Tetrakis(bicyclo[2.2.2]oct-2-ene)-Fused Calix[4]pyrrole

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Tetrakis(bicyclo[2.2.2]oct-2-ene)-fused calix[4]pyrrole, **5**, was obtained starting from (*E*)-1,2-bis(phenylsulfonyl)ethylene. This new calixpyrrole derivative is the prospective precursor of tetrabenzocalix[4]pyrrole, a potential ion-pair receptor and an attractive species as a possible deep-walled 'molecular container'.

Introduction. – The synthesis and development of novel calix[4]pyrroles are attracting considerable attention within the overlapping fields of receptor design, molecular recognition, and heterocyclic chemistry. Much of the interest in this class of molecules (the parent form, **1**, is represented in *Fig. 1*) reflects their ability to act as simple-to-prepare anion-binding agents, as has been extensively demonstrated by various research groups, including our own [1]. One goal within the broad context of this research involves the synthesis of elaborate calix[4]pyrroles with improved anion-recognition characteristics. To this end, several functionalized calixpyrrole derivatives have been prepared. These include simple *meso*-alkyl-substituted [2], halogenated [3], C-rim-modified [4], strapped [5], photoactive and chromophore-modified systems [6], as well as ditopic [7], expanded [8], *N*-confused [9], polyfunctional [10], and oligomeric calix[4]pyrroles [11].

Calix[4]pyrroles are also emerging as useful elements in the construction of ion-pair receptors. At least in principle, such systems may allow for a higher level of control over ion recognition than simpler monotopic receptors. This enhanced recognition capability is expected to correlate with improved sensitivity, something that could be particularly useful in the area of extraction-based separations. Recently, we have made some progress in the latter area, demonstrating, for instance, that poly(methyl methacrylate) (PMMA) polymers containing pendant calix[4]pyrrole groups can extract Bu_4N^+ fluorides and chlorides from aqueous solutions [12]. Subsequently, crown-ether moieties were incorporated into the basic calix[4]pyrrole-containing

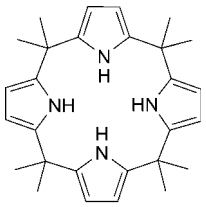

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Fig. 1. *Structure of octamethylcalix[4]pyrrole*

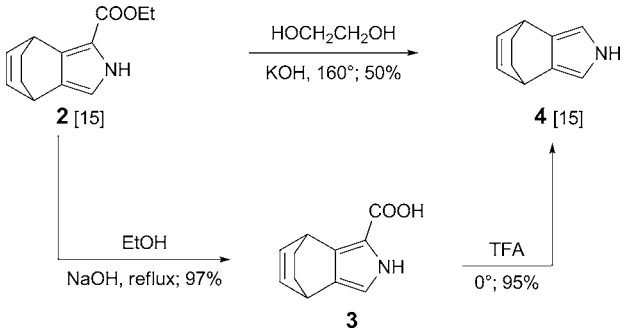
PMMA structure to create organic-soluble polymeric systems capable of extracting KF and KCl from neutral aqueous media [13]. Since the extraction of aforementioned salts was not possible with simple neutral calix[4]pyrrole derivatives, this result highlights the potential benefits that could accrue from being able to extract concurrently both an anion and a corresponding counter cation. On the other hand, *Sessler* and co-workers demonstrated that octamethylcalix[4]pyrrole (**1**) would extract cesium halides as ion pairs [14]. Here, small halide anions were used to organize the octamethylcalix[4]pyrrole framework into a cone conformation, thereby creating an electron-rich cup that favored Cs^+ complexation. Extending the size of this 'cup' beyond the simple 'rim', provided by the β-pyrrolic H-atoms of unfunctionalized calix[4]pyrrole **1**, might allow this approach to work for harder, more highly hydrated cations such as K^+ and Na^+. This, in turn, provides an incentive to prepare new modified calix[4]pyrrole derivatives. Herein, we report the synthesis of bicyclo[2.2.2]oct-2-ene-fused calix[4]pyrrole, **5**, with deep 'walls', together with a stepwise method for the decarboxylation of compound **2** in a better yield.

Results and Discussion. – An attractive synthesis of calix[4]pyrrole target **5** involves the use of 4,7-dihydro-4,7-ethano-2*H*-isoindole (**4**) (*Scheme 1*) as an isoindole equivalent. This intermediate can be built up from (*E*)-1,2-(phenylsulfonyl)ethylene as described in [15]; it was expected to allow access to the bicyclo[2.2.2]oct-2-ene-functionalized calix[4]pyrrole **5**.

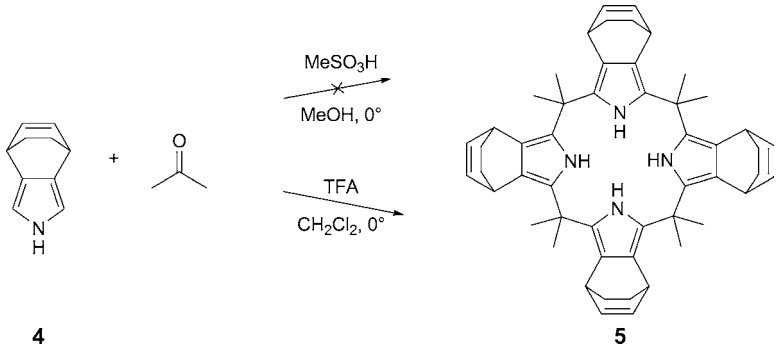
Direct decarboxylation of **2**, as outlined in *Scheme 1*, *via* treatment with KOH in ethylene glycol at 160° for 3.5 h [15b] proved problematic, giving product **4** in only low yield. Therefore, we decided to synthesize compound **4** through a stepwise route that involved first saponification of ester **2** to give **3**, followed by decarboxylation in cold CF_3COOH (TFA). Briefly, **2** was hydrolyzed with NaOH in $EtOH/H_2O$ at reflux temperature. A broad *singlet* at 11.99 ppm in the ^{1}H-NMR spectrum and the mass analysis of the compound confirmed the presence of the carboxylic acid moiety in the structure. Once **3** was obtained, it was decarboxylated by treating with TFA at 0° for 30 min under Ar. Using this strategy, 4,7-dihydro-4,7-ethano-2*H*-isoindole (**4**) was obtained in 92% overall yield.

Efforts were then made to prepare the corresponding calix[4]pyrrole derivative **5** by reacting **4** with acetone in the presence of an acid catalyst, as delineated in *Scheme 2*.

Scheme 1. *Synthesis of Compound* **4**



Scheme 2. *Synthesis of Compound* **5**



Under the general calix[4]pyrrole-forming conditions, involving the use of an acid catalyst (*e.g.*, $MeSO_3H$) in MeOH, the desired calix[4]pyrrole derivative **5** was not obtained in isolable quantities. Therefore, the reaction was carried out in CH_2Cl_2 with TFA as the acid catalyst. In this case, workup and column chromatography gave compound **5** in 73% yield as a white solid. The resonances corresponding to the aliphatic CH H-atoms were detected between δ(H) 1.25 and 1.56 ppm (see *Fig. 2*) in the ^{1}H-NMR spectrum. This result, together with the disappearance of the pyrrole α-H-atom signals and pyrrole N–H peak shift from δ(H) 7.52 to 6.05 ppm, led to the conclusion that product **5** contains an intact calix[4]pyrrole structure.

Furthermore, FAB-MS analysis of compound **5** revealed only one signal at *m*/*z* 742 amu, a value corresponding to the molecular mass of compound **5** plus one H-atom. Although a mixture of four configurational isomers, designated $\alpha\alpha\alpha\alpha$, $\alpha\alpha\beta\beta$, $\alpha\beta\alpha\beta$, and $\alpha\alpha\alpha\beta$ to indicate the relative positions of ethylene bridges (*cf. Fig. 3*), of compound **5** were expected to be formed after the cyclization reaction. We observed isomer spots almost overlapping on silica-gel TLC plate. Therefore, we collected all the isomers together after a flash column chromatography. This new compound has olefin moieties attached to the pyrrole ring. These C=C bonds could be useful for the stronger

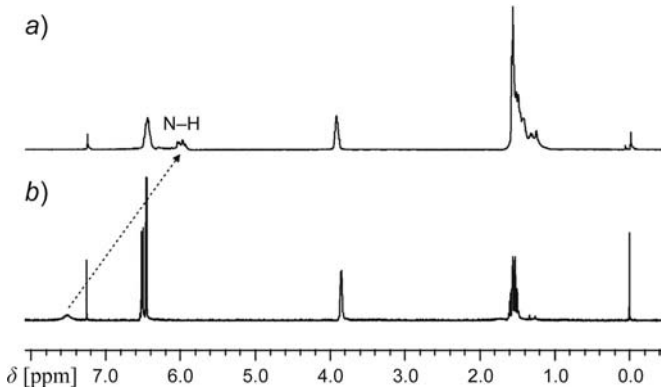


Fig. 2. *^{1}H-NMR Spectra* (recorded in $CDCl_3$) *of compounds* **5** (*a*) *and* **4** (*b*)

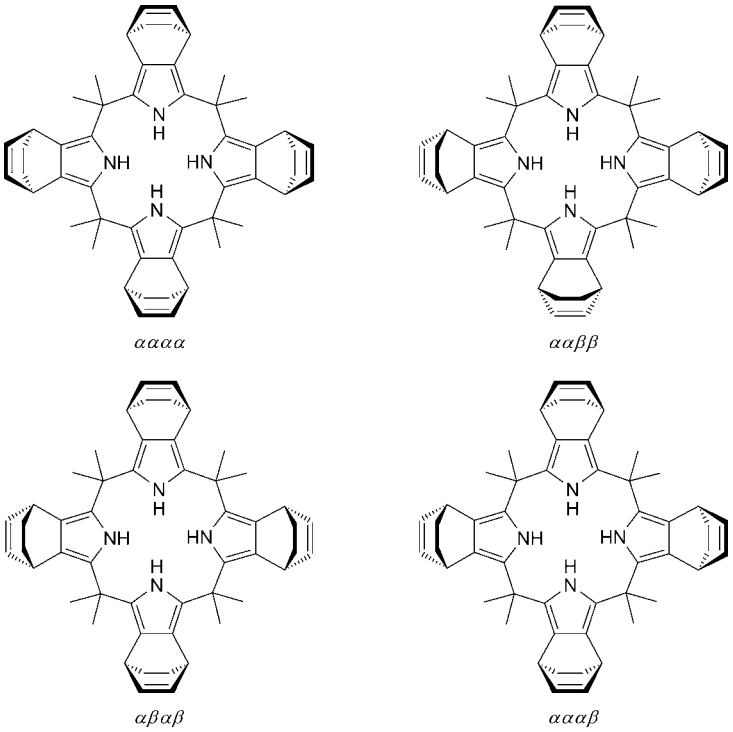


Fig. 3. *Configurational isomers of compound* **5**

interaction with cationic species throughout their π electrons, when this calixpyrrole is used as an ion-pair receptor.

Conclusions. – Herein, we reported the synthesis of the tetrakis(bicyclo[2.2.2]oct-2-ene)-fused calix[4]pyrrole **5**, as well as a stepwise high-yield method for the synthesis of 4,7-dihydro-4,7-ethano-2*H*-isoindole (**4**). The new calixpyrrole derivative **5** could be useful as a new anion receptor and for further derivatization. Currently, efforts are underway to determine the anion binding affinities of **5** towards different anions as a possible ion-pair receptor and deep-walled 'molecular container'.

Experimental Part

General. All solvents were dried before use according to standard procedures. Unless specifically indicated, all other chemicals and reagents used were purchased from commercial sources and used as received. Compound **2** was prepared as described in [15]. M.p.: *Mel-Temp II* instrument; uncorrected. ^{1}H- and ^{13}C-NMR spectra: *Varian Unity 300* and *400* MHz spectrometers; δ in ppm rel. to Me_4Si as internal standard, J in Hz. Low-resolution (LR) FAB- and CI-MS: *Finningan MAT TSQ 70* mass spectrometer; in m/z; high-resolution FAB- and CI-MS: *VG ZAB2-E* mass spectrometer; in m/z.

*4,7-Dihydro-2*H*-4,7-ethanoisoindole-1-carboxylic Acid* (**3**). Compound **2** (0.2 g, 0.92 mmol) was dissolved in 30 ml of EtOH and heated to reflux. Then, NaOH (3.68 g, 147.2 mmol in 30 ml H_2O) was added dropwise, heating at reflux was continued for 5 h, and the mixture was allowed to cool to r.t. The

bulk of the volatiles was then removed under vacuum. The remaining, largely aq. soln. was acidified with HCl (0.2M) until a white precipitate formed. This precipitate, corresponding to product **3** (0.17 g, 97%), was collected by filtration and dried under reduced pressure. M.p. 149–150°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.99 (br. *s*, NH); 10.72 (*s*, COOH); 6.55 (*d*, *J* = 2.8, pyrrole CH); 6.47–6.41 (*m*, 2 CH); 4.24 (br. *d*, *J* = 4.3, CH); 3.81 (br. *d*, *J* = 3.8, CH); 1.51–1.42 (*m*, CH_2); 1.35–1.28 (*m*, CH_2). ^{13}C-NMR (100 MHz, (D_6)DMSO): 162.4; 136.2; 135.8; 135.2; 129.9; 113.8; 113.3; 33.1; 32.4; 26.9; 26.4. LR-MS: 190 ($[M+H]^+$). HR-MS: 190.0866 ($[M+H]^+$, $C_{11}H_{12}NO_2^+$; calc. 190.0868)

*4,7-Dihydro-2*H*-4,7-ethanoisoindole* (**4**). Compound **3** (0.12 g, 0.62 mmol) was dissolved in freshly distilled and degassed TFA (30 ml) at 0° under Ar and stirred for 30 min under protection from light. TFA was removed under vacuum, and the remaining residue was dissolved in CH_2Cl_2 (30 ml) and then washed with sat. $NaHCO_3$ (2 × 30 ml). The soln. was then dried (Na_2SO_4) and filtered. Evaporation of CH_2Cl_2 afforded **4** (85 mg, 95%). White solid. M.p. 129–130°. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.51 (br. *s*, NH); 6.52 (*d*, *J* = 6.5, CH); 6.51 (*d*, *J* = 6.5, CH); 6.46 (*d*, *J* = 6.5, 2 pyrrole CH); 3.84–3.87 (*m*, 2 CH); 1.49–1.62 (*m*, 2 CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): 135.7; 129.3; 108.0; 33.1; 27.6. LR-MS: 145 (M^+). HR-MS: 145.0886 (M^+, $C_{10}H_{11}N^+$; calc. 145.0891).

Tetrakis(bicyclo[2.2.2]oct-2-ene)-Fused Calix[4]pyrrole (=*4,4,13,13,22,22,31,31-Octamethyl-39,40,43,46-tetraazatridecacyclo[32.2.2.2*^{7,10}*.2*^{16,19}*.2*^{25,28}*.1*^{3,32}*.1*^{5,12}*.1*^{14,21}*.1*^{23,30}*.0*^{2,33}*.0*^{6,11}*.0*^{15,20}*.0*^{24,29}*]octatetraconta-2,5,8,11,14,17,20,23,26,29,32,35-dodecaene*; **5**). Compound **4** (70 mg, 0.48 mmol) was dissolved in dry CH_2Cl_2 (50 ml) at 0°, and Ar was bubbled through the soln. for 10 min. Acetone (35.8 µl, 0.48 mmol) was added. Then, TFA (25 µl) was added dropwise within 10 min, while shielding the reaction vessel from light. The mixture was then stirred first at 0° for 3 h and subsequently at r.t. overnight. Then, the mixture was washed with sat. $NaHCO_3$ and dried (Na_2SO_4). After filtration and removing the volatiles, flash chromatography (SiO_2; CH_2Cl_2/hexanes 1:1) yielded **5** (65 mg, 73%). White solid. M.p. 219–220°. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.50–6.40 (br. *m*, 8 CH); 6.10–5.90 (br. *m*, 4 NH); 3.98–3.88 (br. *m*, 8 CH); 1.60–1.30 (br. *m*, 8 Me and 8 CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): 136.6–136.1 (*m*); 126.3–126.0 (*m*); 128.6–124.3 (*m*); 37.5–36.8 (*m*); 34.2–33.4 (*m*); 29.9–28.9 (br. *m*); 28.0–27.2 (*m*). LR-MS: 742 ($[M+H]^+$). HR-MS: 742.4979 ($[M+H]^+$, $C_{52}H_{61}N_4^+$; calc. 742.4974).

REFERENCES

[1] P. A. Gale, J. L. Sessler, V. Kral, V. Lynch, *J. Am. Chem. Soc.* **1996**, *118*, 5140.
[2] P. A. Gale, J. L. Sessler, V. Kral, *Chem. Commun.* **1998**, 1.
[3] P. Anzenbacher, K. Jursikova, V. M. Lynch, P. A. Gale, J. L. Sessler, *J. Am. Chem. Soc.* **1999**, *121*, 11020.
[4] R. Nishiyabu, P. Anzenbacher, *J. Am. Chem. Soc.* **2005**, *127*, 8270; R. Nishiyabu, P. Anzenbacher, *Org. Lett.* **2006**, *8*, 359.
[5] P. K. Panda, C. H. Lee, *Org. Lett.* **2004**, *6*, 671; P. K. Panda, C. H. Lee, *J. Org. Chem.* **2005**, *70*, 3148.
[6] K. A. Nielsen, W. S. Cho, J. O. Jeppesen, V. M. Lynch, J. Becher, J. L. Sessler, *J. Am. Chem. Soc.* **2004**, *126*, 16296; K. A. Nielsen, W. S. Cho, J. Lyskawa, E. Levillain, V. M. Lynch, J. L. Sessler, J. O. Jeppesen, *J. Am. Chem. Soc.* **2006**, *128*, 2444; K. A. Nielsen, L. Martin-Gomis, G. H. Sarovac, L. Sanguinet, D. E. Gross, F. Fernandez-Lazaro, P. C. Stein, E. Levillain, J. L. Sessler, D. M. Guldi, A. Sastre-Santos, J. O. Jeppesen, *Tetrahedron* **2008**, *64*, 8449.
[7] N. Saki, E. U. Akkaya, *J. Incl. Phenom. Macrocycl. Chem.* **2005**, *53*, 269.
[8] C. Bucher, R. C. Zimmerman, V. Lynch, V. Kral, J. L. Sessler, *J. Am. Chem. Soc.* **2001**, *123*, 12744; C. Bucher, R. S. Zimmerman, V. Lynch, J. L. Sessler, *J. Am. Chem. Soc.* **2001**, *123*, 9716.
[9] R. Gu, S. Depraetere, J. Kotek, J. Budka, E. W. Wagner-Wysiecka, J. F. Biernat, A. Dehaen, *Org. Biomol. Chem.* **2005**, *3*, 2921; P. Anzenbacher, R. Nishiyabu, M. A. Palacios, *Coord. Chem. Rev.* **2006**, *250*, 2929.
[10] A. Akar, A. Aydogan, *J. Heterocycl. Chem.* **2005**, *42*, 931.
[11] A. Aydogan, A. Akar, *Chem. – Eur. J.* **2012**, *18*, 1999.
[12] A. Aydogan, D. J. Coady, V. M. Lynch, A. Akar, M. Marquez, C. W. Bielawski, J. L. Sessler, *Chem. Commun.* **2008**, 1455.

[13] A. Aydogan, D. J. Coady, S. K. Kim, A. Akar, C. W. Bielawski, M. Marquez, J. L. Sessler, *Angew. Chem., Int. Ed.* **2008**, *47*, 9648.
[14] R. Custelcean, L. H. Delmau, B. A. Moyer, J. L. Sessler, W. S. Cho, D. Gross, G. W. Bates, S. J. Brooks, M. E. Light, P. A. Gale, *Angew. Chem., Int. Ed.* **2005**, *44*, 2537.
[15] a) T. Okujima, N. Komobuchi, H. Uno, N. Ono, *Heterocycles* **2006**, *67*, 255; b) S. Ito, T. Murashima, H. Uno, N. Ono, *Chem. Commun.* **1998**, 1661.

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