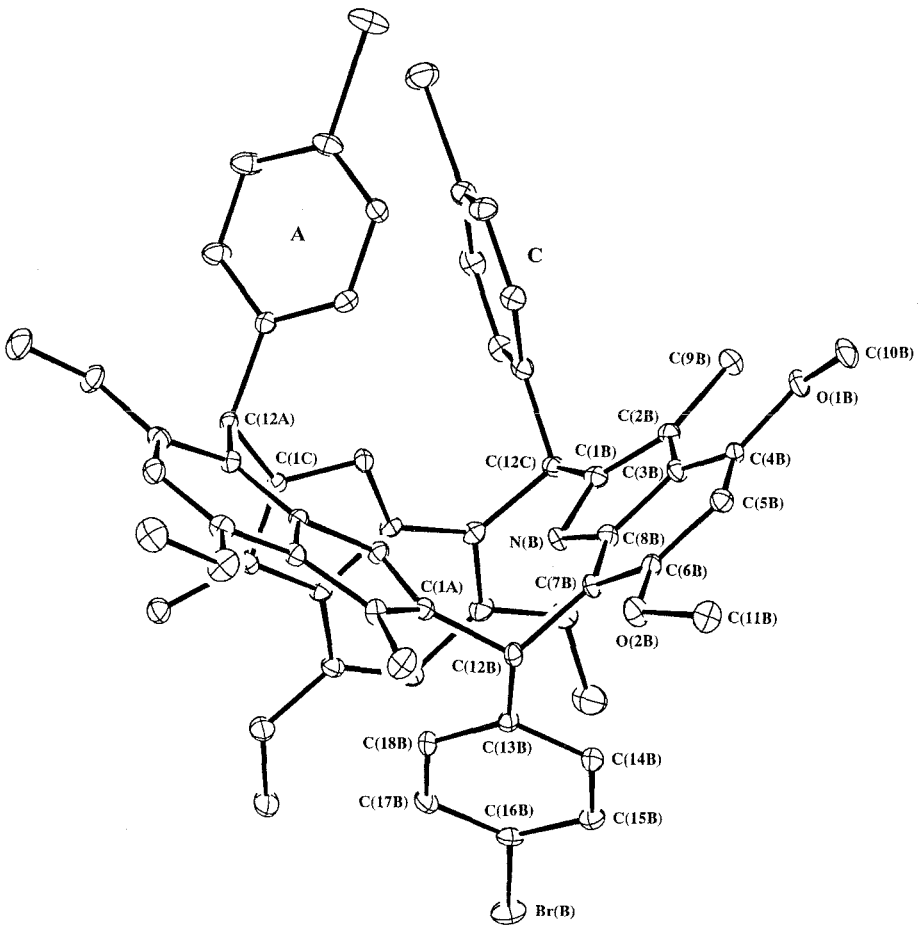


Fig. 1. ORTEP diagram for calix[3]indole (3d). Full numbering for only residue B of the trimer macrocycle is given.

Table 1. Non-hydrogen atomic parameters for (3d)

B_{eq} (Å^2) is the isotropic equivalent of the anisotropic temperature factor. Estimated standard deviations are in parentheses

Atom	x	y	z	B_{eq}	Atom	x	y	z	B_{eq}
Br(A)	0·3847(1)	0·1324(1)	0·8772(1)	8·18(4)	C(8B)	0·1369(3)	0·4905(4)	0·8110(6)	3·3(2)
O(1A)	0·4525(3)	0·6548(3)	0·9796(4)	6·1(2)	C(9B)	0·0579(4)	0·3054(4)	0·7720(6)	4·4(3)
O(2a)	0·5253(3)	0·4586(3)	0·7583(4)	4·9(2)	C(10B)	0·0357(4)	0·3704(4)	1·0899(6)	5·4(3)
N(A)	0·2980(3)	0·5453(3)	0·7752(4)	3·3(2)	C(11B)	0·1137(4)	0·6284(5)	1·1098(6)	5·3(3)
C(1A)	0·2688(4)	0·6001(4)	0·8324(5)	3·3(2)	C(12B)	0·1960(4)	0·6154(4)	0·8257(5)	3·3(2)
C(2A)	0·3165(4)	0·6318(4)	0·8918(5)	3·6(2)	C(13B)	0·1720(4)	0·6402(4)	0·7208(6)	3·3(2)
C(3A)	0·3786(4)	0·5955(4)	0·8709(6)	3·5(2)	C(14B)	0·1029(4)	0·6485(4)	0·7048(6)	4·2(3)
C(4A)	0·4434(4)	0·6011(4)	0·9077(6)	4·0(3)	C(15B)	0·0778(4)	0·6681(4)	0·6105(7)	4·5(3)
C(5A)	0·4924(4)	0·5567(5)	0·8721(6)	4·3(3)	C(16B)	0·1209(5)	0·6787(4)	0·5332(6)	4·1(3)
C(6A)	0·4775(4)	0·5052(4)	0·7973(6)	3·7(3)	C(17B)	0·1892(5)	0·6717(4)	0·5457(6)	4·4(3)
C(7A)	0·4148(4)	0·4963(4)	0·7562(5)	3·0(2)	C(18B)	0·2134(4)	0·6521(4)	0·6396(7)	4·0(3)
C(8A)	0·3656(4)	0·5418(4)	0·7969(5)	3·1(2)	Br(C)	0·2751(1)	0·0674(1)	0·5576(1)	7·36(4)
C(9A)	0·3059(4)	0·6917(5)	0·9674(6)	5·8(3)	O(1C)	0·2823(2)	0·5897(3)	0·3558(4)	5·2(2)
C(10A)	0·5168(5)	0·6594(5)	1·0266(6)	6·4(3)	O(2C)	0·0824(3)	0·4454(3)	0·4161(4)	5·5(2)
C(11A)	0·5906(4)	0·4588(5)	0·8002(7)	6·6(3)	N(C)	0·2868(3)	0·4192(3)	0·6091(4)	3·3(2)
C(12A)	0·4042(3)	0·4389(4)	0·6752(5)	3·0(2)	C(1C)	0·3477(4)	0·4556(4)	0·6034(5)	3·0(2)
C(13A)	0·3970(4)	0·3613(4)	0·7217(6)	3·3(2)	C(2C)	0·3443(4)	0·5066(4)	0·5294(5)	3·3(2)
C(14A)	0·4345(4)	0·3034(5)	0·6858(6)	4·8(3)	C(3C)	0·2790(4)	0·5005(4)	0·4839(6)	3·4(2)
C(15A)	0·4306(5)	0·2342(5)	0·7302(7)	5·8(3)	C(4C)	0·2457(4)	0·5361(4)	0·4035(5)	3·5(3)
C(16A)	0·3885(5)	0·2255(4)	0·8118(7)	4·7(3)	C(5C)	0·1816(4)	0·5172(4)	0·3797(6)	4·1(3)
C(17A)	0·3517(4)	0·2807(5)	0·8485(6)	4·3(3)	C(6C)	0·1483(4)	0·4644(4)	0·4371(6)	4·1(3)
C(18A)	0·3558(4)	0·3503(4)	0·8036(6)	3·9(3)	C(7C)	0·1780(4)	0·4271(4)	0·5166(5)	3·6(2)
Br(B)	0·0879(1)	0·7046(1)	0·4040(1)	6·56(3)	C(8C)	0·2443(4)	0·4465(4)	0·5352(5)	3·0(2)
O(1B)	0·0466(2)	0·3735(3)	0·9833(4)	4·5(2)	C(9C)	0·4000(4)	0·5591(4)	0·5019(6)	4·5(3)
O(2B)	0·1493(3)	0·6132(3)	1·0217(4)	5·1(2)	C(10C)	0·2536(4)	0·6238(5)	0·2692(7)	6·3(3)
N(B)	0·1537(3)	0·4740(3)	0·7133(4)	3·3(2)	C(11C)	0·0431(5)	0·4916(6)	0·3595(8)	8·9(4)
C(1B)	0·1279(4)	0·4050(4)	0·6881(6)	3·6(3)	C(12C)	0·1397(3)	0·3736(4)	0·5844(6)	3·5(2)
C(2B)	0·0943(4)	0·3774(4)	0·7681(6)	3·5(2)	C(13C)	0·1736(4)	0·2980(4)	0·5821(6)	3·6(2)
C(3B)	0·0999(4)	0·4309(4)	0·8475(6)	3·5(3)	C(14C)	0·1740(4)	0·2593(5)	0·4941(6)	4·3(3)
C(4B)	0·0799(3)	0·4344(4)	0·9484(6)	3·5(3)	C(15C)	0·2032(4)	0·1907(5)	0·4867(6)	4·7(3)
C(5B)	0·0953(4)	0·4949(5)	1·0054(6)	3·9(3)	C(16C)	0·2336(4)	0·1608(4)	0·5693(7)	4·5(3)
C(6B)	0·1313(4)	0·5534(4)	0·9640(6)	3·7(3)	C(17C)	0·2351(4)	0·1970(5)	0·6594(6)	4·8(3)
C(7B)	0·1539(3)	0·5534(4)	0·8668(6)	3·2(2)	C(18C)	0·2045(4)	0·2667(4)	0·6660(6)	4·2(3)

−110·6(8) and 72·8(9)° respectively. A Dreiding model of the macrocycle showed very little flexibility indicating structural rigidity. This point was further established by a high-temperature n.m.r. experiment: heating a sample up to 100°C did not produce any change in the spectrum of the macrocycle.

Crystallography

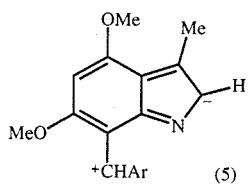
Crystal data for (3d). $(C_{18}H_{16}BrNO_2)_3$, M 1074·7, monoclinic, space group $P2_1/c$, a 20·089(4), b 18·203(2), c 13·287(2) Å, β 90·436(9)°, V 4858(1) Å^3, D_c 1·469 g cm^{-3}, Z 4, μ_{Cu} 35·21 cm^{-1}. Crystal size 0·07 by 0·15 by 0·15 mm, $2\theta_{max}$ 110°, minimum and maximum transmission factors 0·63 and 0·82. The number of reflections was 3012 considered observed out of 6092 unique data, with R_{merge} 0·023 for 167 pairs of equivalent $hk0$ reflections. Final residuals were R 0·040 and R_w 0·047 for the observed data.

Structure determination. Reflection data were measured with an Enraf–Nonius CAD-4 diffractometer in $\theta/2\theta$ scan mode by using nickel-filtered copper radiation (λ 1·5418 Å). Data were corrected for absorption by using the analytical method of de Meulenaer and Tompa.[16] Reflections with $I > 3\sigma(I)$ were considered observed. The structure was determined by direct phasing and Fourier methods. Hydrogen atoms were included in calculated positions and were assigned thermal parameters equal to those of the atom to which they were bonded. Positional and anisotropic thermal parameters for the non-hydrogen atoms were refined by using full matrix least squares. Reflection weights used were $1/\sigma^2(F_o)$, with $\sigma(F_o)$ being derived from $\sigma(I_o) = [\sigma^2(I_o)+(0·04I_o)^2]^{1/2}$. The weighted residuals are defined as $R = \sum \Delta / \sum F_o$ and $R_w = (\sum w\Delta^2 / \sum wF_o^2)^{1/2}$. Atomic scattering factors and anomalous dispersion parameters were from International Tables for X-Ray Crystallography.[17] Structure solution was by MULTAN80[18] and refinement used BLOCKLS, a local version of ORFLS.[19] ORTEP-II[20] running on a Macintosh IIcx computer was used for the structural diagram, and a DEC Alpha-AXP workstation was used for calculations.

The structure and atom numbering scheme, with only one unit of the trimer fully labelled, are shown in Fig. 1. Atomic parameters, bond lengths, and selected bond angles and torsional angles are given in Tables 1–4 respectively. Material deposited comprises all atom and thermal parameters, interatomic distances, angles and torsional angles, and observed and calculated structure factors (copies are available from the Australian Journal of Chemistry, P.O. Box 1139, Collingwood, Vic. 3066).

Mechanism of Formation of the Macrocycle

The formation of the macrocycle could in principle take place by the trimerization of the zwitterionic intermediates (5) or (6). Such intermediates can easily be derived from the corresponding indolemethanols. It was envisaged that benzoylation of the indole followed by sodium borohydride reduction would be the easiest route to these alcohols. Indole is known to react with *N*,*N*-dimethylbenzamide and phosphoryl chloride to yield 3-benzoylindole[21] in good yield. A similar reaction (Scheme 2) of 4,6-dimethoxy-3-methylindole (1) with 4-chloro-*N*,*N*-dimethylbenzamide gave a mixture of 7-(4-chlorobenzoyl)- (7a) and 2-(4-chlorobenzoyl)-indole (8a) in an overall yield of 80%. The 40 : 60 mixture of 7- and 2-benzoylindole was easily separated by column chromatography on silica gel with dichloromethane as eluent. 7-(4-Chlorobenzoyl)indole (7a) has a higher R_F value and was isolated as a fluffy yellow solid. The ^{1}H n.m.r. spectrum showed the presence of a singlet at 6·12 ppm due to H 5 and a broad singlet at 6·80 ppm for H 2. The absence of H 7 and absence of any *meta* coupling for H 5 clearly established the regiochemistry. The relatively non-polar nature of the compound can be explained by a six-membered ring from the hydrogen bond between the oxygen of the carbonyl group and NH of the indole ring.



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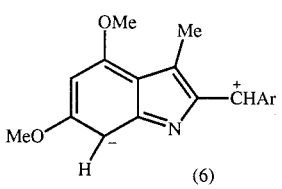


(6)

Table 2. Bond lengths (Å) for (3d)

Estimated standard deviations are in parentheses

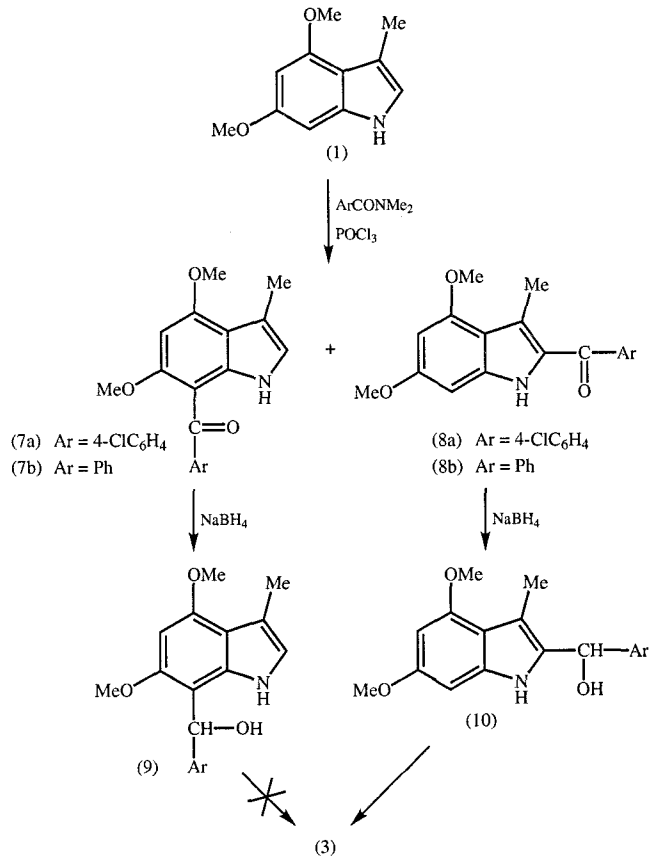
Atoms	Distance	Atoms	Distance
N(A)–C(1A)	1·386(8)	O(1B)–C(10B)	1·435(9)
C(1A)–C(2A)	1·365(9)	C(6B)–O(2B)	1·378(8)
C(2A)–C(3A)	1·440(9)	O(2B)–C(11B)	1·405(8)
C(3A)–C(4A)	1·391(10)	C(7B)–C(12B)	1·515(9)
C(4A)–C(5A)	1·362(10)	C(12B)–C(13B)	1·540(10)
C(5A)–C(6A)	1·397(10)	C(13B)–C(14B)	1·411(9)
C(6A)–C(7A)	1·380(9)	C(14B)–C(15B)	1·394(10)
C(7A)–C(8A)	1·401(9)	C(15B)–C(16B)	1·362(10)
C(8A)–(NA)	1·388(8)	C(16B)–C(17B)	1·387(10)
C(3A)–C(8A)	1·410(9)	C(17B)–C(18B)	1·381(10)
C(1A)–C(12B)	1·492(9)	C(18B)–C(13B)	1·384(9)
C(2A)–C(9A)	1·498(10)	C(16B)–BrB	1·896(7)
C(4A)–O(1A)	1·378(8)	N(C)–C(1C)	1·393(8)
O(1A)–C(10A)	1·434(9)	C(1C)–C(2C)	1·355(8)
C(6A)–O(2A)	1·385(8)	C(2C)–C(3C)	1·444(9)
O(2A)–C(11A)	1·420(8)	C(3C)–C(4C)	1·413(9)
C(7A)–C(12A)	1·514(9)	C(4C)–C(5C)	1·369(10)
C(12A)–C(13A)	1·549(9)	C(5C)–C(6C)	1·400(10)
C(13A)–C(14A)	1·383(9)	C(6C)–C(7C)	1·387(9)
C(14A)–C(15A)	1·393(10)	C(7C)–C(8C)	1·399(9)
C(15A)–C(16A)	1·389(11)	C(8C)–N(C)	1·387(8)
C(16A)–C(17A)	1·342(10)	C(3C)–C(8C)	1·388(9)
C(17A)–C(18A)	1·402(10)	C(1C)–C(12A)	1·508(9)
C(18A)–C(13A)	1·387(9)	C(2C)–C(9C)	1·518(9)
C(16A)–BrA	1·906(8)	C(4C)–O(1C)	1·378(8)
N(B)–C(1B)	1·396(8)	O(1C)–C(10C)	1·425(8)
C(1B)–C(2B)	1·361(9)	C(6C)–(O2C)	1·394(8)
C(2B)–C(3B)	1·439(9)	O(2C)–C(11C)	1·374(10)
C(3B)–C(4B)	1·404(9)	C(7C)–C(12C)	1·537(9)
C(4B)–C(5B)	1·371(9)	C(12C)–C(13C)	1·536(9)
C(5B)–C(6B)	1·402(10)	C(13C)–C(14C)	1·366(10)
C(6B)–C(7B)	1·373(9)	C(14C)–C(15C)	1·384(10)
C(7B)–C(8B)	1·404(9)	C(15C)–C(16C)	1·365(10)
C(8B)–N(B)	1·377(8)	C(16C)–C(17C)	1·367(10)
C(3B)–C(8B)	1·404(9)	C(17C)–C(18C)	1·413(10)
C(1B)–C(12C)	1·511(10)	C(18C)–C(13C)	1·394(9)
C(2B)–C(9B)	1·501(9)	C(16C)–Br(C)	1·901(8)
C(4B)–O(1B)	1·377(8)		

2-(4-Chlorobenzoyl)indole (8a) with a lower R_F value was isolated as yellow prisms, and its structure was established by spectroscopic means. The n.m.r. spectum showed the presence of doublets at 6·11 and 6·35 ppm with a coupling constant of 1·8 Hz for H5 and H7 respectively. The signal for the less deshielded NH was observed at 8·79 ppm, and the absence of a resonance for H2 further confirmed the structure.

Reduction of the separated benzoyl compounds (7a) and (8a) was carried out by using sodium borohydride

Table 3. Selected bond angles (degrees) for (3d)
Estimated standard deviations are in parentheses

Atoms	Angle	Atoms	Angle
C(8A)-N(A)-C(1A)	109·6(6)	C(4B)-C(5B)-C(6B)	120·6(7)
N(A)-C(1A)-C(2A)	109·0(7)	C(5B)-C(6B)-O(2B)	121·1(8)
N(A)-C(1A)-C(12B)	121·3(7)	O(2B)-C(6B)-C(7B)	115·9(7)
C(2A)-C(1A)-C(12B)	129·7(7)	C(5B)-C(6B)-C(7B)	123·0(7)
C(1A)-C(2A)-C(3A)	107·4(6)	C(6B)-C(7B)-C(8B)	114·6(7)
C(1A)-C(2A)-C(9A)	126·5(7)	C(6B)-C(7B)-C(12B)	122·0(7)
C(3A)-C(2A)-C(9A)	126·2(7)	C(8B)-C(7B)-C(12B)	123·4(7)
C(2A)-C(3A)-C(4A)	135·1(8)	C(3B)-C(8B)-N(B)	106·8(7)
C(2A)-C(3A)-C(8A)	107·3(6)	C(7B)-C(8B)-N(B)	128·0(7)
C(4A)-C(3A)-C(8A)	117·5(8)	C(3B)-C(8B)-C(7B)	125·1(7)
C(3A)-C(4A)-O(1A)	114·4(8)	C(1A)-C(12B)-C(7B)	112·9(6)
O(1A)-C(4A)-C(5A)	124·7(7)	C(1A)-C(12B)-C(13B)	114·2(6)
C(3A)-C(4A)-C(5A)	120·8(8)	C(7B)-C(12B)-C(13B)	111·9(6)
C(4A)-C(5A)-C(6A)	119·6(7)	C(8C)-N(C)-C(1C)	109·1(6)
C(5A)-C(6A)-O(2A)	122·1(7)	N(C)-C(1C)-C(12A)	121·8(6)
O(2A)-C(6A)-C(7A)	114·5(7)	C(12A)-C(1C)-C(2C)	129·1(7)
C(5A)-C(6A)-C(7A)	123·4(8)	N(C)-C(1C)-C(2C)	109·0(6)
C(6A)-C(7A)-C(8A)	115·0(7)	C(1C)-C(2C)-C(3C)	106·9(6)
C(6A)-C(7A)-C(12A)	119·0(7)	C(1C)-C(2C)-C(9C)	125·0(7)
C(8A)-C(7A)-C(12A)	125·9(7)	C(3C)-C(2C)-C(9C)	128·1(7)
C(3A)-C(8A)-N(A)	106·7(6)	C(2C)-C(3C)-C(4C)	134·7(8)
C(7A)-C(8A)-N(A)	129·7(7)	C(2C)-C(3C)-C(8C)	107·9(7)
C(3A)-C(8A)-C(7A)	123·6(7)	C(4C)-C(3C)-C(8C)	117·4(7)
C(7A)-C(12A)-C(13A)	111·0(6)	C(3C)-C(4C)-O(1C)	114·9(7)
C(7A)-C(12A)-C(1C)	114·3(6)	O(1C)-C(4C)-C(5C)	125·1(7)
C(1C)-C(12A)-C(13A)	111·3(6)	C(3C)-C(4C)-C(5C)	120·0(7)
C(8B)-N(B)-C(1B)	109·3(6)	C(4C)-C(5C)-C(6C)	119·9(7)
N(B)-C(1B)-C(2B)	109·2(7)	C(5C)-C(6C)-O(2C)	121·2(7)
N(B)-C(1B)-C(12C)	119·9(7)	O(2C)-C(6C)-C(7C)	115·6(7)
C(2B)-C(1B)-C(12C)	130·9(7)	C(5C)-C(6C)-C(7C)	123·2(7)
C(1B)-C(2B)-C(3B)	106·6(7)	C(6C)-C(7C)-C(8C)	114·5(7)
C(1B)-C(2B)-C(9B)	126·4(7)	C(6C)-C(7C)-C(12C)	122·9(7)
C(3B)-C(2B)-C(9B)	127·0(7)	C(8C)-C(7C)-C(12C)	122·4(7)
C(2B)-C(3B)-C(4B)	135·1(8)	C(3C)-C(8C)-N(C)	107·0(6)
C(2B)-C(3B)-C(8B)	108·1(7)	C(7C)-C(8C)-N(C)	128·0(7)
C(4B)-C(3B)-C(8B)	116·8(7)	C(3C)-C(8C)-C(7C)	125·0(7)
C(3B)-C(4B)-O(1B)	115·4(7)	C(1B)-C(12C)-C(7C)	112·2(6)
O(1B)-C(4B)-C(5B)	124·6(8)	C(1B)-C(12C)-C(13C)	115·4(6)
C(3B)-C(4B)-C(5B)	119·9(7)	C(7C)-C(12C)-C(13C)	109·4(6)



Scheme 2

Table 4. Selected torsional angles (degrees) for (3d)
Estimated standard deviations are in parentheses

Atoms	Angle	Atoms	Angle
C(10A)-O(1A)-C(4A)-C(5A)	−5·9(11)	N(B)-C(1B)-C(12C)-C(13C)	123·6(7)
C(11A)-C(2A)-C(6A)-C(5A)	4·8(11)	C(2B)-C(1B)-C(12C)-C(7C)	177·0(7)
N(A)-C(1A)-C(12B)-C(7B)	67·5(9)	C(2B)-C(1B)-C(12C)-C(13C)	−56·9(10)
N(A)-C(1A)-C(12B)-C(13B)	−61·8(8)	C(6B)-C(7B)-C(12B)-C(1A)	95·1(8)
C(2A)-C(1A)-C(12B)-C(7B)	−110·6(8)	C(6B)-C(7B)-C(12B)-C(13B)	−134·4(7)
C(2A)-C(1A)-C(12B)-C(13B)	120·0(8)	C(8B)-C(7B)-C(12B)-C(1A)	−82·5(9)
C(6A)-C(7A)-C(12A)-C(13A)	80·4(8)	C(8B)-C(7B)-C(12B)-C(13B)	48·0(9)
C(6A)-C(7A)-C(12A)-C(1C)	−152·7(6)	C(1A)-C(12B)-C(13B)-C(14B)	173·6(6)
C(8A)-C(7A)-C(12A)-C(13A)	−98·1(8)	C(1A)-C(12B)-C(13B)-C(18B)	−3·7(10)
C(8A)-C(7A)-C(12A)-C(1C)	28·8(10)	C(7B)-C(12B)-C(13B)-C(14B)	43·8(9)
C(7A)-C(12A)-C(13A)-C(14A)	−129·9(7)	C(7B)-C(12B)-C(13B)-C(18B)	−133·5(7)
C(7A)-C(12A)-C(13A)-C(18A)	46·3(8)	C(10C)-O(1C)-C(4C)-C(5C)	−5·9(11)
C(1C)-C(12A)-C(13A)-C(14A)	101·6(8)	C(11C)-O(2C)-C(6C)-C(5C)	−18·9(12)
C(1C)-C(12A)-C(13A)-C(18A)	−82·2(8)	C(6C)-C(7C)-C(12C)-C(1B)	−107·6(8)
C(7A)-C(12A)-C(1C)-N(C)	−104·2(7)	C(6C)-C(7C)-C(12C)-C(13C)	123·0(7)
C(7A)-C(12A)-C(1C)-C(2C)	72·8(9)	C(8C)-C(7C)-C(12C)-C(1B)	67·1(9)
C(13A)-C(12A)-C(1C)-N(C)	22·5(9)	C(8C)-C(7C)-C(12C)-C(13C)	−62·3(9)
C(13A)-C(12A)-C(1C)-C(2C)	−160·5(7)	C(1B)-C(12C)-C(13C)-C(14C)	167·0(7)
C(10B)-O(1B)-C(4B)-C(5B)	−8·6(10)	C(1B)-C(12C)-C(13C)-C(18C)	−13·3(10)
C(11B)-O(2B)-C(6B)-C(5B)	−21·8(10)	C(7C)-C(12C)-C(13C)-C(14C)	−65·4(8)
N(B)-C(1B)-C(12C)-C(7C)	−2·6(9)	C(7C)-C(12C)-C(13C)-C(18C)	114·3(8)

in either ethanol or ethanol/tetrahydrofuran to give the indole alcohols (9) and (10) respectively. The yields were quantitative and the reactions were followed by the disappearance of the deep yellow colour of the benzoyl compounds. The ^{1}H n.m.r. spectrum of the alcohol (9) showed the presence of the benzylic and hydroxyl hydrogens at 5·03 and 6·41 ppm respectively. These alcohols (9) and (10) were very sensitive to acid, and were purified by recrystallization from aqueous ethanol.

Reaction of the 2-alcohol (10) with phosphoryl chloride in chloroform gave a 65% yield of the trimer (3) whereas the corresponding reaction of the 7-alcohol (9) gave a complex mixture of products. Based upon these observations it could be argued that the macrocyclization might be mediated only by the attack of the aldehyde on C 2 of the indole leading to intermediate (6) and not by aldehyde attack at C 7 to give intermediate (5). However, it is likely that the failure of the reaction of the 7-alcohol (9) to form a macrocycle is caused by the sensitivity of such an indole with a free C 2 position to acidic conditions, and not to any intrinsic lack of reactivity of intermediate (5).

Experimental

General

Melting points are uncorrected. Microanalyses were performed by Dr H. P. Pham of the University of New South Wales. ^{1}H n.m.r. spectra were obtained in the designated solvents on a Bruker CXP 300 (300 MHz), a Bruker AC300F (300 MHz) or a Bruker AM 500 (500 MHz) spectrometer. ^{13}C n.m.r. were obtained in the designated solvents on a Bruker AC300F (300 MHz) or a Bruker AM 500 (500 MHz) spectrometer. Ultraviolet spectra were measured on a Hitachi U-3200 spectrometer and refer to solutions in absolute methanol. Infrared spectra were recorded on a Perkin–Elmer 298 or a Perkin–Elmer 580B spectrometer and refer to paraffin mulls. The e.i. mass spectra were recorded on an AEI MS 12 mass spectrometer at 70 eV ionizing potential and 8000 V accelerating voltage with an ion source temperature of 210°C. F.a.b. spectra were recorded on an AutoSpecQ mass spectrometer. Flash column chromatography was carried out by using Merck silica gel 7736 60H, whilst analytical thin-layer chromatography was performed on 0·2-mm plates precoated with silica gel 60 F_{254}.

Di(4,6-dimethoxy-3-methylindol-2-yl)phenylmethane (2a)

To an ice-cooled solution of 4,6-dimethoxy-3-methylindole (1) (1·5 g, 7·8 mmol) and benzaldehyde (0·4 ml, 3·9 mmol) in methanol (45 ml), concentrated hydrochloric acid (12 ml) was added rapidly. After stirring for 30 min the mixture was left at room temperature overnight. The resulting white solid was filtered off, washed with water followed by a small amount of methanol and dried. Recrystallization from dichloromethane/methanol afforded the diindolylphenylmethane (2a) (1·57g, 85%) as white *prisms* m.p. 236–238° (Found: C, 73·8; H, 6·3; N, 5·7. $C_{29}H_{30}N_2O_4$ requires C, 74·0; H, 6·4; N, 5·0%). ν_{max} 3442, 3406, 1626, 1602, 1573, 1515, 1495, 1464, 1380, 1343, 1313, 1236, 1216, 1156, 1129, 1067, 816 cm^{-1}. ^{1}H n.m.r. [$(CD_3)_2SO$] δ 2·29, s, Me; 3·71, 3·78, s, each OMe; 5·79, s, CH; 6·10, d, J 1·8 Hz, H 5; 6·41, d, J 1·8 Hz, H 7; 7·06, d, J 8·0 Hz, ArH; 7·31, m, 4H, ArH; 10·15, s, NH. m/z 470 (M, 14%), 281 (58), 280 (28), 261 (58), 266 (41), 252 (30), 191 (100), 176 (84).

(4-Chlorophenyl)di(4,6-dimethoxy-3-methylindol-2-yl)methane (2b)

Compound (2b) was prepared from 4,6-dimethoxy-3-methylindole (1) (0·93 g, 4·9 mmol) and 4-chlorobenzaldehyde (0·34 g, 2·4 mmol) in methanol (27 ml) and concentrated hydrochloric acid as described for compound (2a). The crude product was dried and recrystallized from dichloromethane/methanol to yield (2b) (0·97 g, 79%) as white *prisms*, m.p. 233–235° (Found: C, 69·3; H, 5·8; N, 5·3. $C_{29}H_{29}ClN_2O_4$ requires C, 69·0; H, 5·8; N, 5·6%). ν_{max} 3428, 3396, 1624, 1605, 1567, 1514, 1490, 1462, 1380, 1345, 1313, 1230, 1213, 1200, 1151, 1138, 1103, 1089, 1067, 1037, 1016, 1003, 937, 819, 806 cm^{-1}. ^{1}H n.m.r. [$(CD_3)_2SO$] δ 2·30, s, Me; 3·69, 3·79, s, each OMe; 5·79, s, CH; 6·14, d, J 1·9 Hz, H 5; 6·42, d, J 1·9 Hz, H 7; 7·08, d, J 8·3 Hz, ArH; 7·38, d, J 8·3 Hz, ArH; 10·15, s, NH. m/z 506 (M, ^{37}Cl, 13%), 505 (13), 504 (M, ^{35}Cl, 48), 316 (30), 315 (26), 314 (87), 205 (35), 191 (100), 176 (78).

(2-Chlorophenyl)di(4,6-dimethoxy-3-methylindol-2-yl)methane (2c)

Compound (2c) was prepared from 4,6-dimethoxy-3-methylindole (1) (0·74 g, 3·9 mmol) and 2-chlorobenzaldehyde (0·22 ml, 1·9 mmol) as described for compound (2a). The product was recrystallized from dichloromethane/methanol to yield (2c) (0·79 g, 81%) as white *prisms*, m.p. 227–229° (Found: C, 69·1; H, 5·6; N, 5·3. $C_{29}H_{29}ClN_2O_4$ requires C, 69·0; H, 5·8; N, 5·6%). ν_{max} 3427, 1625, 1605, 1568, 1513, 1464, 1380, 1344, 1312, 1271, 1245, 1230, 1217, 1202, 1156, 1129, 1067, 1055, 1037, 817, 756 cm^{-1}. ^{1}H n.m.r. [$(CD_3)_2SO$] δ 2·11, s, Me; 3·69, 3·77, s, each OMe; 5·98, s, CH; 6·08, d, J 2·0 Hz, H 5; 6·44, d, J 2·0 Hz, H7; 7·15, m, 1H, ArH; 7·29, m, 2H, ArH; 7·44, m, 1H, ArH; 10·07, br s, NH. m/z 506 (M, ^{37}Cl, 20%), 505 (17), 504 (M, ^{35}Cl, 46), 316 (46), 315 (29), 314 (100), 278 (17), 191 (26).

(4-Bromophenyl)di(4,6-dimethoxy-3-methylindol-2-yl)methane (2d)

Compound (2d) was prepared from 4,6-dimethoxy-3-methylindole (1) (0·76 g, 4·0 mmol) and 4-bromobenzaldehyde (0·37 g, 2·0 mmol) in methanol (22 ml) and concentrated hydrochloric acid (6·0 ml) as described for compound (2a). The crude product was dried and recrystallized from dichloromethane/methanol to yield (2d) (0·96 g, 87%) as white *prisms*, m.p. 201–202° (Found: C, 63·1; H, 5·2; N, 5·2. $C_{29}H_{29}BrN_2O_4$ requires C, 63·4; H, 5·3; N, 5·1%). ν_{max} 3418, 1631, 1607, 1593, 1571, 1515, 1461, 1381, 1343, 1312, 1235, 1214, 1156, 1130, 1067, 1040, 1010, 806 cm^{-1}. ^{1}H n.m.r. [$(CD_3)_2SO$] δ 2·25, s, Me; 3·70, 3·78, s, OMe; 5·76, s, CH; 6·08, d, J 1·9 Hz, H 5; 6·41, d, J 1·9 Hz, H7; 7·00, d, J 8·4 Hz, ArH; 7·49, d, J 8·4 Hz, ArH; 10·08, br s, NH. m/z 550 (M, ^{81}Br, 32%), 548 (M, ^{79}Br, 32), 360 (100), 358 (100), 278 (18), 191 (50), 176 (27).

6,8,14,16,22,24-Hexamethoxy-4,12,20-trimethyl-2,10,18-triphenyl-26,28,30-triazaheptacyclo-[17.5.2.2^{3,9}.2^{11,17}.0^{5,29}.0^{13,27}.0^{21,25}]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21(25),22-dodecaene (3a)

Method A. Phosphoryl chloride (0·2 ml) was added to an ice-cooled solution of 4,6-dimethoxy-3-methylindole (1) (0·2 g, 1·05 mmol) and benzaldehyde (0·11 ml, 1·05 mmol) in dry chloroform (15 ml). After warming to room temperature the mixture was refluxed for 1 h. Cold water (15 ml) was added to the mixture and the chloroform layer was washed with sodium hydroxide (2%, 50 ml), dried over magnesium sulfate and concentrated to give a bluish residue. The crude product was chromatographed on silica gel with dichloromethane as eluent. The product with R_F 0·8 was separated and recrystallized from dichloromethane/light petroleum (60–80°) to yield the macrocycle (3a) (0·035 g 12%) as colourless *prisms*, m.p. 221°

(Found: C, 77·4; H, 6·2; N, 4·7. $C_{54}H_{51}N_3O_6$ requires C, 77·4; H, 6·1; N, 5·0%). ν_{max} 3414, 1622, 1602, 1576, 1539, 1518, 1466, 1381, 1343, 1265, 1238, 1208, 1160, 1132, 1099, 1034, 994, 934, 795 cm^{-1}. ^1H n.m.r. ($CDCl_3$) δ 2·01, 2·14, 2·88, s, each Me; 3·64, 3·69, 3·89, 3·91, 3·93, 3·94, s, each OMe; 6·01, s, 2H, CHPh; 6·14, 6·24, 6·30, s, indole H5; 6·26, 6·37, s, NH; 6·50, d, J 8·0 Hz, ArH; 6·81, s, CHPh; 6·70–7·20, m, ArH; 7·64, s, NH. m/z 839 (22), 838 (63), 837 (M, 100%), 822 (11), 762 (11), 761 (19), 646 (11), 631 (11), 418 (13).

Method B. Phosphoryl chloride (0·1 ml) was added to a cooled solution of di(4,6-dimethoxy-3-methylindol-2-yl)phenylmethane (2a) (0·2 g, 0·4 mmol) in dry chloroform (10 ml). After warming to room temperature the mixture was refluxed for 2 h. Cold water (20 ml) was added and the chloroform layer washed with sodium hydroxide (2 N, 50 ml), dried, evaporated and chromatographed to yield the macrocycle (3a) (0·14 g, 48%) identical to that obtained by method A.

2,10,18-Tri(4-chlorophenyl)-6,8,14,16,22,24-hexamethoxy-4,12,20-trimethyl-26,28,30-triazaheptacyclo-[17.5.2.2^{3,9}.2^{11,17}.0^{5,29}.0^{13,27}.0^{21,25}]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21(25),22-dodecaene (3b)

This macrocycle was prepared from 4,6-dimethoxy-3-methylindole (1) (0·2 g, 1·05 mmol), 4-chlorobenzaldehyde (0·15 g, 1·05 mmol) and phosphoryl chloride (0·2 ml) in chloroform as described for the phenyl macrocycle (3a). The product was chromatographed and recrystallized from absolute ethanol to yield the chlorophenyl macrocycle (3b) (0·30 g, 83%) as a white *powder*, m.p. 289–290° (Found: C, 68·6; H, 5·3; N, 4·2. $C_{54}H_{48}Cl_3N_3O_6$ requires C, 68·9; H, 5·1; N, 4·5%). ν_{max} 3424, 3410, 1622, 1605, 1578, 1521, 1492, 1467, 1404, 1381, 1346, 1326, 1292, 1274, 1261, 1239, 1211, 1184, 1164, 1130, 1101, 1016, 994, 929, 880, 869, 811, 790 cm^{-1}. ^1H n.m.r. ($CDCl_3$) δ 2·07, 2·12, 2·53, s, each Me; 3·71, 3·72, 3·91, 3·93, 3·94, 4·05, s, each OMe; 5·99, 6·00, s, each CHAr; 6·20, d, J 8·5 Hz, ArH; 6·24, s, indole H5; 6·30, s, 2H, indole H5; 6·38, d, J 8·3 Hz, ArH; 6·66, s, NH; 6·71, d, J 8·5 Hz, ArH; 6·74, s, NH; 6·76, s, CHAr; 6·81, d, J 8·5 Hz, ArH; 6·91, d, J 8·4 Hz, ArH; 7·09, d, J 8·4 Hz, ArH; 7·52, s, NH. m/z 944 (21), 943 (45), 942 (53), 941 (M, 100%), 940 (53), 939 (87), 927 (16), 926 (34), 925 (16), 924 (34).

2,10,18-Tri(2-chlorophenyl)-6,8,14,16,22,24-hexamethoxy-4,12,20-trimethyl-26,28,30-triazaheptacyclo-[17.5.2.2^{3,9}.2^{11,17}.0^{5,29}.0^{13,27}.0^{21,25}]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21(25),22-dodecaene (3c)

This macrocycle was prepared from 4,6-dimethoxy-3-methylindole (1) (0·2 g, 1·05 mmol), 2-chlorobenzaldehyde (0·15 g, 1·05 mmol) and phosphoryl chloride (0·2 ml) in chloroform as described for the phenyl macrocycle (3a). The product was chromatographed and recrystallized from dichloromethane/light petroleum (60–80°) to yield the chlorophenyl macrocycle (3c) (0·036 g, 10%) as colourless *prisms*, m.p. >300° (Found: C, 69·1; H, 5·3; N, 4·3. $C_{54}H_{48}Cl_3N_3O_6$ requires C, 68·9; H, 5·1; N, 4·5%). ν_{max} 3425, 3411, 1623, 1608, 1575, 1520, 1490, 1464, 1402, 1381, 1345, 1326, 1292, 1273, 1260, 1235, 1208, 1184, 1160, 1133, 1101, 995, 881, 864, 805, 789 cm^{-1}. ^1H n.m.r. ($CDCl_3$) δ 2·12, 2·29, 2·54, s, each Me; 3·56, 3·65, 3·86, 3·88, 3·88, 3·90, s, each OMe; 5·90, 6·08, s, each CHAr; 6·13, m, ArH; 6·20, 6·23, 6·25, s, each indole H5; 6·10, m, ArH; 6·55, s, NH; 6·85, s, CHAr; 6·70–7·15, m, ArH+NH; 7·71, s, NH. m/z 944 (18), 943 (44), 942 (56), 941 (M, 100%), 940 (56), 939 (90), 315 (54), 314 (36), 300 (33), 222 (58).

2,10,18-Tri(4-bromophenyl)-6,8,14,16,22,24-hexamethoxy-4,12,20-trimethyl-26,28,30-triazaheptacyclo-[17.5.2.2^{3,9}.2^{11,17}.0^{5,29}.0^{13,27}.0^{21,25}]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21(25),22-dodecaene (3d)

This macrocycle was prepared from 4,6-dimethoxy-3-methylindole (1) (0·2 g, 1·05 mmol), 4-bromobenzaldehyde (0·19 g, 1·05 mmol) and phosphoryl chloride (0·2 ml) in chloroform as described for the phenyl macrocycle (3a). The product was chromatographed and recrystallized from absolute ethanol to yield the bromophenyl macrocycle (0·30 g, 81%) as colourless *prisms*, m.p. >300° (Found: C, 60·5; H, 4·5; N, 4·1. $C_{54}H_{48}Br_3N_3O_6$ requires C, 60·4; H, 4·5; N, 3·9%). ν_{max} 3431, 3419, 1623, 1605, 1583, 1521, 1488, 1466, 1381, 1343, 1322, 1295, 1278, 1263, 1243, 1230, 1214, 1185, 1166, 1133, 1104, 1094, 1077, 1014, 996, 969, 928, 871, 809, 792 cm^{-1}. ^1H n.m.r. ($CDCl_3$) δ 2·07, 2·12, 2·53, s, each Me; 3·72, 3·73, 3·91, 3·93, 3·94, 4·08, s, each OMe, 5·98, 6·00, s, each CHAr; 6·16, s, 1H, ArH; 6·25, 6·30, 6·35, s, each indole H5; 6·26, s, ArH; 6·31, d, J 8·1 Hz, ArH; 6·67, s, NH; 6·69, br s, 2H, CHAr+NH; 6·71, d, J 8·3 Hz, ArH; 6·95, d, J 8·4 Hz, ArH; 7·07, d, J 8·3 Hz, ArH; 7·27, d, J 8·2 Hz, ArH; 7·55, s, NH. ^{13}C n.m.r. (C_6D_6) δ 11·21, 11·66, 13·17, Me; 36·41, 38·34, 39·65, CHAr; 55·34, 55·52, 57·25, 57·65, 58·08, OMe; 89·24, 90·16, 90·58, indole C5; 130·0, 131·11, 132·56, 139·91, 133·64, Ar CH; 105·76, 106·29, 107·74, 110·05, 110·20, 110·49, 115·20, 116·86, 117·30, 120·54, 120·71, 121·60, 136·19, 136·21, 137·79, 140·81, 141·47, 142·16, 153·63, 154·76, 155·14, 155·16, 155·50, Ar C.

7-(4-Chlorobenzoyl)-4,6-dimethoxy-3-methylindole (7a) and 2-(4-Chlorobenzoyl)-4,6-dimethoxy-3-methylindole (8a)

Phosphoryl chloride (0·52 ml, 5·6 mmol) was added to warm (60°) 4-chloro-*N*,*N*-dimethylbenzamide (2·0 g, 10·9 mmol). The mixture was stirred for 5 min and 4,6-dimethoxy-3-methylindole (1) (1·0 g, 5·2 mmol) was added. The mixture was heated to 80°C and maintained at that temperature for 30 min. After cooling, sodium hydroxide (2 N, 100 ml) was added and the resulting sticky syrup was stirred with a glass rod and left standing at room temperature. The mixture was extracted with dichloromethane (3×50 ml), the extract washed with sodium hydroxide (2 N, 50 ml), water, dried and concentrated to give a yellow solid. The solid was chromatographed on silica with dichloromethane as eluent. The yellow band with R_F 0·6 in dichloromethane was isolated and recrystallized from dichloromethane/light petroleum (60–80°) to yield the 7-benzoyl compound (7a) (0·65 g, 38%) as a fluffy yellow *solid*, m.p. 188–189° (Found: C, 65·0; H, 4·7; N, 4·0. $C_{18}H_{16}ClNO_3.\frac{1}{4}H_2O$ requires C, 64·7; H, 5·0; N, 4·2%). ν_{max} 3381, 1613, 1591, 1556, 1506, 1467, 1440, 1400, 1381, 1364, 1299, 1286, 1277, 1246, 1220, 1192, 1175, 1135, 1108, 1090, 1072, 1015, 985 cm^{-1}. ^1H n.m.r. ($CDCl_3$) δ 2·43, s, Me; 3·60, 3·99, s, each OMe; 6·12, s, H5; 6·80, br s, H2; 7·36, d, J 8·4 Hz, ArH; 7·54, d, J 8·4 Hz, ArH; 9·83, br s, NH. m/z 331 (M, ^{37}Cl, 36%), 330 (42), 329 (M, ^{35}Cl, 100), 328 (76), 279 (26).

The yellow band with R_F 0·3 in dichloromethane was eluted with dichloromethane/methanol (95:5) and recrystallized from dichloromethane/methanol to yield the 2-benzoyl compound (8a) (0·84 g, 49%) as yellow *prisms*, m.p. 220° (Found: C, 65·3; H, 4·6; N, 4·3. $C_{18}H_{16}ClNO_3$ requires C, 65·6; H,4·9; N, 4·3%). ν_{max} 3300, 1632, 1600, 1580, 1566, 1523, 1465, 1441, 1425, 1381, 1323, 1294, 1226, 1206, 1156, 1130, 1089, 1071, 951, 847, 809 cm^{-1}. ^1H n.m.r. ($CDCl_3$) δ 2·34, s, Me; 3·84, 3·87, s, each OMe; 6·11, d, J 1·8 Hz, H5; 6·35, d, J 1·8 Hz, H2; 7·45, d, J 8·4 Hz, ArH; 7·67, d, J 8·4 Hz, ArH; 8·79, br s, NH. m/z 331 (M, ^{37}Cl, 32%), 330 (30), 329 (M, ^{35}Cl, 100), 328 (38), 294 (24), 279 (26).

7-Benzoyl-4,6-dimethoxy-3-methylindole (7b) and 2-Benzoyl-4,6-dimethoxy-3-methylindole (8b)

These compounds were prepared from 4,6-dimethoxy-3-methylindole (1·0 g, 5·2 mmol) and *N,N*-dimethylbenzamide as described for indoles (7a) and (8a). The crude product was chromatographed on silica gel with dichloromethane as eluent. The yellow band with R_F 0·6 in dichloromethane was isolated and recrystallized from dichloromethane/light petroleum (60–80°) to yield the 7-benzoyl compound (7b) (0·65 g, 38%) as a fluffy yellow *solid*, m.p. 161–162° (Found: C, 73·5; H, 5·7; N, 4·9. $C_{18}H_{17}NO_3$ requires C, 73·2; H, 5·8; N, 4·7%). ν_{max} 3330, 1618, 1598, 1556, 1561, 1408, 1381, 1362, 1316, 1304, 1276, 1254, 1218, 1155, 1141, 1090, 985, 840 cm^{-1}. ^1H n.m.r. [$(CD_3)_2SO$] δ 2·35, s, Me; 3·57, 3·97, s, each OMe; 6·37, s, H5; 6·81, br s, H2, 7·43–7·60, m, 5H, ArH; 10·58, br s, NH. *m/z* 295 (M, 100%), 294 (85), 279 (24), 265 (20).

The yellow band with R_F 0·3 in dichloromethane was eluted with dichloromethane/methanol (95 : 5) and recrystallized from dichloromethane/methanol to yield the 2-benzoyl compound (8b) (0·84 g, 49%) as yellow *prisms*, m.p. 212° (Found: C, 73·3; H, 5·7; N, 5·0. $C_{18}H_{17}NO_3$ requires C, 73·2; H, 5·8; N, 4·7%). ν_{max} 3319, 1629, 1603, 1567, 1522, 1466, 1439, 1422, 1381, 1367, 1321, 1292, 1225, 1204, 1181, 1154, 1148, 1130, 1069, 1032, 954, 809 cm^{-1}. ^1H n.m.r. [$(CD_3)_2SO$ δ 2·32, s, Me; 3·77, 3·82, s, each OMe; 6·12, d, *J* 1·8 Hz, H5; 6·44, d, *J* 1·8 Hz, H2; 7·45, m, 5H, ArH; 11·23, br s, NH. *m/z* 295 (M, 100%), 294 (78), 279 (21), 265 (15).

α-(4-Chlorophenyl)-4,6-dimethoxy-3-methylindole-7-methanol (9; Ar = 4-Chlorophenyl)

Sodium borohydride (0·6 g, 15·8 mmol) was added to a suspension of the ketone (7a) (0·6 g, 1·8 mmol) in absolute ethanol (20 ml). The mixture was refluxed for 30 min and after cooling to room temperature evaporated to dryness. Sodium hydroxide (40 ml, 0·1 N) was added to the residue, and the white solid was filtered off, washed with water and recrystallized from aqueous ethanol to yield the alcohol (9) (0·58 g, 96%) as white *prisms*, m.p. 153–154° (Found: C, 65·2; H, 5·5; N, 4·5. $C_{18}H_{18}ClNO_3$ requires C, 65·2; H, 5·5; N, 4·2%). ν_{max} 3441, 3394, 1623, 1601, 1580, 1557, 1519, 1493, 1464, 1439, 1420, 1380, 1344, 1328, 1297, 1253, 1235, 1208, 1163, 1141, 1105, 1082, 1019, 1007, 981, 856, 806 cm^{-1}. ^1H n.m.r. [$(CD_3)_2SO$] δ 2·33, s, Me; 3·85, 3·88, s, each OMe; 5·03, d, *J* 3·9 Hz, CHO**H**; 6·34, s, indole H5; 6·41, d, *J* 3·9 Hz, C**H**OH; 6·73, s, indole H2; 7·23, d, *J* 8·5 Hz, ArH; 7·47, d, *J* 8·5 Hz, ArH; 9·40, br s, NH. *m/z* 333 (M, ^{37}Cl, 12%), 331 (M, ^{35}Cl, 32), 305 (20), 304 (38), 303 (30), 302 (100), 297 (34), 278 (70), 191 (18), 176 (14).

α-(4-Chlorophenyl)-4,6-dimethoxy-3-methylindole-2-methanol (10; Ar = 4-Chlorophenyl)

This compound was prepared from 2-(4-chlorobenzoyl)-4,6-dimethoxy-3-methylindole (8a) (1·0 g, 3·03 mmol) and sodium borohydride as described for the 7-methanol (9). The crude product was recrystallized from aqueous ethanol to yield the 2-alcohol (10) (0·95 g, 94%) as a white *powder*, m.p. 133° (Found: C, 65·0; H, 5·3; N, 4·0. $C_{18}H_{18}ClNO_3$ requires C, 65·2; H, 5·5; N, 4·2%). ν_{max} 3415, 3279, 1634, 1621, 1606, 1572, 1521, 1492, 1466, 1420, 1408, 1380, 1317, 1266, 1251, 1221, 1205, 1157, 1141, 1094, 1071, 1041, 1001, 942, 811 cm^{-1}. ^1H n.m.r. [$(CD_3)_2SO$] δ 2·30, s, Me; 3·69, 3·77, s, each OMe; 5·85, d, *J* 4·6 Hz, C**H**OH; 5·90, d, *J* 4·6 Hz, CHO**H**; 6·01, d, *J* 2·0 Hz, indole H5; 6·36, d, *J* 2·0 Hz, indole H7; 7·30, d, *J* 8·5 Hz, ArH; 7·36, d, *J* 8·5 Hz, ArH; 10·31, br s, NH. *m/z* 333 (M, ^{37}Cl, 6%), 331 (M, ^{35}Cl, 17), 315 (26), 314 (15), 313 (26), 312 (15), 278 (37), 207 (52), 191 (100).

Reaction of 2-Alcohol (10; Ar = 4-Chlorophenyl) with Phosphoryl Chloride

To a solution of 2-alcohol (10) (100 mg, 0·3 mmol) in dichloromethane (10 ml), phosphoryl chloride (5 drops) was added with stirring. After 30 min at room temperature the solution was washed with sodium hydroxide (0·1 N, 10 ml), dried and concentrated to yield a brownish residue. After chromatography on silica gel the product was recrystallized from ethanol to yield the 4-chlorophenyl macrocycle (3b) identical to the one obtained by method A or method B.

Reaction of 7-Alcohol (9; Ar = 4-Chlorophenyl) with Phosphoryl Chloride

The 7-alcohol (9) (0·1 g, 0·3 mmol) in dichloromethane (10 ml) was treated with phosphoryl chloride (5 drops) as described for the 2-alcohol (10). The product did not show the presence of any 4-chlorophenyl macrocycle (3b) but only contained a mixture of decomposed material.

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