SYNTHESIS OF A MULTIDENTATE FURAN, ESTER/AMIDO, THIOETHER AND POLYETHER CONTAINING MACROCYCLES

Pedro Molina*, Alberto Tárraga, and Carmen Ibáñez

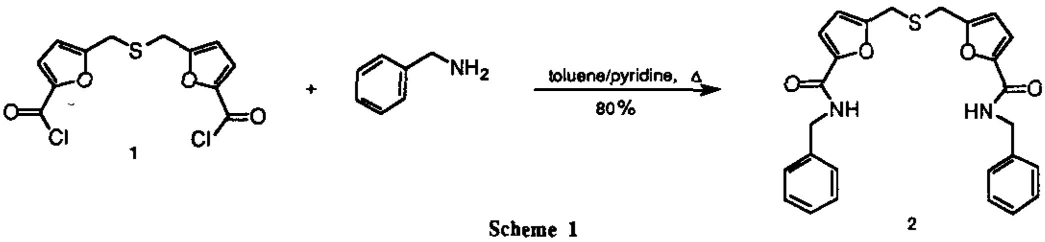
Departamento de Química Orgánica, Facultad de Química, Universidad de Murcia, Campus de Espinardo, E-30071, Murcia, Spain

Dedicated to Prof. A.R. Katritzky in recognition of his contribution to Heterocyclic Chemistry

Abstract - A synthethic route to tetrafuran-containing macrocycles, which allows for variation in the cavity size, is described using 5,5´-(thiodimethylene)-bis(2-furoyl chloride) as heterocyclic building block.

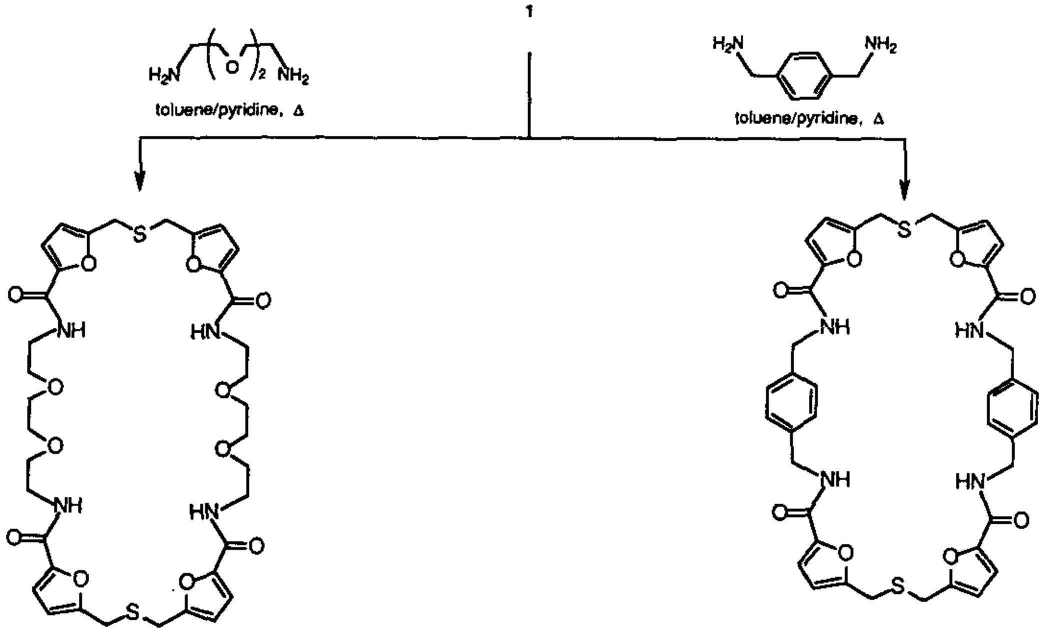
The wide interest in macrocycles containing subheterocyclic rings has led to a range of macrocycles which include five and six membered heterocyclic rings as subunits.[1] In particular, macrocyclic polyethers containing one or two furan subcyclic units have been studied in some detail and certain of these macrocyclic polyether ligands have been shown to form complexes with alkylammonium salts and to be effective carriers of metal cations across a liquid membrane separating aqueous phases.[2-7]

We wish to report the first macrocyclic polyether-tetraester (amido) compounds containing four furan subcyclic units from a synthetic route that contains the potential for variation in cavity size. The macrocyclization step involves the nontemplated formation of the ester (amido) subunits. The key starting material for the preparation of the tetrafuran-containing cycles was the commercially available methyl 5-chloromethyl-2-furoate, which by conventional methods[8,9] was converted to dichloride (1). The macrocyclization step was first modelled using benzylamine in place of α,ω-diamino compounds. Compound (2) also provided a model for the assignments of the nmr spectra of the macrocycles (Scheme 1). The (2+2) macrocyclization of dichloride (1) and an equimolecular



Scheme 1

of either *p*-xylylenediamine or 1,8-diamino-3,6-dioxaoctane was carried out by heating moderately dilute solutions at reflux in toluene in the presence of pyridine. Macrocycle (3a) (36%) or (3b) (31%) were obtained as yellow prisms (Scheme 2). The ir spectra of macrocycles (3) show bands at ν = 3258-3316 cm^{-1} and ν = 1642 cm^{-1} due to the stretching vibration of the amido group. The ^{1}H nmr spectra show the expected signals and among these a broad singlets at δ = 7.01-8.75 ppm corresponding to the presence of an amido linkage. In the ^{13}C nmr spectra, the carbonyl group appears in the range δ = 157.64-158.29 ppm. In the electron mass spectra, the molecular ion peaks of macrocycles (3) could not be seen, however the FAB mass spectra obtained from a solution of 3 in *m*-nitrobenzyl alcohol shown a molecular ion peak at m/z 765 and 789 for 3a and 3b, respectively.

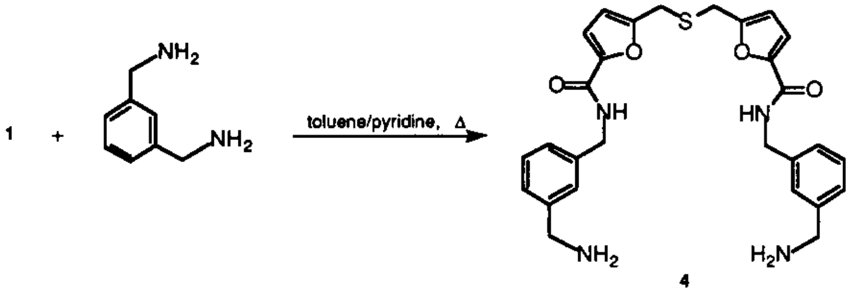


3a 3b

Scheme 2

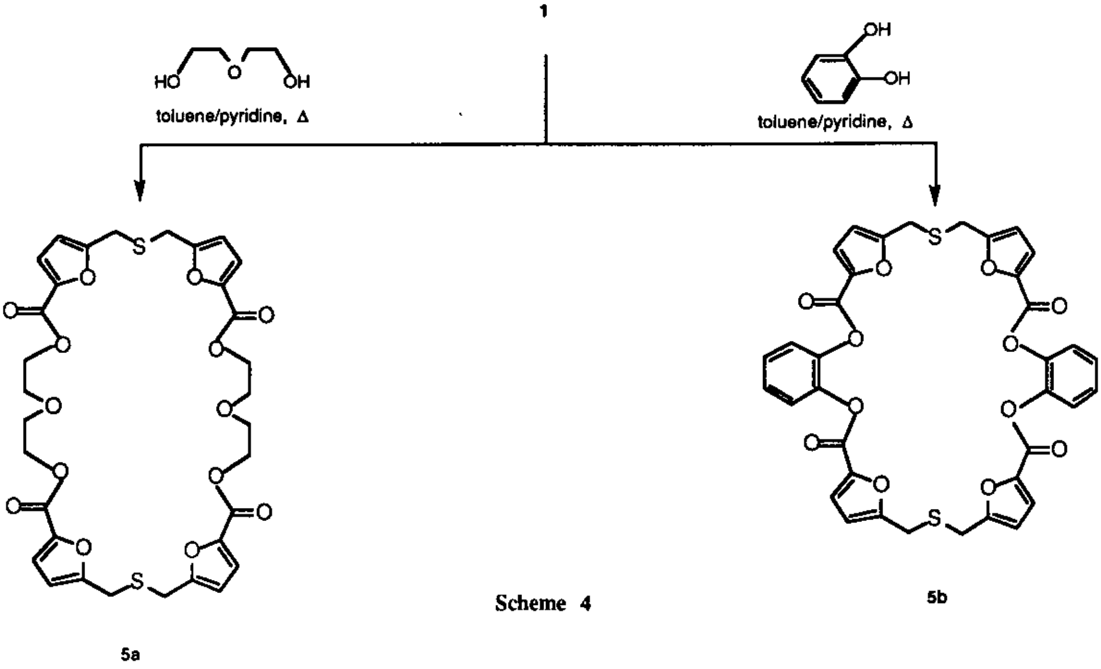
Dichloride (1) also reacted with *m*-xylylenediamine under the same conditions to give the podand (4) in 48% yield (Scheme 3). Elucidation of structure (4) was accomplished by microanalytical and spectral data. The ^{1}H nmr spectrum shows a broad singlet at δ = 2.50 ppm due to the amino primary group and in the ^{13}C nmr appears three different methylene carbon atoms at δ = 28.03 (CH_2S), 41.22 (Ar-CH_2-NHCO) and 45.14 (Ar-CH_2NH_2) ppm, respectively. All attempts to promote cyclization of compound (4) by the action of an excess of dichloride (1) under a variety or reaction conditions were unsuccessful.

On the other hand, dichloride (1) reacted either with 2-hydroxyethyl ether or 1,2-dihydroxybenzene, under the conditions employed for the reactions with α,ω-diamino compounds, to provide the macrocycles (5a) (30%) and



Scheme 3

(5b) (39%) which were isolated as crystalline solids (Scheme 4). The ir spectra of macrocycles (5) show a strong absorption band at ν = 1755-1732 cm^{-1} due to the stretching vibration of the carbonyl bond of the ester group. In the ^{13}C nmr spectra of macrocycles (5), the carbonyl carbon atom appears at δ = 158.29-158.26 ppm and the quaternary carbon atoms C-2 and C-5, of the furan ring, are in the range δ = 156.24-156.40 and δ = 142.31-143.59 ppm, respectively. However, in compounds (3) these carbon atoms were found at δ = 153.70-154.80 and δ = 147.21-147.61 ppm, respectively, while the rest of the common signals did not show any significant difference. The FAB mass spectra of compound (5a) exhibited a peak at m/z 705 (M$^+$+1) and compound (5b) at m/z 713 (M$^+$+1). Compound (3b) has been found to be a new ionophore in ion-selective electrodes for the determination of some antiarrhythmic drugs such as verapamil, propanolol and lidocaine. These results will be published in a future time.



Scheme 4

EXPERIMENTAL

Melting points were obtained in a Kofler hot-stage apparatus and are uncorrected. Ir spectra were run using NaCl plates on a Nicolet FT-5DX spectrophotometer in Nujol emulsions.^{1}H Nmr spectra were recorded using a Varian Unity (300 MHz) apparatus and tetramethylsilane as internal reference. ^{13}C Nmr spectra, were determined on a Varian Unity (75.4 MHz) apparatus. The EI-mass spectra were obtained with a Hewlett-Packard 5993 C spectrometer at 70 eV. The FAB mass spectra were obtained with a Jeol DX 300 spectrometer, using a beam of Xe and *m*-nitrobenzyl alcohol as a matrix. Elemental'analyses were performed with an Eager 200 instrument.

5,5´-Bis(tolylaminocarbonyl)-2,2'-(thiodimethylenedifurane), (2). To a well stirred mixture of 1 (0.25 g, 0.78 mmol), pyridine (0.123 g, 1.5 mmol) and dry toluene (25 ml), a solution of benzylamine (0.17 g, 1.5 mmol) in the same solvent (15 ml) was added dropwise. The resultant solution was stirred at reflux temperature for 20 h. After cooling, the precipitated solid was collected by filtration and recrystallized from EtOH to give 2. Yield: 0.29 g (80%), colorless prisms; mp 193-194 °C. Anal. Calcd for $C_{26}H_{24}N_2O_4S$: C, 67.81; H, 5.25; N, 6.08. Found: C, 67.58; H, 5.18; N, 5.95. ν_{max} (cm^{-1}) 3300, 1647; δ (^{1}H, 300 MHz) (DMSO-d$_6$) 8.86 (1H, d, J = 6.00 Hz, NH), 7.30 (5H, m, aromatics), 7.08 (1H, d, J = 3.18 Hz, H-3), 6.47 (1H, d, J = 3.18 Hz, H-4), 4.41 (2H, d, J = 6.00 Hz, CH$_2$NH), 3.84 (2H, s, CH$_2$S); δ (^{13}C)157.62 (C=O), 153.68 (C-2), 147.22 (C-5), 139.50 (Ci), 128.18, 127.23, 126.67, 114.28 (C-3), 109.81 (C-4), 41.78 (CH$_2$NH), 27.43 (CH$_2$S); m/z (%) 460 (M, 10), 215 (25), 106 (100), 91 (99).

General Procedure for the Preparation of Macrocycles (3) and (5). To a well stirred solution of pyridine (0.12 g, 1.5 mmol) in dry toluene (10 ml), solutions of 1 (0.25 g, 0.78 mmol) in toluene (25 ml) and the corresponding diamino or dihydroxy compound (0.78 mmol) in the same solvent (25 ml) were simultaneously added dropwise. The resultant solution was heated at reflux temperature for the appropriate time (3 h for 3a, 24 h for 3b, 36 h for 5a, 48 h for 5b). After cooling, the precipitated solid was collected by filtration, slurried with EtOH (2x5 ml), air dried and recrystallized from the adequate solvent to give 3 or 5 as crystalline solids.

5,5''':5',5''-Bis[ethanediylbis(oxyethylaminocarbonyl)-2,2':2'',2'''-bis(thiodimethylenedifurylo)phane(3a).- Yield: 0.095 g (31%) yellow prisms; mp 142-144 °C (from EtOH/ether, 1:1). Anal. Calcd for $C_{36}H_{44}N_4O_{12}S_2$: C, 54.81; H, 5.62 ; N, 7.10. Found: C, 54.60 ; H, 5.45; N, 6.89 . ν_{max} (cm^{-1}) 3216, 1642 ; δ (^{1}H, 300 MHz) (CDCl$_3$) 7.01 (1H, s, NH), 6.97 (1H, d, J = 3.28 Hz, H-3), 6.23 (1H, d, J = 3.28 Hz, H-4), 3.70 (2H, s, CH$_2$O), 3.57 (6H, m); δ (^{13}C) 158.29 (C=O), 153.80 (C-2), 147.61 (C-5), 115.62 (C-3), 110.12 (C-4), 70.82 (OCH$_2$CH$_2$O), 70.58 (O$\underline{C}$H$_2$CH$_2$N), 39.20 (CH$_2$N), 28.38 (CH$_2$S); FAB, m/z (%) 789 (M$^+$+1, 10).

5,5''':5',5''-Bis[*p*-xylylenebis(aminocarbonyl)]-2,2':2'',2'''-bis(thiodimethylenedifurylo)phane(3b).- Yield: 0.11 g (36%) yellow prisms; mp 186-187 °C (from toluene). Anal. Calcd for $C_{40}H_{36}N_4O_8S_2$: C, 62.81; H, 4.74 ; N, 7.32. Found: C, 62.75 ; H, 4.57; N, 7.16 . ν_{max} (cm^{-1}) 3358, 1642 ; δ (^{1}H, 300 MHz) (DMSO-d$_6$) 8.75 (1H, s, NH), 7.18 (2H, s, aromatics), 7.00 (1H, d, J = 3.10 Hz, H-3), 6.40 (1H, d, J = 3.10 Hz, H-4), 4.33 (2H; s, CH$_2$N), 3.76 (2H, s, CH$_2$S); δ (^{13}C) 157.64 (C=O), 153.70 (C-2), 147.21 (C-5), 138.16(Ci), 127.30, 114.31 (C-3), 109.80 (C-

4), 41.74 (CH_2NH), 27.41 (CH_2S); FAB, m/z (%) 765 (M^++1, 8).

5,5‴:5′,5″-Bis[oxybis(ethyloxycarbonyl)]-2,2′:2″,2‴-bis(thiodimethylenedifurylo)phane(5a).- Yield: 0.082 g (30%) yellow prisms; mp 136-138 °C (from EtOH/ether, 1:1). Anal. Calcd for $C_{32}H_{32}O_{14}S_2$: C, 54.54; H, 4.58. Found: C, 54.30 ; H, 4.35. ν_{max} (cm^{-1}) 1732 ; δ (^{1}H, 300 MHz) ($CDCl_3$) 7.11 (1H, d, J = 3.00 Hz, H-3), 6.34 (1H, d, J = 3.00 Hz, H-4), 4.45 (2H, br s, CH_2OCO), 3.83 (2H, br s, CH_2OCH_2), 3.75 (2H, s, CH_2S); δ (^{13}C) 158.26 (C=O), 156.40 (C-2), 143.59 (C-5), 119.52 (C-3), 110.04 (C-4), 68.63(CH_2OCO), 63.09(CH_2OCH_2), 27.88 (CH_2S); FAB, m/z (%) 705 (M^++1, 15).

5,5‴:5′,5″-Bis[*o* -phenylenebis(oxycarbonyl)]-2,2′:2″,2‴-bis(thiodimethylenedifurylo)phane (5b).- Yield: 0.11 g (39%) yellow prisms; mp 124-126 °C (from EtOH). Anal. Calcd for $C_{36}H_{24}O_{12}S_2$: C, 60.67; H, 3.39. Found: C, 60.55; H, 3.12. ν_{max} (cm^{-1}) 1755 ; δ (^{1}H, 300 MHz) ($CDCl_3$) 7.33 (2H, m, aromatics), 7.21 (1H, d, J = 3.56 Hz, H-3), 6.22 (1H, d, J = 3.56 Hz, H-4), 3.77 (2H, s, CH_2S); δ (^{13}C) 158.14 (C=O), 156.24 (C-2), 142.31 (C-5), 142.11 (q), 126.63, 123.32, 121.68 (C-3), 110.36 (C-4), 28.11 (CH_2S); FAB, m/z (%) 713 (M^++1, 5).

5,5′-Bis(*m*-aminoxylyleneaminocarbonyl)-2,2′-(thiodimethylenedifurane), (4).- To a well stirred solution of pyridine (0.12 g, 1.5 mmol) in dry toluene (10 ml) solutions of 1 (0.25 g, 0.78 mmol) in dry toluene (25 ml) and *m*-xylylenediamine (0.11 g, 0.78 mmol) in dry $CHCl_3$ (25 ml) were simultaneously added dropwise. The resultant solution was stirred at reflux temperature for 3 h. After cooling, the separated solid was collected by filtration and recrystallized to give 4. Yield: 0.19 g (48%) colorless prisms; mp 262-263 °C (from toluene). Anal. Calcd for $C_{28}H_{30}N_4O_4S$: C, 64.85; H, 5.83; N, 10.80. Found; C, 64.58; H, 5.55; N, 10.59. ν_{max} (cm^{-1}) 3256, 3144, 1647 ; δ (^{1}H, 300 MHz) (DMSO-d_6) 8.27 (1H, t, J = 6.04 Hz, CONH), 6.75 (4H, m, aromatics), 6.47 (1H, d, J = 3.15 Hz, H-3), 5.90 (1H, d, J = 3.15 Hz, H-4), 4.03 (2H, d, J = 6.04 Hz, CH_2NHCO), 3.45 (2H, s, CH_2NH_2), 2.50 (2H, br s, NH_2); δ (^{13}C) 157.64 (C=O), 153.68 (C-2), 147.24 (C-5), 144.10 (q), 139.89 (q), 128.07, 125.99, 125.13, 124.93, 114.55 (C-3), 110.14 (C-4), 45.14 (CH_2NH_2), 41.22 (CH_2NH), 28.03 (CH_2S).

ACKNOWLEDGEMENT

The authors are indebted to Dirección General de Investigación Científica y Técnica for financial support (project number PB89-0436).

REFERENCES

1. For a review see, G.R. Newkome, J.D. Sauer, J.M. Roper, and D.C. Hager, *Chem. Rev.*, 1977, **77**, 513.
2. J.M. Timko, S.S. Moore, D.M. Walba, P.C. Hiberty, and D.J. Cram, *J. Am. Chem. Soc.*, 1977, **99**, 4207.
3. F. de Jong, D.N. Reinhoudt, and R. Huis, *Tetrahedron Lett.*, 1977, 3985.

4. J.S. Bradshaw, S.L. Baxter, D.C. Scott, R.M. Izatt, and J.J. Christensen, *Tetrahedron Lett.*, 1979, 3383.
5. J.S. Bradshaw, S.L. Baxter, J.D. Lamb, R.M. Izatt, and J.J. Christensen, *J. Am. Chem. Soc.*, 1981, **103**, 1821.
6. J.S. Bradshaw, S.T. Jolley, and R.M. Izatt, *J. Org. Chem.*, 1982, **47**, 1229.
7. J.A. Bryant, R.C. Helgeson, C.B. Knobler, M.P. de Gtandpre, and D.J. Cram, *J. Org. Chem.*, 1990, **55**, 4622.
8. A.L. Mndzhoyan, G.T. Tatevosyan, S.G. Agbalayan, and N.M. Divanyan, *Doklady Akad. Nauk. Armyan S.S.R.*, 1957, **25**, 207 (Chem. Abstr., 1958, **52**, 8116e).
9. A.L. Mndzhoyan, V.G. Afrikyan, G.T. Tatevosyan, S.G. Agbalayan, M.T. Grigoryan, N.M. Divanyan, V. E. Badalayan, and E.A. Markaryan, *Doklady Akad. Nauk. Armyan S.S.R.*, 1958, **27**, 305 (Chem. Abstr., 1960, **63**, 481e).

Received, 1st October, 1993