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Synthesis of isocorrole and the higher homologues
Jun-ichiro Setsune,* Aki Tsukajima, and Junko Watanabe
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1) r.t, 16h
2) DDQ
3) OH-

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2\text{Cl}_2 \\
4n \\
(n = 1 - 11)
\end{align*}
\]
Synthesis of isocorrole and the higher homologues

Jun-ichiro Setsune,* Aki Tsukajima, and Junko Watanabe

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Abstract—Bis(azafulvene) derivative of gem-dimethyldipyrrylmethane reacted with 2,2'-bipyrrrole under neutral conditions without catalyst to give a mixture of expanded isocorroles in ca. 50% total yields. GPC separation gave eleven porphyrinoids containing 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44 units of pyrrole. © 2007 Elsevier Science. All rights reserved.

Isocorrole is a tautomeric form of corrole where one of three meso-carbons of the (1.1.1.0)-type tetrapyrrolic macrocycle is sp<sup>3</sup>-hybridized and two NH protons are inside the cavity, although a (2.0.1.0)-type structural isomer is also called the same name. The isocorrole nucleus has only recently been synthesized by the condensation of two parts of 3,4-diethyl-2-formylpyrrole with gem-dimethyl-3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylic acid followed by the oxidative coupling of the resulting a,c-biladiene in the presence of Ni(OAc)<sub>2</sub>•4H<sub>2</sub>O. On the other hand, the [2+2]-type condensation of the diacid and 5,5'-diformyl-3,3',4,4'-tetraethyl-2,2'-bipyrrrole did not give isocorrole at all, but afforded cyclooctapyrrole and cyclododecapyrrole (see Scheme 1). These expanded isocorroles are closely related to the calixphyrins where both sp<sup>2</sup>- and sp<sup>3</sup>-hybridized bridging carbons are present in the porphyrin framework. Thus, more flexible ring structure is expected for the expanded isocorroles in comparison with the expanded porphyrins with complete cycloconjugation. In view of the fact that there has been very little work on the isocorrole derivatives in spite of their importance as a member of porphyrinoids, we have applied our original synthetic method using bis(azafulvene) to the preparation of gem-dimethylisocorrole and the higher homologues.

Scheme 1: Synthesis of cyclooctapyrrole and cyclododecapyrrole by Vogel and co-workers (ref. 1). A CH<sub>2</sub>Cl<sub>2</sub> solution (40 ml) of gem-dimethyl-2,2'-bis(6-phenylazafulvenyl)methane (0.48 mmol) and 3,3'-di-isobutyl-4,4'-dimethyl-2,2'-bipyrrrole (0.48 mmol) was stirred at room temperature for 16 h under argon. After oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (abbreviated hereafter as DDQ) (1.44 mmol), the reaction mixture was purified by column chromatography to give isocorrole 4 in 27.8% yield. The higher homologues, 8, 12, 16, 20, and 24 containing 8, 12, 16, 20, and 24 pyrrole units were separated by gel permeation chromatography (GPC) in 9.5%, 5.8%, 3.2%, 2.5%, and 1.5% yield, respectively, as shown in Table 1. When the reactant concentration was increased from 0.012 to 0.027 mol/L, the yield of higher homologues increased in sacrifice of the yield of 4 and the total yield of the macrocycles decreased from 50.5% to 44.2% (Table 1, entry 2). Addition of 2 molar equivalents

Keywords: porphyrinoids, calixphyrin, macrocycle, porphyrins, expanded porphyrins, corrole

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of zinc(II) $p$-$t$-butylbenzoate further changed the products distribution in favor of the higher homologues without affecting the total yield (Table 1, entry 3). Thus, expanded isocorroles 28 and 32 with 28 and 32 pyrrole units were isolated in 1.6% and 0.7% yield, respectively. The first fraction in the GPC was further separated by using polystyrene-polydivinylbenzene gel with a larger pore size to result in the isolation of giant homologues 36, 40, and 44 with 36, 40, and 44 pyrrole units in the yield of 0.5% ~ 0.1%. However, the total yield decreased to only 15% at the reactant concentration of 0.080 mol/L.

Table 1. Synthesis of cyclopolypyrroles $4n$.

<table>
<thead>
<tr>
<th>entry</th>
<th>Additive $^{a)}$</th>
<th>conc. $^{b)}$</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
<th>32</th>
<th>total</th>
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<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>0.012</td>
<td>27.8</td>
<td>9.5</td>
<td>5.8</td>
<td>3.2</td>
<td>2.5</td>
<td>1.5</td>
<td>tr</td>
<td></td>
<td>50.5</td>
</tr>
<tr>
<td>2</td>
<td>none</td>
<td>0.027</td>
<td>10.3</td>
<td>10.4</td>
<td>9.4</td>
<td>6.8</td>
<td>3.8</td>
<td>2.3</td>
<td>1.2</td>
<td>tr</td>
<td>44.2</td>
</tr>
<tr>
<td>3</td>
<td>Zn($p$-$t$-BuC$_6$H$_4$CO$_2$)$_2$</td>
<td>0.027</td>
<td>4.5</td>
<td>12.8</td>
<td>9.6</td>
<td>7.6</td>
<td>4.6</td>
<td>2.7</td>
<td>1.6</td>
<td>0.7</td>
<td>44.1</td>
</tr>
</tbody>
</table>

$^{a)}$ Zinc $p$-$t$-butylbenzoate (2 molar equiv) was added. $^{b)}$ concentration of 2 and 3 (mol/L).

These expanded isocorroles were identified by ESIMS. The largest homologue, cycloctatetracontapyrrole 44, (MW = 6807.1) showed seven signals corresponding to the di-protonated species at 3405.6 mass (3404.6 calc. for C$_{473}$H$_{506}$N$_{44}$ + 2H$^+$) through the octa-protonated species at 852.0 mass (851.9 calc. for C$_{473}$H$_{506}$N$_{44}$ + 8H$^+$) as depicted in Figure 1.

![Figure 1](image1.png)

**Figure 1.** ESIMS spectrum of 44. The calculated mass and the number of charges are indicated in the parenthesis.

The UV-vis absorption band is red-shifted with increasing the ring size as shown in Figure 2; 420, 541, 538, 574, 582, and 584 nm for 4, 8, 12, 16, 20, 24, and 28, respectively. The larger homologues 32, 36, 40 and 44 showed virtually the same UV-vis feature with an absorption maximum at 586–587 nm. It is noteworthy that the UV-vis feature of 8 (a strong band at 541 nm with shoulders at 459 and 642 nm) is quite different from that of 8a (a strong band at 435 nm with a weak band at 523 nm), whereas 12 and 12a show similar UV-vis spectra with a weak band at around 430 nm (433 nm for 12 and 429 nm for 12a) and a strong band at around 540 nm (538 nm for 12 and 544 nm for 12a). These UV-vis spectra seem to depend on the conformation of the π-conjugated tetrapyrrolic units and the electronic interaction beyond the bridging sp$^3$ carbons, that is, homoconjugation or transannular π-π interaction. Thus, the UV-vis spectrum converged to that expected for linear oligomers as the ring size increased.

![Figure 2](image2.png)

**Figure 2.** UV-vis spectra of isocorrole 4 and the higher homologues 8, 12, 16, 20, 24, 28, and 32 in CH$_2$Cl$_2$. 
The cyclopolypyrroles larger than cyclododecapyrroles have never been reported in the porphyrinoid chemistry except our previous work on the expanded porphyrins having 16, 20, and 24 pyrrole units. To the best of our knowledge, a free base form of isocorrole has never been reported so far either. The isocorrole 4 shows a B-type band at 420 nm and Q-type bands at 620 and 675 nm in the UV-vis spectrum and signals due to the NH protons at 13.6 ppm and pyrrole β-protons at 6.53 and 6.38 ppm in the 'H-NMR. The NaBH₄ reduction of 4 in a mixture of CH₂Cl₂ and ethanol quantitatively gave the dihydrocorrole 4b (see Scheme 2), which showed three 'H NMR signals due to the NH protons at 12.6, 8.56, and 8.23 ppm and a singlet due to the meso-proton at 5.49 ppm. Therefore, reduction occurred at one meso-carbon and one pyrrole nitrogen but not at two meso-carbons. Although condensation of 2a and 3a in the presence of a large excess amount of BF₃·Et₂O failed to give isocorrole, it has recently been reported that the acid-catalyzed condensation of dipyrromethane 5,5'-dicarbinol with 2,2'-bipyrrole gave the acid-catalyzed condensation of dipyrrylmethane 5,5'-dicarbinol. 6

It has been reported that the 

dimethylidipyrrylmethane units are at the crossing point of the figure 8 loop of 8a on the basis of the X-ray crystallographic analysis and the NOE NMR experiment in solution. 3 A remarkable difference in the UV-vis feature between 8a and 8b noted above suggests that the loop conformation of 8 is not similar to the figure 8 conformation of 8a. The 2D ROESY NMR spectrum of 8 showed a cross peak between doublets (6.33, 6.18 ppm) due to the β-pyrrole protons and doublets (0.48, 0.47 ppm) due to the methyl protons of the iso-butyl group. Therefore, the conformation of 8 is close to the figure 8 loop where the bipyrrrole units are at the crossing point as shown in Scheme 3. The conformation of the macrocycle is dependent on the substitution pattern in the macrocycle periphery, especially on the steric bulk of the meso-phenyl groups in this case.

The formation of macrocycles using bis(azafulvene) derivative of gem-dimethylidipyrrylmethane and 2,2'-bipyrrole proceeded under neutral conditions to give gem-dimethylisocorrole as the smallest member through cyclotetratetracontapyrrole as the largest member. The yield and products distribution were dependent on the reaction conditions and the substitution pattern of the macrocycle periphery as compared with the result of Vogel and coworkers. 1 Availability of these nano-scale cyclooligomers of different ring sizes with the intervals of 4 pyrrole units is of significance in view of their combinatorial application. Further studies aiming at more selective formation of the giant porphyrinoids as well as their use in the supramolecular chemistry are based on this work.

Acknowledgements

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6. Bis(azafulvene)methane 2 was obtained from gem-dimethylidipyrrylmethane dicarbino in more than 90% yield (Setsune, J.; Tanabe, A.; Watanabe, J.; Maeda, S. to be submitted): To a mixture of the dicarbino (0.53 mmol) and 4-dimethylaminopyridine (0.028 mmol) in dry ether (8 ml) was added a dry ether solution (8 ml) of di-t-butyl dicarbonate (1.57 mmol) under argon. After stirring for 3 h at room temperature, the color of the solution turned bright yellow. Aqueous K₂CO₃ solution (8 mL, 0.02 mol/L) was added to the reaction mixture and it was extracted with diethyl ether. After drying over anhydrous K₂CO₃, hexane (5 ml) was added to the ether solution and condensed under reduced pressure. A small
amount of precipitates formed at first was removed by filtration and the filtrate was evaporated to give 2. UV-vis (λ_{max} nm (logε)) in CHCl₃ 350 (4.61). 1H NMR (δ-value in CDCl₃) 8.33 (d, 4H, J=8.3 Hz, o-Ph-H); 7.43 (t, 4H, J=7.3 Hz, m-Ph-H); 7.38 (t, 2H, J=7.2 Hz, p-Ph-H); 6.89 (s, 2H, -CH=); 7.06, 6.62 (dc2, 2H, J=4.5 Hz, β-pyrene-H); 1.82 (s, 6H, -CH3). MS (EI) (found/calcd for C₂₃H₂₅N₂O) 350 (M⁺). Analysis caked (%) for C₂₃H₂₅N₂O: C, 85.68; H, 6.33; N, 7.99. Found: C, 85.48; H, 6.39; N, 8.17.

7. 2,2'-Bipyrolyle 3 was prepared in a similar manner as 3,3' -dimethyl-4,4'-diethyl-2,2'-bipyrolyle 1,2. 1H NMR (δ-value in CDCl₃) 7.73 (br, 2H, NH); 6.54 (d, 2H, J=2.5 Hz, α-py-H); 2.34 (d, 4H, CH₂CHMe); 2.06 (s, 6H, -β-py-CH₃); 1.72 (m, 2H, -CH₂CH₂Me); 0.82 (d, 12H, -CH₂CH₂Me). MS (EI) (found/calcd for C₃₆H₄₄N₂) 272/272 (M⁺). Analysis caked (%) for C₃₆H₄₄N₂: C, 78.96; H, 10.41; N, 10.19. Found: C, 79.36; H, 10.36; N, 10.28.

8. Typical procedure: A mixture of gem-dimethyl-2,2'-bis(6-phenylazafulvenyl)-methane 2 (0.50 mmol), 3,3'-di-iso-butyl-4,4'-dimethyl-2,2'-bipyrolyle 3 (0.50 mmol), and Zn(II) p-t-butylbenzoate (1.0 mmol) in dry CH₂Cl₂ (18 ml) was stirred for 16 h at room temperature under argon. DDQ (1.60 mmol) was then added to the reaction mixture and stirring was continued for additional 2 h at room temperature. The resulting blue-green solution was passed through Celite that was washed with CH₂Cl₂ and then with acetone. The acetone washings were evaporated and the residue was dissolved in a mixture of CH₂Cl₂ and methanol (20/1). The combined organic solution was shaken with 2% aqueous HClO₄ solution, water, and 0.5% aqueous NaOH solution, sequentially. The organic layer was separated, dried over Na₂SO₄, and evaporated to dryness. The residue was chromatographed on Al₂O₃ (activity II-III) with toluene to give a mixture of expanded iscororoles. A CHCl₃ solution of these expanded iscororoles was injected to HPLC with a combination of GPC columns of JAIbEGEL-3H (20 × 600 mm, exclusion limit MW 70000 polystyrene) and JAIbEGEL-2H (20 × 600 mm, exclusion limit MW 5000 polystyrene) and the separation was performed by using a recycle loop. 4, 8, 12, 16, 20, 24, 28, and 32 were separated at the retention time of 190 (at the 3rd cycle), 188 (at the 3rd cycle), 344 (at the 6th cycle), 499 (at the 9th cycle), 486 (at the 9th cycle), 475 (at the 9th cycle), 466 (at the 9th cycle), and 254 (at the 5th cycle) min, respectively, with a CHCl₃ flow rate of 3.8 ml/min. The fraction running faster than 32 was further separated by the combination of GPC columns of JAIbEGEL-3H and JAIbEGEL-2.5H (20 × 600 mm, exclusion limit MW 20000 polystyrene). 36, 40, and 44 were separated at the retention time of 859, 852, and 844 min at the 16th cycle, respectively, with a CHCl₃ flow rate of 3.8 ml/min. The separated fractions corresponding to 4 through 32 were evaporated. Reprecipitation by slowly evaporating the CH₂Cl₂-methanol solution and filtration afforded pure materials of 4 through 32. The yields of 36, 40, and 44 were roughly estimated on the basis of their UV-vis absorbances at 500 nm relative to that of 32 during the GPC separation. Isocorrole 4: UV-vis (λ_{max} nm (logε)) in CHCl₃ 420 (4.77), 620 (3.88), 675 (3.96). 1H NMR (δ-value in CDCl₃) 13.6 (br, 2H, NH); 7.44–7.48 (m10H, meso-Ph-H); 6.53, 6.38 (dc2, 2H, J=4.3 Hz, β-py-H); 2.51 (d, 4H, J=7.5 Hz, -CH₂CHMee); 1.79 (s, 6H, -β-py-CH₃); 1.43 (s, 6H, gem-CH₃); 1.72–1.77 (m, 2H, -CH₂CHMee); 0.87 (d, 12H, J=6.8 Hz, -CH₂CHMee).

9. Spectroscopic data of 2b: UV-Vis (λ_{max} nm (logε)) in CHCl₃ 374 (3.93), 425 (3.59), 508 (4.20), 541 (sh, 413). 1H NMR (δ-value in CDCl₃) 12.6, 8.56, 8.23 (ox2, 1H=3, NH); 7.22–7.45 (m, 10H, meso-Ph-H); 6.05, 5.91 (dc2, 1H=2, 1H=2, J=4.0 Hz, β-py-H); 5.97, 5.73 (ox2, 1H=2, J=3.0 Hz, β-py-H); 5.49 (s, 1H, meso- H); 2.32, 2.45, 2.49, 2.56 (dd4, 1H=4, 1H=4, J=14.2, 7.5 Hz, -CH₂CHMee); 1.70, 1.66 (ox2, 3H=2, β-py-CH₃); 1.78, 1.33 (ox2, 3H=2, gem-CH₃); 1.80–1.85 (m, 2H, -CH₂CHMee); 0.91, 0.90, 0.87, 0.78 (dd4, 3H=2, J=6.5 Hz, -CH₂CHMee).