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A NEW METHOD FOR THE SYNTHESIS OF DIAZACORONANDS *VIA* DOUBLE-AMIDATION REACTION[1]

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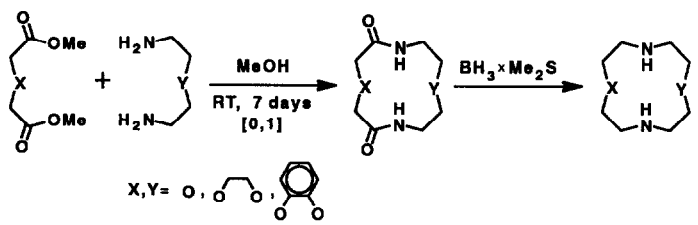
Abstract- *α,ω-Diamino aliphatic ethers react under ambient conditions with dimethyl α,ω-dicarboxylates, in methanol as a solvent, to give the cyclic diamides in good yields Their subsequent reduction with a borhoydride-dimethyl sulphide complex affords the respective diazacoronands*

There is continuing interest in the preparation of diazacoronands which have important uses as macrocyclic molecular receptors[2] as well as being valuable intermediates for the synthesis of cryptands and related compounds [3] The methods for the formation of diazacoronands have been extensively reviewed [4,5] Recently, Morphy *et al* [6] have reported that, consistent with the earlier findings of Tabushi *et al* ,[7,8] no high dilution technique was required for the reaction of dimethyl malonates with α,ω-diamines to form the cyclic diamides This fact prompted us to apply a similar approach to the synthesis of diazacoronands, and very recently we presented[1] a preliminary information on this new and general method for the synthesis of diazacoronands We now report the extention of these studies

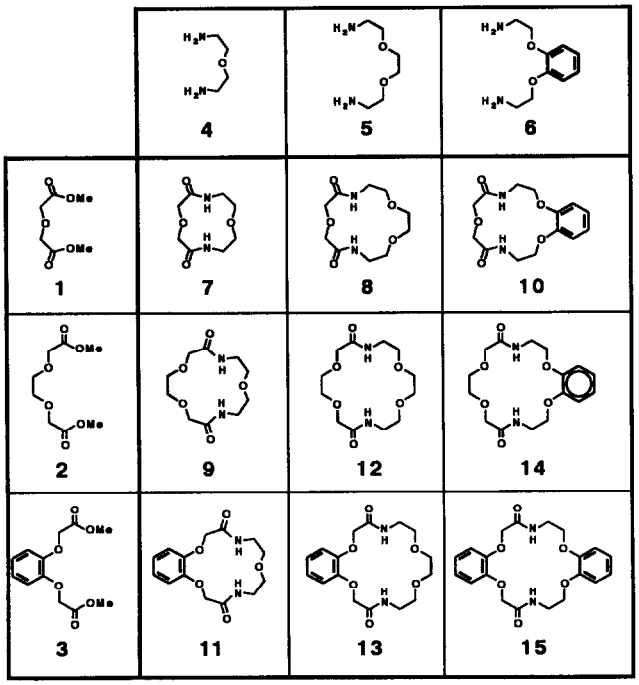
The general equation of examined reactions is presented in Scheme 1



Scheme 1

The starting materials for the preparation of target macrocyclic diamides are commercially available or procurable with minimal expenditure of work The established optimal reaction conditions are as follows solvent - methanol, temperature - ambient, time - seven days, concentration - 0 1 M The typical reaction has been performed as a bath process This implies that the values of effective molarity (EM) of substrates reacting under these conditions are high enough to afford the desired product in a reasonable yield

Diamides leading to the best known diazacoronands were selected, as the targets of the present synthetic investigations Specification of the reactions of diesters **1**, **2** and **3** with diamines **4**, **5** and **6**, is presented in Scheme 2 The yields of all products are summarized in Table 1



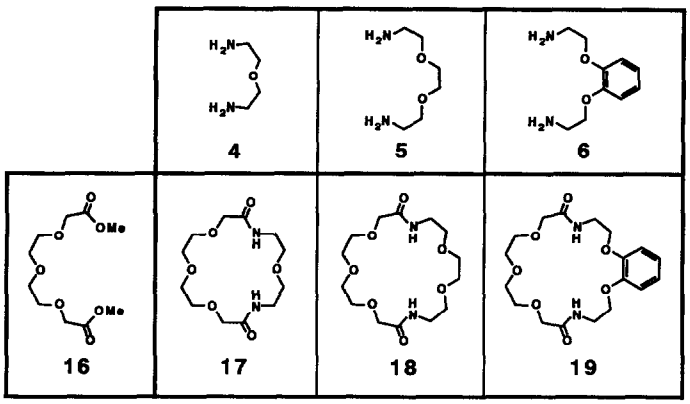
Scheme 2

Table 1

Comp	Yield	4		5		6	
1		**7**	**43%**	**8**	50%	**10**	66%
2		**9**	70%	**12**	68%	**14**	72%
3		**11**	80%	**13**	73%	**15**	85%

All products were crystalline, and except for compound **7** all yields were greater than 50% [9] It seems that the reaction yield is slightly higher when at least one of substrates is a derivative of catechol The phenyl ring increases the rigidity of the molecule and at the same time improves preorganization of the whole system Moreover, the products with the phenyl subunit partly precipitated from the reaction mixture, after a few attempts we managed to obtain the crystals of compound **10** suitable for X-Ray analysis [10]

The yield of reactions seems to be sufficiently high for most practical purposes, it appears to be slightly dependent on the size of the macrocycle In order to prove this relationship we performed a series of reactions of ester **16** with diamines **4**, **5** and **6**, leading to products with 18- and 21-membered rings These reactions are specified in Scheme 3 The yields of products are listed in Table 2



Scheme 3

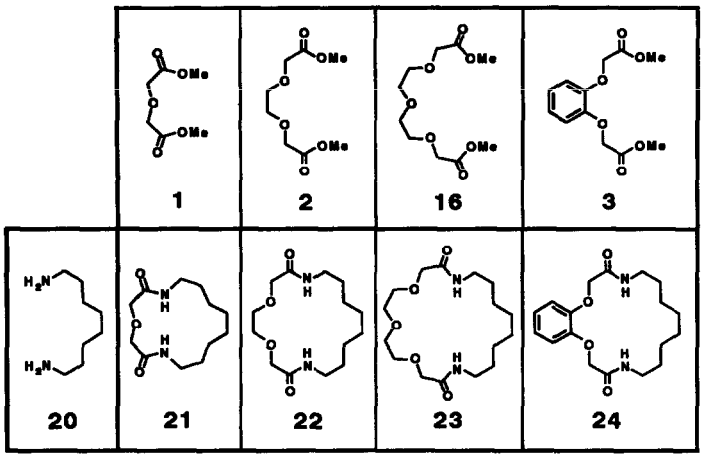
Table 2

Comp	Yield	4		5		6	
16		**17**	68%	**18**	50%	**19**	44%

These results indicate that indeed the yields of the performed reactions depend on the ring size of the products, the preference to form 18-membered rings is evidenced by the present and the previous series of reaction (Tables 1 and 2) The long aliphatic chain of substrate **16** forming a 21-membered ring seems to be more resistant to preorganization, owing to its higher flexibility Here again, the catechol derivative **19** partly crystallized from the reaction mixture, and well-shaped crystals for X-Ray analysis were obtained X-Ray investigations will be published [11]

Preorganization of substrate molecules, which we believe to be crucial for the formation of the presented macrocycles, is probably achieved *via* hydrogen bonds formed between the molecules of methanol and the ethereal oxygen atoms of substrate In this case a drop in the number of ethereal binding sites in the substrates would probably decrease the yields of macrocyclic diamides

In order to confirm this assumption, the reactions of diesters **1**, **2**, **3** and **16** with 1,8-diaminooctane (**20**) were performed Specification of these reactions as well as of their yields are shown in Scheme 4 and Table 3

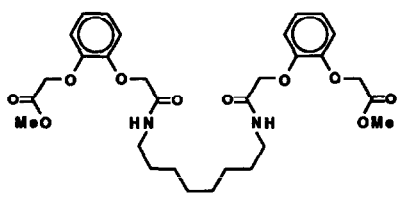


Scheme 4

Table 3

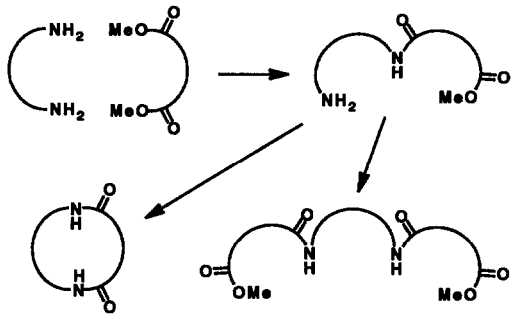
Comp	Yield	1		2		3		16	
20		21	18%	22	28%	23	15%	24	38%

The yields of diamides **21**, **22**, **23** and **24** are indeed substantially lower, in comparison to their fully ethereal counterparts **8**, **12**, **18** and **13**, respectively Moreover, the products are highly contaminated with oligomeric substances ^{1}H NMR analysis showed that the major by-products of these reactions consist of two subunits of diester and of one subunit of diamine in the form of a linear diamide-diester In the reaction between **20** and **3**, leading to **24**, the presence of the contaminating product **25** was confirmed by ^{1}H NMR investigations [12]



25

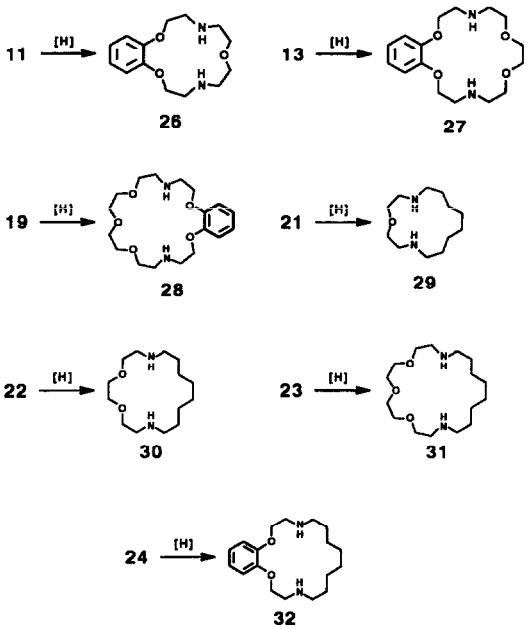
This seems to be consistent with the assumed course of the reaction, according to which the diester and diamine form a linear amido compound which then undergoes the cyclization or oligomerization (Scheme 5) Both latter processes are competitive and the EM values indicate which one is preferred under the reaction conditions used



Scheme 5

In the case of fully ethereal compounds, the hydrogen bonds between the substrates and solvent force the self-assembly of the linear dimers and cause theirs cyclization A compound without oxygen binding sites is poorly preorganized by methanol

Macrocyclic diamides can be readily transformed into macrocyclic diamines[13] which are of great importance in the chemistry of molecular receptors Since many of the above-described diamides and their respective diamines have not yet been reported, we carried out several reductions of the obtained diamides using the $BH_3 \times Me_2S$ complex as reducing agent in boiling THF These reductions are presented in Scheme 6



Scheme 6

The present work deals with the syntheses of diazacoronand derivatives *via* the diamidation reaction The obtained compounds differ in molecular size and in the number of oxygen atoms incorporated to macrocyclic ring The reactions proceed efficiently under ambient conditions The course of the reactions is assumed to depend on the occurrence of self-assembly phenomena which are probably stimulated by a properly selected solvent

The performed experiments allow, for the following conclusions

1 Diamidation reactions can be utilized for preparation of simple diazacoronands of various molecular sizes
2 These reactions are effective and proceed under ambient conditions
4 No additional external cyclization factors (as high-dillution approach or template effect) is required to obtain satisfactory results
5 The self-assembly approach to investigations of the macrocyclization reactions may provide satisfactory explanations, and leads to constructive conclusions concerning of the course and yield of examined processes

EXPERIMENTAL

General

^{1}H NMR spectra were recorded at 500 MHz with a BRUKER AM 500 spectrometer in $CDCl_3$ using TMS as an internal standard ^{13}C NMR spectra were measured at 125 MHz with a BRUKER AM 500 spectrometer High-resolution mass spectrometry (HRMS) experiments were performed on an AMD-200 spectrometer Melting points are uncorrected Elemental analyses were performed on a micro scale

All high-pressure reactions were carried out in a piston-cylinder type apparatus with initial working volume of about 90 mL Construction details of the apparatus have been reported previously [14]

General procedure for synthesis of cyclic diamides under atmospheric pressure

An equimolar 0 1M methanolic solution (5 mmol) of α,ω-diamine and α,ω-diester was left at room temperature for 7 days Then the solvent was evaporated and the residue was passed through a short alumina column to remove polymeric products using $CHCl_3$ as an eluent The further purification was performed by chromatography on silicagel using 1-5% mixtures of methanol in $CHCl_3$ Products were recrystallized from acetone

1,7-Diaza-4,10-dioxacyclododeca-2,6-dione (**7**)

Anal calcd for $C_8H_{14}N_2O_4$ C, 47 5, H, 6 9, N, 13 8 Found C, 47 3, H, 6 9, N, 13 5

^{1}H NMR δ 3 49 (dt, 4H), 3 65 (t, 4H), 4 12(s, 4H), 7 27 (bm, 2H)

^{13}C NMR δ 38 7, 68 6, 74 0, 170 0

m p 179-180°C

1,7-Diaza-4,10,13-trioxacyclopentadeca-2,6-dione (**8**)

Anal calcd for $C_{10}H_{18}N_2O_5$ C, 48,7, H, 7 3, N, 11 4 Found C, 48 7, H, 7 4, N, 11 2

^{1}H NMR δ 3 53(m, 4H), 3 55(s, 4H), 3 59(m, 4H), 4 05(s,4H), 7 09(m, 2H)

^{13}C NMR δ 38 2, 68 5, 69 9, 70 0, 167 6

m p 146-147°C

1,10-Diaza-4,7,13-trioxacyclopentadeca-2,9-dione (**9**)

Anal calcd for $C_{10}H_{18}N_2O_5$ C, 48 7, H, 7 3, N, 11 4 Found C, 48 9, H, 7 6, N, 11 4

^{1}H NMR δ 3 53(m,4H), 3 60(t,4H), 3 72(s,4H), 4 02(s,4H), 7 17(m,2H)

^{13}C NMR δ 38 1, 68 9, 70 1, 70 2, 169 0

m p 174°C

11,12-Benzo-1,7-diaza-4,10,13-trioxacyclopentadeca-2,6-dione (**10**)

Anal calcd for $C_{14}H_{18}N_2O_5$ C, 57 1, H, 6 1, N, 9 5 Found C, 57 0, H, 5 9, N, 9 5

^{1}H NMR δ 3 79(m, 4H), 4 08(s, 4H), 4 14(m, 4H), 6 93(m, 4H), 7 26(bm, 2H)

^{13}C NMR δ 37 2, 66 6, 70 1, 112 8, 121 6, 147 6, 167 7

m p 194-195°C

5,6-Benzo-1,10-diaza-4,7,13-trioxacyclopentadeca-2,9-dione (**11**)

Anal calcd for $C_{14}H_{18}N_2O_5$ C, 57 1, H, 6 1, N, 9 5 Found C, 57 3, H, 6 4, N, 9 3

^{1}H NMR δ 3 64(m, 4H), 3 67(m, 4H), 4 49(s, 4H), 6 85-7 03(m, 4H), 7 37(bm, 2H)

^{13}C NMR δ 38 3, 66 9, 70 0, 112 4, 122 1, 146 1, 167 1

m p 221-222°C

1,10-Diaza-4,7,13,16-tetraoxacyclooctadeca-2,9-dione (**12**)

Anal calcd for $C_{12}H_{22}N_2O_6$ C, 49 6, H, 7 6, N, 9 6 Found C, 49 4, H, 7 9, N, 9 6

^{1}H NMR δ 3 55(m, 4H), 3 56(m, 4H), 3 61(s, 4H), 3 69(s, 4H), 4 02(s, 4H), 7 15(bm, 2H)

^{13}C NMR δ 38 4, 69 6, 70 2, 70 3, 70 5, 169 0

m p 111-112°C

5,6-Benzo-1,10-diaza-4,7,13,16-tetraoxacyclooctadeca-2,9-dione (**13**)

Anal calcd for $C_{16}H_{22}N_2O_6$ C, 56 8, H, 6 5, N, 8 3 Found C, 57 0, H, 6 7, N, 8 3

^{1}H NMR δ 3 57(m, 8H), 3 59(s, 4H), 4 59(s, 4H), 6 89-7 02(m, 4H), 7 16(bm, 2H)

^{13}C NMR δ 38 7, 67 6, 69 7, 70 2, 113 2, 122 4, 146 7, 167 9

m p 174°C

14,15-Benzo-1,10-diaza-4,7,13,16-tetraoxacyclooctadeca-2,9-dione (**14**)

Anal calcd for $C_{16}H_{22}N_2O_6$ C, 56 8, H, 6 5, N, 8 3 Found C, 56 8, H, 6 6, N, 8 5

^{1}H NMR δ 3 70(s, 4H), 3 81(m, 4H), 4 02(s, 4H), 4 08(m, 4H), 6 89(m, 4H), 7 23(bm, 2H)

^{13}C NMR δ 38 0, 67 2, 70 3, 70 4, 112 1, 121 3, 147 8, 169 1

m p 196°C

1,10-Diaza-5,6,14,15-dibenzo-4,7,13,16-tetraoxacyclooctadeca-2,9-dione (**15**)

Anal calcd for $C_{20}H_{22}N_2O_6$ C, 62 2; H, 5 7, N, 7 3 Found C, 62 0, H, 5 9, N, 7 3

^{1}H NMR δ 3 89(m, 8H), 4 10(t, 4H), 4 57(s, 4H), 6.82-7 01(m, 8H), 7 25(bm, 2H)

^{13}C NMR δ. 38 1, 66 8, 67 1, 111 3, 112 7, 121 0, 122 0, 146 1, 147 2, 168 6

m p 280-281°C

1,13-Diaza-4,7,10,16-tetraoxacyclooctadeca-2,12-dione (**17**)

Anal calcd for $C_{12}H_{22}N_2O_6$ C, 49 6, H, 7 6, N, 9 7 Found C, 49 7, H, 7 8, N, 9 5

^{1}H NMR δ 3 54(m, 4H), 3 55(s, 4H), 3 69(dt, 8H), 4 01(s, 4H), 7 17(m, 2H)

^{13}C NMR δ 38 7, 69 9, 70 0, 70 2, 70 4, 169 3

m p. 117-118°C

1,13-Diaza-4,7,10,16,19-pentaoxacycloheneicosa-2,12-dione (**18**)

Anal calcd for $C_{14}H_{28}N_2O_7x0\ 5H_2O$ C, 49 0, H, 7 9, N, 8 2 Found C, 48 7, H, 8 1, N, 8 0

^{1}H NMR δ 3 52(m, 4H), 3 60(t, 4H), 3 61(s, 4H), 3 69(m, 8H), 4 01(s, 4H), 7 51(bm, 2H)

^{13}C NMR δ 38 7, 69 7, 70 0, 70 1, 70 5, 169 8

m p 69-70°C

17,18-Benzo-1,13-diaza-4,7,10,16,19-pentaoxacycloheneicosa-2,12-dione (**19**)

Anal calcd for $C_{18}H_{26}N_2O_7x0\ 5\ H_2O$ C, 55 2, H, 7 0, N, 7 2 Found C, 55 8, H, 7 1, N, 7 1

^{1}H NMR δ 3 70(s, 8H), 3 73(m, 4H), 4 02(s, 4H), 4 10(t, 4H), 6 92(m, 4H), 7 92(bm, 2H)

^{13}C NMR δ 38 6, 68 8, 70 3, 70 6, 70 9, 114 7, 122 0, 148 7, 169 9

m p 121-122°C

1,7-Diaza-4-oxacyclopentadeca-2,6-dione (**21**)

Anal calcd for $C_{12}H_{22}N_2O_3$ C, 59 5, H, 9 2, N, 11 6 Found C, 59 5, H, 9 4, N, 11 3

^{1}H NMR δ 1 40(m, 8H), 1 56(m, 4H), 3 37(m, 4H), 4 07(s, 4H), 6 46(bm, 2H)

^{13}C NMR δ 23 5, 25 7, 27 3, 38 2, 70 8, 168 4

m p 168°C

1,10-Diaza-4,7-dioxacyclooctadeca-2,9-dione (**22**)

Anal calcd for $C_{14}H_{26}N_2O_4$ C, 58 7, H, 9 2, N, 9 8 Found C, 59 1, H, 9 4, N, 9 8

^{1}H NMR δ 1 31(m, 8H), 1 52(m, 4H), 3 29(m, 4H), 3 71(s, 4H), 4 01(s, 4H), 6 74(bm, 2H)

^{13}C NMR δ 24 5, 26 8, 28 3, 38 2, 70 1, 70 4, 168 9

m p 122-123°C

1,13-Diaza-4,7,10-trioxacycloheneicosa-2,12-dione (**23**)

Anal calcd for $C_{16}H_{30}N_2O_5$ C, 58 2, H, 9 2, N, 8 5 Found C, 58 0, H, 9 1, N, 8 2

^{1}H NMR δ. 1 37(m, 8H), 1 55(m, 4H), 3 34(m, 4H), 3 70(s, 4H), 3 99(s, 4H), 6 86(bm, 2H)

^{13}C NMR δ 25 6, 28 0, 28 5, 38 6, 70 3, 70 4, 70 8, 169 4

m p 75-77°C

5,6-Benzo-1,10-diaza-4,7-dioxacyclooctadeca-2,9-dione (**24**)

Anal calcd for $C_{18}H_{26}N_2O_4x0\,5\,CH_3OH$ C, 63 4, H, 8 1, N, 7 9 Found C, 63 6, H, 7 9, N, 8 1

^{1}H NMR δ 1 38(m, 8H), 1 55(m, 4H), 3 43(m, 4H), 4 56(s, 4H), 6 66(bm, 2H), 6 93-7 05(m, 4H)

^{13}C NMR δ 24 1, 26 4, 28 1, 38 3, 68 3, 114 4, 122 9, 147 0, 167 8

m p 181-182°C

General procedure for reduction of macrocyclic diamides

A methanolic (15mL) solution of 1 equiv of diamide (0 1 mmol) and 2 2 equiv of $BH_3{\times}Me_2S$ was stirred at reflux for 2 h After evaporation, 10 mL of conc HCl was added and the reaction mixture was furthermore refluxed for 1h The 20% NaOH aq was added to pH 14, and the mixture was extracted with $CHCl_3$ (3×20 mL) The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated The crude product was then distilled on a bubble-to-bubble apparatus and, if crystalline, recrystallized from ethanol

2,3-Benzo-7,13-diaza-1,4,10-trioxacyclopentadecan (**26**)

HRMS m/z (M^+, $C_{14}H_{22}N_2O_3$) calcd 266 1630, found 266 1629

^{1}H NMR δ 2 72(s, 2H), 2 86(t, J=5 Hz, 4H), 3 02(t, J=5 Hz, 4H), 3 63(t, J=5 Hz, 4H), 4 11(t, J=5 Hz, 4H), 6 88(s, 4H)

^{13}C NMR δ 48 5, 49 32, 67 76, 69 03, 112 55, 120 84, 148 49

m p 97-100°C

2,3-Benzo-7,16-diaza-1,10,13-tetraoxacyclooctadecan (**27**)

HRMS m/z (M^+, $C_{16}H_{26}N_2O_4$) calcd 310 1893, found 310 1894

^{1}H NMR δ 2 61(s, 2H), 2 87(t, J=4 8 Hz, 4H), 3 06(t, J=4 6 Hz, 4H), 3 61(s, 4H), 3 67(t, J=4 8 Hz, 4H), 4 13(t, J=4 6 Hz, 4H), 6 88(s, 4H)

^{13}C NMR δ 48 62, 49 17, 67 70, 70 24, 70 31, 112 01, 120 7, 148 6

m p 86-92°C

2,3-Benzo-7,19-diaza-1,5,10,13,16-pentaoxacycloheneicosan (**28**)

HRMS m/z (M^+, $C_{18}H_{30}N_2O_5$) calcd 354 2154, found 354 2153

^{1}H NMR δ 2 96(t, J=5 Hz, 4H), 3 11(t, J=5 Hz, 4H), 3 65(s, 8H), 3 72(t, J=4 7 Hz, 4H), 4 18(t, J=4 7 Hz, 4H), 4 36(s, 2H), 6 93(s, 4H)

^{13}C NMR δ 48 6, 49 0, 68 4, 69 6, 70 2, 70 5, 115 1, 122 0, 148 9

m p 55-58°C

1,7-Diaza-4-oxacyclopentadecan (**29**)

HRMS m/z (M^+, $C_{12}H_{26}N_2O$) calcd 214 2045, found 214 2026

^{1}H NMR δ 1 37(m, 8H), 1 54(m, 4H), 2 05(s, 2H), 2 67(t, J=5 Hz, 4H), 2 79(t, J=4 8 Hz, 4H), 3 59(t, J=5 Hz, 4H)

^{13}C NMR δ 24 7, 26 8, 27 9, 47 9, 49 0, 70 2

Oil

1,10-diaza-4,7-dioxacyclooctadecan (**30**)

HRMS m/z (M^+, $C_{14}H_{30}N_2O_2$) calcd 258 2229, found 258 2229

^{1}H NMR δ 1 38(m, 8H), 1 53(m, 4H), 2 05(bs, 2H), 2 68(t, J=6 Hz, 4H), 2 80(t, J=4 7 Hz, 4H), 3 61(m, 8H)

^{13}C NMR δ 24 7, 27 3, 28 3, 48 7, 49 1, 70 1, 70 3

Oil

1,13-Diaza-4,7,10-trioxacycloheneicosan (**31**)

HRMS m/z (M^+, $C_{16}H_{34}N_2O_3$) calcd 302 2569, found 302 2562

^{1}H NMR δ 1 36(s, 8H), 1 45(m, 4H), 2 48(bs, 2H), 2 65(t, J=6 Hz, 4H), 2 79(t, J=4 9 Hz, 4H), 3 65(m, 12H)

^{13}C NMR δ 25 8, 28 4, 29 1, 49 0, 49 0, 76 4, 77 0, 77 6

Oil

5,6-Benzo-1,10-diaza-4,7-dioxacyclooctadecan (**32**)

HRMS m/z (M^+, $C_{18}H_{30}N_2O_2$) calcd 306 2307, found 306 2308

^{1}H NMR δ 1 40(s, 8H), 1 56(m, 4H), 2 18(bs, 2H), 2 75(t, J=4 8 Hz, 4H), 3 03(t, J=5 Hz, 4H), 4 14(t, J=4 8 Hz, 4H), 6 90(s, 4H)

^{13}C NMR δ 24 7, 27 0, 28 3, 48 5, 48 6, 68 3, 112 8, 121 0, 148 8

m p 35-37°C, semicrystal

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REFERENCES AND NOTES

1 Jurczak, J , Kasprzyk, S , Sałański, P , Stankiewicz, T *J Chem Soc , Chem Commun* **1991**, 956

2 Sutherland, I O *Chem Soc Rev* **1986**, *15*, 63

3 Jurczak, J , Pietraszkiewicz, M in *High Pressure Chemical Synthesis*, Jurczak, J , Baranowski, B (Eds), Elsevier, Amsterdam, 1989, pp 294-321

4 Gokel, G W , Korzeniowski, S H *Macrocyclic Polyether Synthesis*, Springer Verlag, Berlin-Heidelberg-New York, 1982

5 Krakowiak, K E , Bradshaw, J S , Zamecka-Krakowiak, D J *Chem Rev* **1989**, *89*, 929

6 Morphy, R J , Parker, D , Alexander, R , Bains, A , Carne, A F , Eaton, M A , Harrison, A , Millican, A , Phipps, A , Rhind, S K , Tetmas, R , Weatherby, D *J Chem Soc , Chem Commun* **1988**, 156

7 Tabushi, I , Okino, H , Kuroda, Y *Tetrahedron Lett* **1976**, 4339

8 Tabushi, I , Taniguchi, Y , Kato, H *Tetrahedron Lett* **1977**, 1049

9 Very recently, we found that for reactions of **1** with **4** and of **1** with **5**, apart from cyclic diamides, the cyclic tetra-amides are formed in yields 30% and 8%, respectively Surprisingly, no cyclic tetra-amide was found for the reaction of **2** with **4**

10 Krajewski, J W , Gluziński, P , Sałański, P , Kasprzyk, S , Stankiewicz, T , Jurczak, J , Kemme, A , Mishnyov, A *J Cryst Sepctr Res* **1992**, *22*, 9

11 Urbańczyk-Lipkowska, Z , Kasprzyk, S , Stankiewicz, T , Jurczak, J , Suwińska, K *J Cryst Spectr Res* in press

12 Similar products were observed in ^{1}H NMR spectra for reactions of **1** with **4** and of **1** with **5**

13 Dietrich, B , Lehn, J M , Sauvage, J P , Blanzat, J *Tetrahedron* **1973**, *29*, 1629

14 Jurczak, J , Chmielewski, M , Filipek, S *Synthesis* **1979**, 41