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SYNTHESIS OF NOVEL SYMMETRIC CYCLIC INDOLE-TETRAMERS

Hidetaka Hiyoshi,[a]* Takaaki Sonoda,[b] and Shuntaro Mataka[b]

[a]Ihara Chemical Industry Co. Ltd., 2256 Nakanogo, Fujikawa, Ihara, Shizuoka, 412-3306, Japan

[b]Institute for Materials Chemistry and Engineering, Kyushu University, 6-1 Kausga-koh-en, Kasuga, Fukuoka, 816-8050, Japan

Abstract –The reaction of 5-bromoindolin-2-one with phosphoryl chloride in chlorobenzene gave a novel symmetric isomer of a cyclic indole-tetramer. This novel isomer was used in Suzuki-Miyaura coupling reaction to give tetraarylated derivatives of the cyclic indole-tetramer.

INTRODUCTION

Indole is one of the most versatile heterocycles among biologically active natural products and various types of derivatives have been synthesized and used as pharmaceuticals and pesticides as well as colorants and dyes. Recently, indole-oligomers and -polymers have attracted wide interest because of their potential as organic electronic and optoelectronic materials.[1] Cyclic indole-trimers and polyindoles have been used as active ingredients of cathode of batteries[2] or electroconducting polymers.[3] The synthesis of some indole derivatives and their oligomers has been reported up to date.[4]

Figure 1 shows representative indole oligomers prepared heretofore where symmetric and unsymmetric cyclic trimers have been known.[5]

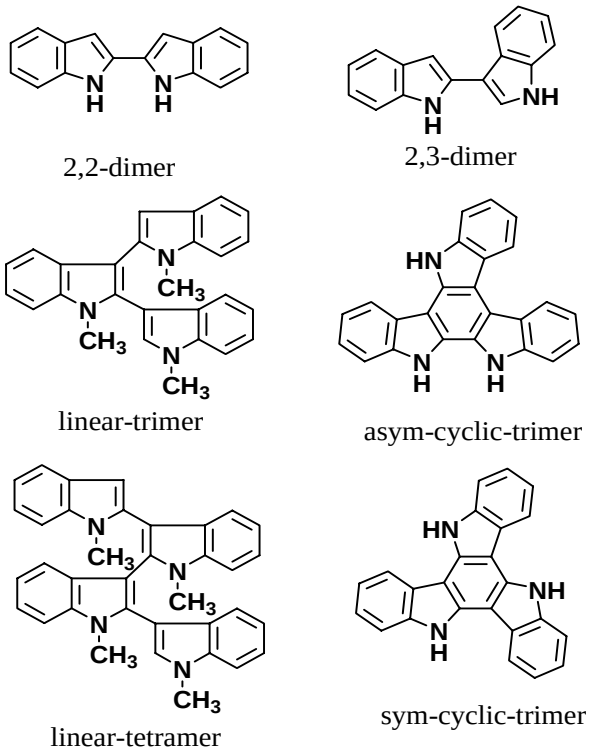
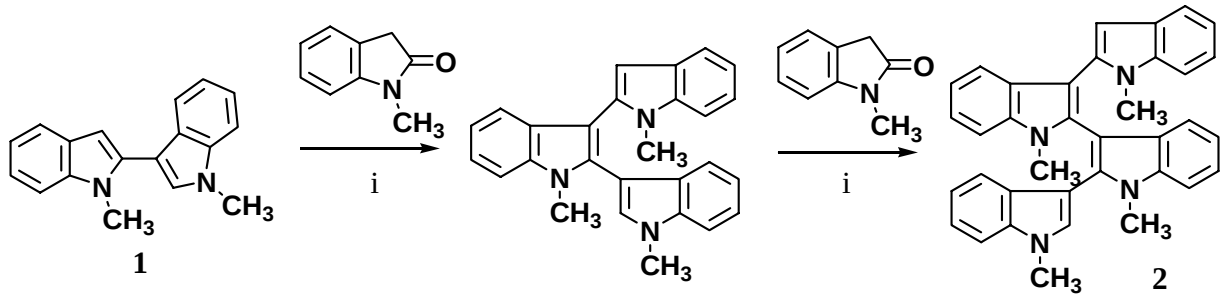


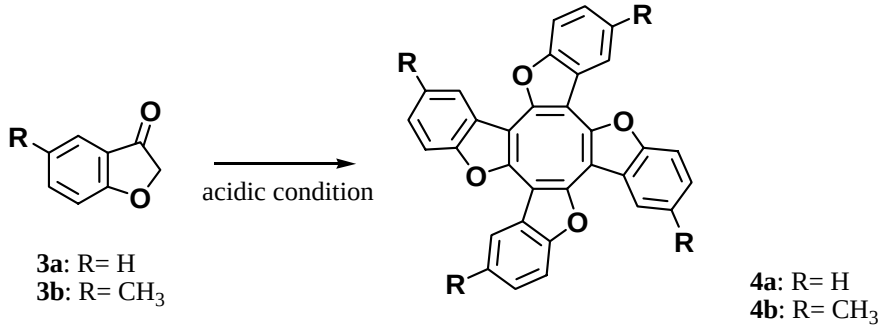
Figure 1 Structures of representative indole oligomers

Bergman and Ekulund reported that liner 2, 3-linked indole tetramer **(2)** was prepared when bisindole **(1)** which was synthesized from *N*-methyl-2-iodoindole, and *N*-methylindolin-2-one treated with phosporyl chloride[6] (Scheme 1).



Scheme 1 *Reagents and conditions:* i, $POCl_3$, CH_2Cl_2, 2 h, reflux

On the other hand, symmetric cyclotetramerization of 3(2*H*)-benzofuranone **(3)** which gave cyclic tetrabenzofurans **(4)**, have been reported until now.[7] (Scheme 2)



Scheme 2 Formation of cyclic tetrabenzofuran

Four cyclic tetramers are shown in Figure 2 as their higher homologue wherein the 2- and 3-positions of each indole ring are linked to form a central eight-membered ring. However, to the best of our knowledge, none of the cyclic tetramers has been known until the present time.[8]

In this paper, we report the first synthesis of the symmetric isomer of cyclic indole tetramers.

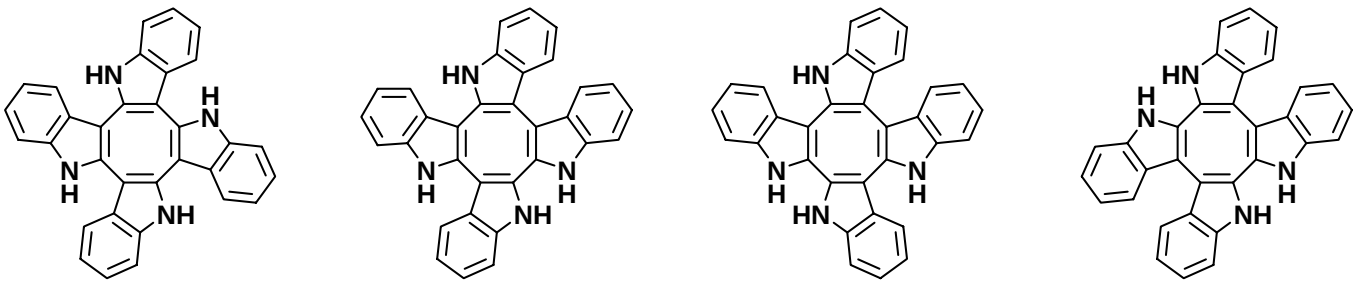


Figure 2 Structures of cyclic tetramers.

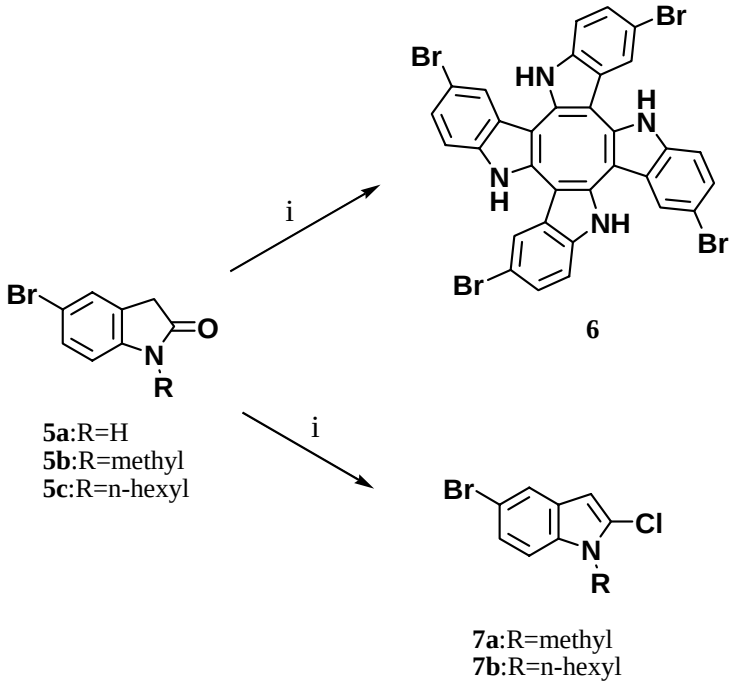
RESULTS AND DISCUSSION

The reaction products of indole derivatives with phosphoryl chloride were found to be significantly dependent upon the substituent on the nitrogen atom of the indole ring and the solvent used.

When 5-bromoindolin-2-one (**5a**) was treated with phosporyl chloride in chlorobenzene as a solvent at 100 ˚C for 8 h, green fluorescent product was obtained in 9% yield after silica gel column chromatography of the reaction mixture.

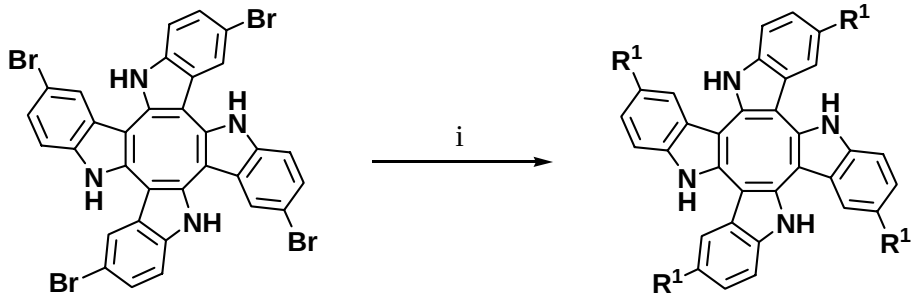
The structure of reaction product was elucidated based on EA, FAB-MS, and ^{1}H- and ^{13}C-NMR spectra. FAB-MS spectrum shows the molecular ion peaks, 774, 775, 776, 777, and 778 of the 5-bromoindole tetramer. The symmetric structure of **6** was established by the ^{1}H-NMR spectrum, which shows three signals of aromatic protons (each at 7.29 (d), 7.51 (dd), and 7.78 (d) ppm). The NH-protons at 10.90 ppm disappeared on treatment with D_2O. Further evidences were also given in the ^{13}C-NMR spectrum, in which eight carbon signals were exhibited at 105.7, 113.3, 113.5, 121.3, 124.8, 129.5, 136.2, and 136.7 ppm. NOESY spectra was observed between 10.90 ppm (NH) and 7.78 ppm (indole H_4) protons. Compound (**6**) gave satisfactory elemental analytical data. These spectrum data, formation of 2, 3-linked linear indole tetramer and cyclotetramerization of benzofuranone, suggested that the structure of **6** was symmetric cyclic indole tetramer.

On the other hand, the reactions of the 1-alykyl-5-bromoindolin-2-ones (**5b**) and (**5c**) with phosphoryl chloride in chlorobenzene gave unstable 2-chloroindoles (**7a**) and (**7b**) in 45% and 75% yields, respectively.[9]



Scheme 3 *Reagents and conditions:* i, $POCl_3$, chlorobenzene, 8 h, 100 ˚C

The bromo substituent of **6** was replaced by phenyl or 1-naphthyl groups by the Suzuki-Miyaura coupling reaction with the corresponding boronic acids.[10] As expected, the symmetric isomers of tetraarylated cyclic indole-tetramers (**8a**) and (**8b**) were obtained, albeit in low yields (17% and 15 % yields, respectively). The structures of compound (**8a**) and (**8b**) were identified by MS and NMR spectra.



6

8a:R=phenyl
8b:R=1-naphthyl

Scheme 4 *Reagents and conditions:* i, $Pd(PPh_3)_4$, arylboronic acid in EtOH, sat. $NaHCO_3$ aq., toluene, 4 h, reflux

The UV/VIS spectra of **8b** indicated the tube-shaped structure of the cyclooctatetraene ring, which showed λmax around 316 nm. Tetraarylated compound (**8b**) showed weak emission at 422nm.[11]

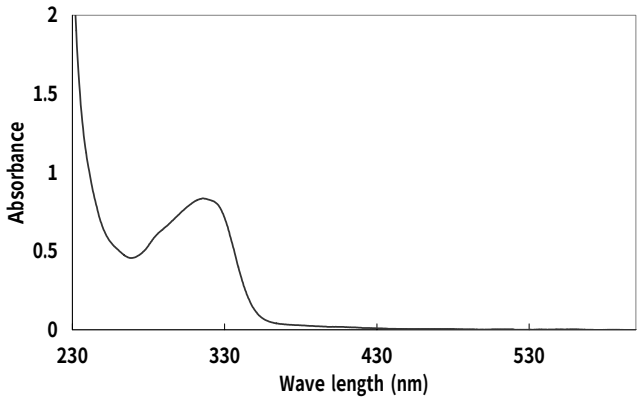


Figure 3 UV/VIS-spectra of **8b**

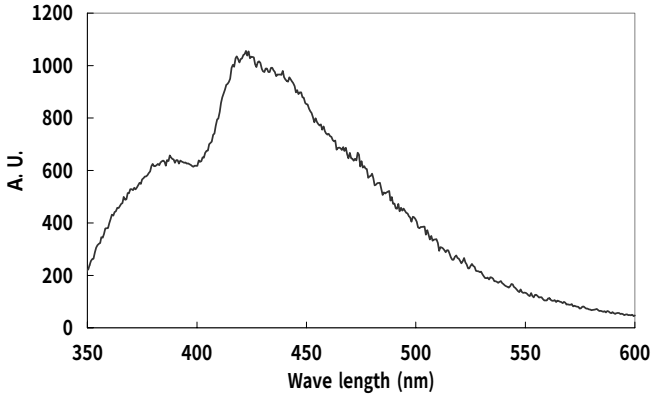


Figure 4 FL spectra of **8b**

CONCLUSION

The preparation of the symmetric isomer of cyclic indole-tetramer (**6**) was achieved in the reaction of 5-bromoindolin-2-one (**5a**) with phosphoryl chloride. Suzuki-Miyaura coupling reaction of **6** gave tetra arylated derivatives.

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5. a) The formation of indole trimer (2,3,7,8,12,13-hexabromo-10,15-dihydro-5*H*-diindolo-[3,2-*a*:3',2'-*c*]carbazole) was reported in the reaction of indole with Br_2. (Preparation, X-Ray structure and properties of a hexabrominated, symmetric indole trimer and its TCQN adduct: a new route to functional molecular systems. R. Neil, P. S. MacLean, E. J. Coxall, and A. R. Mount, *J. Mater. Chem.*, 2000, **10**, 2043.); b) T. Kaneko, M. Matsuo, and Y. Iitaka, *Chem. Pharm. Bull.*, 1981, **29**, 3499; c) V. Bocchi and G. Palla, *Tetrahedron*, 1986, **42**, 5019; d) J. G. Mackintosh, C. R. Redpath, A. C. Jones, P. R. R. Langridge-Smith, D. Reed, and A. R. Mount, *J. Electroanalytical Chemistry*, 1994, **375**, 163; e) M. Eissenstat, M. R. Bell, T. E. D'Ambra, E. J. Alexander, S. J. Daum, J. H. Ackerman, M. D. Gruett, V. Kumar, K. G. Estep, E. M. Olefirowicz, J. R. Wetzel, M. D. Alexander, J. D. Weaver, III, D. A. Haycock, D. A. Luttinger, F. M. Casiano, S. M. Chippari, J. E. Kuster, J. I. Stevenson, and S. J. Ward, *J. Med. Chem.*, 1995, **38**, 3094; f) V. Bocchi, A. Colombo, and W. Porozio, *Synthetic Metals*, 1996, **80**, 309.
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11. Measurement conditions: UV/VIS; c = 1.0 x 10^{-5} M in CH_2Cl_2: FL; c = 1.0 x 10^{-5} M in CH_2Cl_2, λ_{ex} = 316 nm.
12. Spectral data for **6-8** are given below.

2,7,12,17-Tetrabromocyclooctano[1,2-*b*:3,4-*b'*:5,6-*b''*:7,8-*b'''*]tetrakis-1*H*-indole (**6**):

yellow - brown powders: mp = >300°C: FAB-MS(NBA, positive); m/z 774[$(M+H)^+$], 775, 776, 777, 778: ^{1}H-NMR (300 MHz, acetone-d_6) δ 7.29 (dd, *J*=1.8, 8.4 Hz, 4H), 7.51 (d, *J*=8.4 Hz, 4H), 7.78 (d, *J*=1.8 Hz, 4H), 10.90 (s, 4H): ^{13}C-NMR (75 MHz, acetone-d_6) δ 105.7, 113.3, 113.5, 121.3, 124.8, 129.5, 136.2, 136.7: HR-MS (FAB); Calcd for $C_{32}H_{16}N_4Br^{79}{}_2Br^{81}{}_2$: 775.8071, Found: 775.8069: Anal. Calcd for $C_{32}H_{16}N_4Br_4$ H_2O: C, 48.40; H, 2.28; N, 7.06; Found: C, 48.36; H, 2.00; N, 6.90.

5-Bromo-2-chloro-1-methylindole (**7a**):

white solid: mp = 71 - 72°C: EI-MS; m/z 243(M^+), 245, 247: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 3H), 6.40 (d, *J*=0.6 Hz, 1H), 7.13 (d, *J*=8.6 Hz, 1H), 7.29 (dd, *J*=1.8, 8.6 Hz, 1H), 7.64 (dd, *J*=0.6, 1.8 Hz, 1H): ^{13}C-NMR (75 MHz, $CDCl_3$) δ 30.2, 99.4, 110.9, 113.7, 122.5, 124.7, 127.5, 128.7, 135.0: Anal. Calcd for C_9H_7NBrCl: C, 44.21; H, 2.89; N, 5.73; Found: C, 44.40; H, 2.83; N, 5.74.

5-Bromo-2-chloro-1-hexylindole (**7b**):

colorless liquid: EI-MS; m/z 313(M^+), 315, 317: ^{1}H-NMR (270 MHz, $CDCl_3$): δ 0.87 (t, *J*=7.0 Hz, 3H), 1.24-1.35 (m, 6H), 1.67-1.80 (m, 2H), 4.12 (t, *J*=7.3 Hz, 2H), 6.38 (d, *J*=0.9 Hz, 1H), 7.13 (d, *J*=8.8 Hz, 1H), 7.27 (dd, *J*=1.6, 8.8 Hz, 1H), 7.64 (d, *J*=1.6 Hz, 1H): HR-Mass (EI); Calcd: 315.0211, Found: 315.0210: Anal. Calcd for $C_{14}H_{17}NBrCl$: C, 53.44; H, 5.45; N, 4.45; Found: C, 53.62; H, 5.49; N, 4.38.

2,7,12,17-Tetraphenylcyclooctano[1,2-*b*:3,4-*b'*:5,6-*b''*:7,8-*b'''*]tetrakis-1*H*-indole (**8a**):

yellow - browns powders: FAB-MS (NBA, positive); m/z 765 [$(M+H)^+$]: ^{1}H-NMR (600 MHz, acetone-d_6) δ 7.20 (t, *J*=7.4 Hz, 4H, phenyl_H), 7.33 (t, *J*=7.4 Hz, 8H, phenyl_H), 7.37 (dd, *J*=1.7, 8.2 Hz, 4H, indole_H), 7.51 (d, *J*=8.2 Hz, 4H, indole_H), 7.59 (d, *J*=7.4Hz, 8H, phenyl_H), 7.84(s, 4H, indole_H), 10.79 (s, 4H, NH): HR-MS (FAB); Calcd: 765.3018, Found: 765.3015.

Anal. Calcd for $C_{56}H_{36}N_4$ 0.2$CHCl_3$: C, 85.57; H, 4.63; N, 7.10; Found: C, 85.74; H, 4.79; N, 6.74

2,7,12,17-Tetra(1-naphthyl)cyclooctano[1,2-*b*:3,4-*b'*:5,6-*b''*:7,8-*b'''*]tetrakis-1*H*-indole (**8b**):

yellow - brown powders: FAB-MS (NBA, positive); m/z 965 [$(M+H)^+$]: ^{1}H-NMR (600 MHz, acetone-d_6) δ 7.16(dd, *J*=1.6, 8.2 Hz, 4H, indole_H), 7.35(t, *J*= 7.6 Hz, 4H, naphthyl_H), 7.41(t, *J*=7.6 Hz, 4H, naphthyl_H), 7.41(d, *J*=7.4 Hz, 4H, naphthyl_H), 7.46(d, *J*=8.2 Hz, 4H, indole_H), 7.47(t, *J*=8.6 Hz, 4H, naphthyl_H), 7.76(s, 4H, indole_H), 7.81(d, *J*= 8.2Hz, 4H, naphthyl_H), 7.87(d,

J=8.0 Hz, 4H, naphthyl_H), 7.92(d, *J*= 8.2Hz, 4H, naphthyl_H), 10.84(s, 4H, NH): HR-MS (FAB); Calcd: 965.3644, Found: 965.3651. Anal. Calcd for $C_{72}H_{44}N_4$ $2.5H_2O$: C, 85.61; H, 4.89; N, 5.55; Found: C, 85.75; H, 4.68; N, 5.44.