Calix[3]indoles, New Macrocyclic Tris(indolylmethylene) Compounds with 2,7-Linkages†

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A series of macrocyclic tris(indolylmethylene) compounds (calix[3]indoles] can be obtained from 7- or 2-hydroxymethylindoles or from the combination of either an indole with a bis(hydroxymethyl)-2,7'-diindolylmethane or a bis(hydroxymethyl)indole with a 2,7'-diindolylmethane; an isomeric series can be obtained from the combination of an indole with a bis(hydroxymethyl)-2,2'-diindolylmethane.

We report several methods for the synthesis of the tris(indolyl-methylene) macrocycles **8**, in which three indole rings are linked by methylene groups between C-2 and C-7 in each case.‡ We have previously shown that 4,6-dimethoxy-3-methylindole¹ undergoes reaction with aryl aldehydes and phosphoryl chloride to give the related macrocycles with arylmethine links.² The same macrocycles can alternatively be produced from the presumed intermediate hydroxymethyl compound.

The same reactions occur when the 3-methylindole is replaced by several 3-aryl-4,6-dimethoxyindoles 1³⁻⁵ and therefore appear to be quite general. On the other hand, reaction of the 3-arylindoles 1 with formaldehyde and phosphoryl chloride yields a multitude of uncharacterised products. We have therefore investigated acid-catalysed reactions of various hydroxymethyl-substituted indoles, derived by reduction of the related aldehydes.⁶

Formylation of the 3-arylindoles 1 with one equivalent of the Vilsmeier reagent gives a strong predominance of the 7-carbaldehydes 2 over the 2-carbaldehydes 3: two or more equivalents readily yield the 2,7-dicarbaldehydes 4. All of these aldehydes can be easily reduced by sodium borohydride to give the respective alcohols 5, 6 and 7 (Scheme 1).

The 7-hydroxymethyl compounds 5 undergo rapid acidcatalysed reaction to generate the macrocycles 8 in approximately 60% yield. Compound 8c can also be obtained by similar treatment of the 2-hydroxymethyl compound 6c (Scheme 2). Appropriate conditions include toluene-p-sulfonic acid in glacial acetic acid for 2–5 min, toluene-p-sulfonic acid in dichloromethane, or boron trifluoride-ether in tetrahydrofuran.

An alternative approach to the triindolyl macrocycles 8 involves the combination of a 2,7-diindolylmethane fragment with an indole. Suitable 2,7-diindolylmethanes 9 can be

POCI3-DMF СНО 0 °C MeO ĊHO 2 major 3 minor POCI₃(excess) DMF, room temp. NaBH₄ NaBH₄ ОМе OMe OMe CH₂OH СНО MeO MeO

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prepared by reaction of the 7-hydroxymethylindoles 5a,c with

indole 1c in glacial acetic acid (Scheme 3). Formylation of

diindolylmethanes 9 gave the dialdehydes 10, which were

polymeric material. More usefully, compound 8c was similarly formed in 36% yield from the diindolylmethane 9c and the

dialcohol 7c (Scheme 4). This synthetic route enables the

incorporation of different indoles into the macrocycle. For

example, the similar combination of diindolylmethane 9a and dialcohol 7c gives a macrocycle related to 8, but in which the

indole 3-substituents are one phenyl and two p-methoxy-

Combination of the dialcohol 11c with indole 1c in acetic acid gave the macrocycle 8c in 30% yield together with

reduced to the dialcohols 11.

phenyl groups.

Scheme 1 DMF = dimethylformamide

† These compounds can also be named using cyclophane nomenclature. Compounds **8** are [1.1.1](2,7) indolophanes and compounds **14** are [1.1.1](2,2)(7,2)(7,7) indolophanes.

‡ All new compounds gave spectroscopic and microanalytical data in accord with assigned structures. Data are quoted for the dialcohols 11c and 13c and the macrocycles 8c and 14c.

8c: 57% yield; m.p. 220–222 °C (decomp.); ¹H NMR (300 MHz, CDCl₃) δ 3.66, 3.68 and 3.85 (each s, 9H, OMe), 4.13 (6H, s, CH₂) 6.21 (3H, s, CH), 6.88 and 7.30 (each d, *J* 8.7 Hz, 6H, ArH), 7.82 (3H, br. s, NH); MS *m*/z 885 (M±, 100%).

(3H, br s, NH); MS *m/z* 885 (M⁺, 100%).

11c: 86% yield; m.p. 164–166 °C; ¹H NMR [300 MHz, (CD₃)₂SO] δ 3.61, 3.64, 3.65, 3.75, 3.76 and 3.79 (each s, 3H, OMe), 4.17 (2H, s, CH₂), 4.37 and 4.62 (each d, *J* 4.6 Hz, 2H, CH₂OH), 4.92 and 5.01 (each d, *J* 4.6 Hz, 1H, OH), 6.26 and 6.31 (each s, 1H, CH), 6.88, 6.94, 7.29 and 7.34 (each d, *J* 8.7 Hz, 2H, ArH), 9.76 and 10.14 (each s, 1H, NH).

13c: 96% yield; m.p. 194–196 °C; ¹H NMR [300 MHz, (CD₃)SO], δ 3.62, 3.76 and 3.80 (each s, 6H, OMe), 3.98 (2H, br s, CH₂), 4.77 (4H, br s, CH₂OH), 6.29 (2H, s, CH), 6.72 and 7.03 (each d, *J* 8.7 Hz, 4H, ArH).

14c: 38% yield; m.p. 244–246 °C; ¹H NMR (300 MHz, CDCl₃) δ 3.59, 3.67, 3.68, 3.73, 3.79, 3.81, 3.85, 3.88 and 3.99 (each s, 3H, OMe), 3.71, 4.15 and 4.37 (each s, 2H, CH₂); 6.29, 6.30 and 6.34 (each s, 1H, CH), 6.67 and 6.75 (each d, *J* 8.7 Hz, 2H, ArH), 6.95 (4H, t, *J* 8.8 Hz, ArH), 7.05 and 7.44 (each d, *J* 8.7 Hz, 2H, ArH), 7.36, 7.69 and 8.39 (each br s, 1H, NH); MS *m/z* 885 (M⁺, 100%).

$$\begin{array}{c} \text{Sa,c} \\ \text{HOAc} \\ \text{Ic} \\ \\ \text{Ar'} \\ \text{NH} \\ \\ \text{MeO} \\ \text{OMe} \\ \text{SOMe} \\ \text{SOMe} \\ \text{SOMe} \\ \text{SOMe} \\ \text{OMe} \\ \text{SOMe} \\ \text{OMe} \\ \text{OMe$$

The regiochemistry of the above reactions is of considerable significance. Two orientations of addition are possible, one leading to the observed 2,7:2,7:2,7-linkages, the other to a 2,2:7,2:7,7-set of linkages. None of the latter products were observed. We have found that in general, the indoles 1 undergo acid-catalysed addition to benzylic alcohols preferentially at C-2 rather than C-7. Furthermore, the 7-hydroxymethyl compounds 5 are more reactive than the 2-hydroxymethyl compounds 6. Consequently, in the reaction of 5 with 1, the initial step would involve combination of the 7-hydroxymethyl group with an indole C-2 position, and this would be followed by a slower combination of a 2-hydroxymethyl group with an indole C-7 position to complete the macrocycle. The initial formation of a 2,7-link thus establishes the regiochemistry. Similar behaviour would occur in the reaction of 9

Scheme 5

13

with 7. The nature of the methylene linkages is clearly shown by NMR spectroscopy. For example, macrocycle 8c shows three methoxy methyl proton signals, one methylene singlet and one indole 5-H singlet. When different C-3-aryl substituents are introduced, the ¹H NMR spectrum shows different methoxy, methylene and 5-H chemical shifts resulting from the removal of symmetry. The presence of singlet methylene proton resonances shows that these macrocycles are flexible and even at low temperature, no generation of AB systems can be seen. Reaction of 11c with the N-methyl analogue of 1c gives a macrocycle with an NMR spectrum showing three AB methylene patterns.

Compounds 8 are related to the calix[3]arenes, 7.8 but with the replacement of an ambident 4-substituted phenol by ambident indoles 1.† Unlike the 4-substituted phenols, indoles 1 do not show orientational symmetry and two isomeric calix[3]indoles are possible.

We also report an efficient method for the synthesis of the isomeric [1.1.1](2,2)(7,2)(7,7)indolophane 14. The indole-7-carbaldehydes 2 undergo reaction with formaldehyde in acetic acid to give the dialdehydes 12 in quantitative yield. 9.10 These can be reduced quantitatively with sodium borohydride to the corresponding dialcohols 13 (Scheme 5). Reaction of the dialcohols 13 with the indole 1c in acetic acid gives the macrocycles 14 in 30–40% yields, together with the linear tetraindolyl oligomers 15 and 16 in yields of 20 and 5%, respectively (Scheme 6). The dialcohol 13c can be combined

equally effectively with the *N*-methyl analogue of **1c** to give an *N*-methyl-substituted macrocycle in 40% yield.

The ¹H NMR spectrum of **14c** shows nine methoxy proton resonances, three 5-H singlets and three singlets at δ 3.7, 4.15 and 4.38 for the 2,2'-, 2",7- and 7',7"-linked methylene groups, respectively. This data clearly reflects the unsymmetrical arrangement of indole rings, but also shows that there is enough flexibility for inversion from one conformer to another. However, at lower temperature, the methylene signlets start to broaden, commencing with the 2",7-linked methylene resonance.

The tetraindolyl oligomers 15 potentially provide excellent starting materials for higher indolylmethylene oligomers.

Received, 31st December 1992; Com. 2/06933D

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