HETEROCYCLES, Vol. 65, No. 1, 2005, pp. 1 - 4
Received, 13th October, 2004, Accepted, 7th December, 2004, Published online, 10th December, 2004

SYNTHETIC STUDIES ON AZACYCLOTRIBENZYLENES

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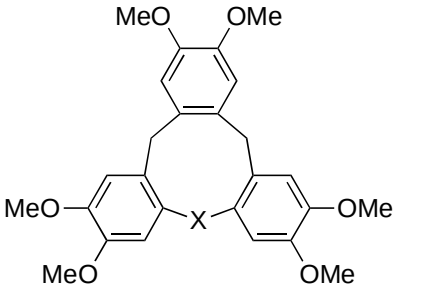
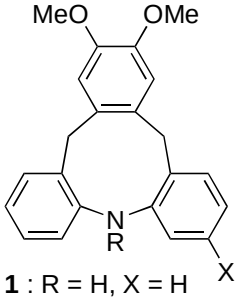
Abstract – Azacyclotribenzylene compounds (**1**, **2**) and several of their *N*-alkyl derivatives (**3-6**) were synthesized *via* biarylamines (**12**, **14**) in good yield. Conformational studies of them are also discussed.

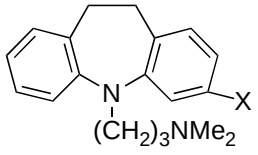
Much attention has been focused on the synthesis of cyclophanes, such as cyclotriveratrylene (CTV), crown ether, calixarenes and so on, because of their interesting structures and properties (Figure 1).[1,2] However, there is no report involving the usage of cyclophanes as drugs so far. Probably, their bulkiness and high hydrophobicity are not thought to be adequate for binding receptors or enzymes. Recently, some biological activities have been found in fullerene derivatives, in spite of their high hydrophobicity. The fullerene derivatives may break DNA and inhibit cell growth and the activity of enzymes.[3-5] These results suggest that cyclophanes might also have some potential as candidates for drugs. Although, many studies on the synthesis of oxa- or thiacyclotriveratrylenes have been carried out,[6-9] azacyclotribenzylene (**1**) has not yet been synthesized. We expected that **1** and its derivatives (**2**-**6**) have potential for pharmacological activities, since an amine group acts as acceptor and donor in a hydrogen bond. Also the



Cyclotriveratrylene (CTV) : X = CH_2
Oxacyclotriveratrylene : X = O
Thiacyclotriveratrylene : X = S



1 : R = H, X = H
2 : R = H, X = Cl
3 : R = Me, X = H
4 : R = $(CH_2)_3NMe_2$, X = H
5 : R = Me, X = Cl
6 : R = $(CH_2)_3NMe_2$, X = Cl



7 : X = H
8 : X = Cl

Figure 1

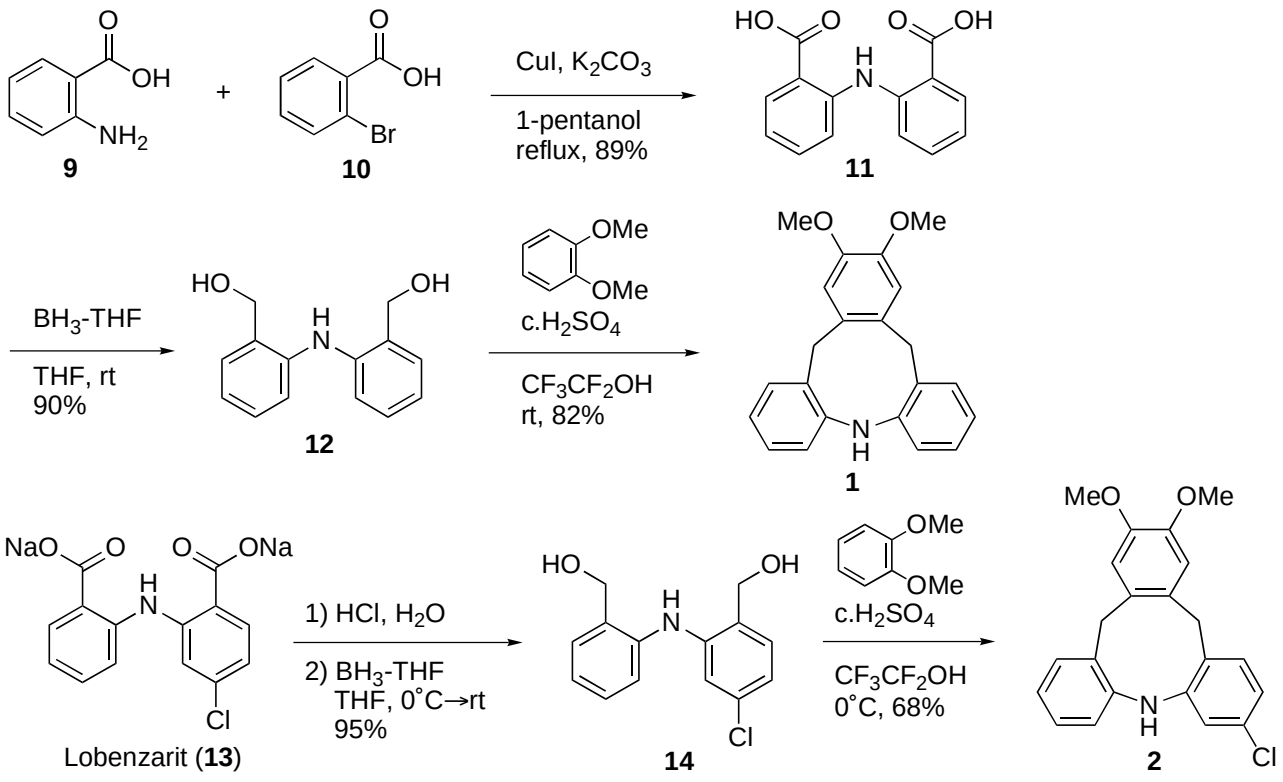
azacyclotribenzylenes have a structure similar to tricyclic anti-depressant drugs, imipramine (**7**) and clomipramine (**8**). Here, we wish to describe our preliminary results on the synthesis of six kinds of

azacyclotribenzylenes (**1**-**6**)

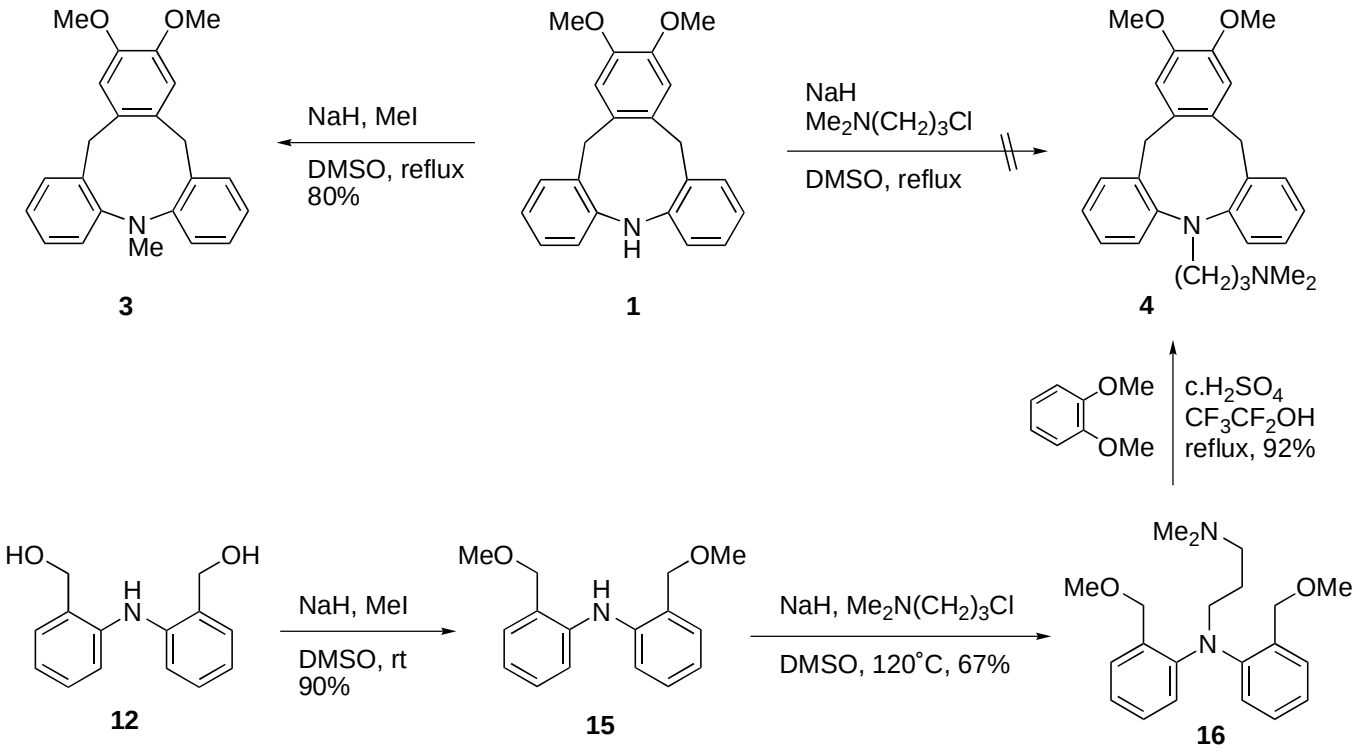
At first, synthesis of azacyclotribenzylene (**1**) was carried out. The Ulluman reaction of 2-aminobenzoic acid (**9**) with 2-bromobenzoic acid (**10**) in the presence of copper iodide and potassium carbonate in 1-pentanol afforded a diarylamine (**11**) in a yield of 89%.[10,11] Reduction of **11** with BH_3-THF gave diol (**12**) which was reacted with veratrole under acid conditions successfully to furnish azacyclophane (**1**) (Scheme 1). Similarly, a 4-chloro congener (**2**) of **1** could be synthesized *via* **14** from Lobenzarit (**13**) in three steps.

Previously, we observed that methylene protons in CTV appeared as a couple of doublet (δ 3.65 and 4.87) showing the crown conformation.[12] As expected, ^{1}H NMR spectral data of **1** and **2** also showed their flexible conformation by the appearance of methylene protons as one singlet peak (δ 4.45) in **1** and two singlet peaks (δ 3.73 and 3.81) in **2**.

With azacyclotribenzylenes (**1**, **2**) in hand, their *N*-alkylation was examined (Scheme 2). Treatment of **1** with NaH and iodomethane in DMSO easily gave an *N*-methyl derivative (**3**) in 80% yield. The conformation of **3** was analyzed to be flexible in the ^{1}H NMR spectrum, similar to that of **1**. A similar reaction of **1** with *N*,*N*-dimethylaminopropyl chloride failed to yield an *N*-alkyl derivative (**4**). Despite treatment under several reaction conditions with various bases and solvents, all attempts for *N*-alkylation were not successful.



Scheme 1



Scheme 2

To obtain the imipramine analogue (**4**), introduction of the *N,N*-dimethylaminopropyl group onto nitrogen was carried out before cyclization as an alternative route.[13,14] Thus, diol (**12**) was converted to dimethyl ether (**15**), followed by alkylation with *N,N*-dimethylaminopropyl chloride to afford **16**. Acid treatment of **16** with veratrole gave the expected compound (**4**) in 92% yield as a mixture of two conformational isomers, the ratio of which was estimated to be 4 : 3 by ^{1}H NMR spectroscopic analysis. Methylene protons of two isomers are shown as a couple of doublets (δ 3.43 and 5.35, *J*=12.5Hz) [15] and one singlet revealing their conformation as crown and flexible types, respectively. Although the two isomers could be isolated by preparative TLC, each one isomerized gradually at room temperature and completely reached an equilibrium mixture (4 : 3) in two days (Figure 2).

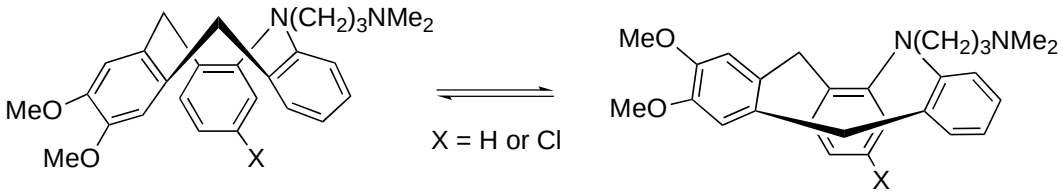
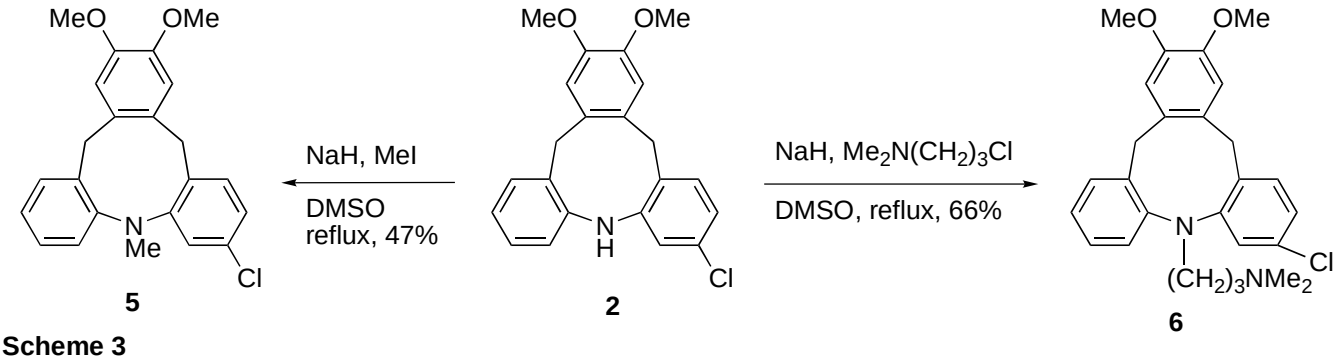


Figure 2

In the case of derivarization of 3-chloroazacyclophane (**2**), not only methylation but also *N,N*-dimethylaminopropylation on the nitrogen atom in the cyclic system was successfully performed to furnish **5** and **6** in moderate yields by direct alkylation (Scheme 3). Two singlet peaks (δ 3.46 and 3.92) of the ^{1}H NMR spectrum showed that the conformation of **5** was flexible. The product (**6**) was obtained as a mixture of two conformational isomers which were separable but liable to come to equilibrium (4 : 3) at ambient temperature as similar to **4**.



Scheme 3

In conclusion, we have shown a facile construction of the azacyclotribenzylene system (**1**, **2**) *via* biarylamines (**12**, **14**). Four *N*-alkyl derivatives (**3**-**6**) of them were also synthesized. Pharmacological studies on the obtained azacyclophanes are now in progress.

ACKNOWLEDGEMENTS

The authors are indebted to Chugai Pharmaceutical Co., Ltd. for the supply of Lobenzarit , and to Mrs. F. Hasegawa of this faculty for her MS spectral measurements.

REFERENCES AND NOTES

1. F. Diedrich, "*Cyclophanes*", The Royal Society of Chemistry, Cambridge, 1991.
2. S. K. Collins, G. P. A. Yap, and A. G. Fallis, *Org. Lett.*, 2000, **2**, 3189.
3. E. Nakamura, H. Tokuyama, S. Yamago, T. Shinkai, and Y. Sugiyama, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 2143.
4. A. W. Jensen, S. T. Wilson, and D. I. Schuster, *Bioorg. Med. Chem.*, 1996, **6**, 767.
5. T. Mashino, N. Usui, K. Okuda, T. Hirota, and M. Mochizuki, *Bioorg. Med. Chem.*, 2003, **11**, 1433.
6. A. S. Lindsey, *J. Chem. Soc.*, 1965, 1685.
7. A. Collet and J. Gabard, *J. Org. Chem.*, 1980, **45**, 5400.
8. A. Collet, *Tetrahedron*, 1987, **43**, 5725.
9. J. Y. Corey and E. R. Corey, *Tetrahedron Lett.*, 1972, **13**, 4669.
10. Y. Horiguchi, S. Sakuma, H. Suzuki, and T. Sano, *Heterocycles*, 2000, **53**, 1305.
11. M. Tanemura, S. Kaiho, K. Mizuno, I. Matsunaga, S. Hata, and M. Shindo, *Yakugaku Zasshi*, 1985, **105**, 659.
12. B. Umezawa, O. Hoshino, H. Hara, and J. Sakakibara, *Chem. Pharm. Bull.*, 1968, **16**, 177.
13. S. J. Schmolka and H. Zimmer, *Synthesis*, 1984, 29.
14. W. G. Elberlein, G. Trummlitz, W. W. Engel, G. Schmidt, H. Pelzer, and N. Mayer, *J. Med. Chem.*, 1987, **30**, 1378.
15. In the case of CTV, signal of the methylene proton are shown as two doublets (δ 3.65 and 4,87, *J*=13.5Hz).