Efficient Synthesis of a Range of Benzo-Substituted Macrocyclic Diamides

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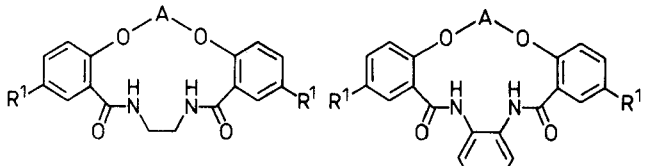
Sixteen new 14-17-macrocyclic dibenzo and tribenzodioxadiamides and trioxadiamides (macrooxacyclams, e.g., 5,6,7,8,9,10,16,17-octahydrodibenzo[*e*,*m*][1,4,8,11]dioxadiazatetradecine-5,10-dione) **13–28** have been prepared. Moderate to good yields (40–90%) of **13–28** were achieved in the macrocyclization step by reacting the dipotassium salts of 1,2-bis(2-hydroxybenzoylamino)ethanes **6**, **7** and 1,2-bis(2-hydroxybenzoylamino)benzenes **8**, **9** with the appropriate dihaloalkane or ditosylate in dimethylformamide. Alkylation of **13** and **25** with an appropriate halo compound in tetrahydrofuran and sodium hydride yielded the corresponding *N,N'*-dialkylmacrooxacyclams **29–33**. The stereochemical purity of the latter was proved by ^{1}H NMR and ^{13}C NMR.

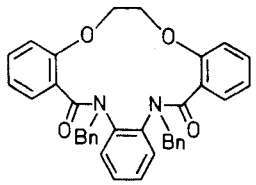
The design and synthesis of new functionalized macrocycles for specific application is a subject of continuous recent interest. Among these macrocycles, derivatives of crown ethers and azacrown ethers are of great interest due to their application in catalysis,[1,2] chromatographic separation of metal cations,[3] molecular recognition[4] and biological applications.[5–7] Azacrown ethers and their precursors have recently been the subject of many reviews.[8–17]

A number of dibenzoazacrown ethers were prepared from salicylaldehyde derivatives and the appropriate diamino compound followed by reduction and were shown to possess wide applications in selective metal cation extraction.[18–27]



13-24

25-28



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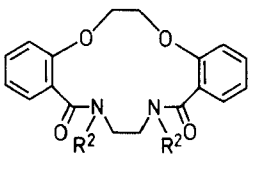


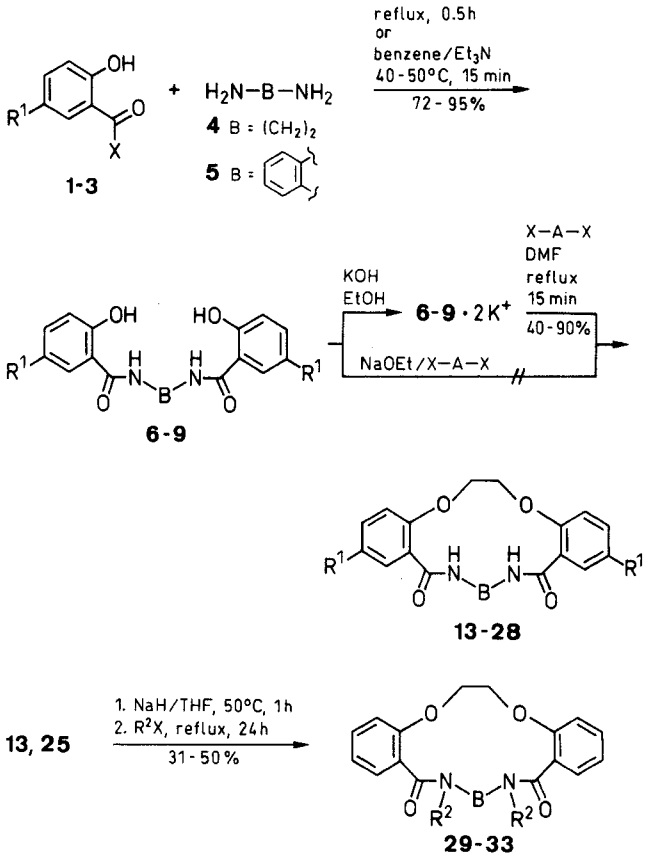
29 R^2 = Me 31 R^2 = Bu
30 R^2 = Et 32 R^2 = Bn

No.	A	R^1	No.	A	
13	$(CH_2)_2$	H	**21**	$(CH_2)_3$	Cl
14	$(CH_2)_3$	H	**22**	$(CH_2)_4$	Cl
15	$(CH_2)_4$	H	**23**	$CH_2C(=CH_2)CH_2$	Cl
16	$(CH_2)_5$	H	**24**	$(CH_2)_2O(CH_2)_2$	Cl
17	$CH_2C(=CH_2)CH_2$	H	**25**	$(CH_2)_2$	H
18		H	**26**	$(CH_2)_3$	H
19	$(CH_2)_2O(CH_2)_2$	H	**27**	$(CH_2)_2$	Cl
20	$(CH_2)_2$	Cl	**28**	$(CH_2)_3$	Cl

Figure 1. New 14-17-macrocyclic oxacyclams

Recently, we reported the useful application of 14 and 15-cyclic dioxadiamides in the lithium ion selective electrode.[28,29] We have now studied synthetic routes towards modified derivatives of these cyclic oxadiamides and possibly larger or smaller rings. The target molecules were intended to include two and possibly three benzo-condensed systems with the macrocycles to study their effect on their selective behavior toward lithium. Also, these products are potential precursors which yield by reduction many useful known[30] as well as new azacrown ethers.

14–17 Macrocyclic oxacyclams **13–33** (Figure 1) were prepared as shown in Schemes 1 and 2. In Scheme 1, 1,2-Bis(2-hydroxybenzoylamino)ethane **(6)**, 1,2-bis(2-hydroxybenzoylamino)benzene **(8)** and their dichloro derivatives **7**, **9** were used as starting materials for the macrocyclization step. Compounds **6–9** were readily

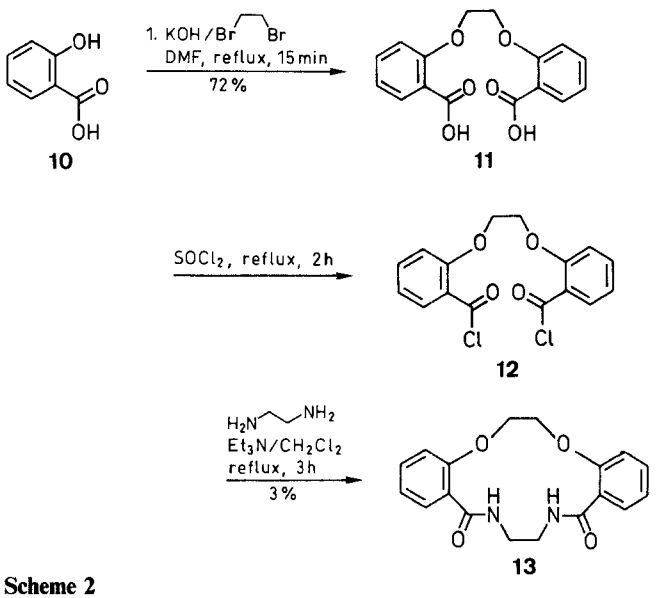


No.	X	R^1	No.	R^1	B
1	OMe	H	**6**	H	$(CH_2)_2$
2	Cl	H	**7**	Cl	$(CH_2)_2$
3	Cl	Cl	**8**	H	
			9	Cl	

Scheme 1

obtained by reacting the appropriate salicylic acid derivatives **1–3** with ethylenediamine or *o*-phenylenediamine. Attempts to cyclize compound **6** with ethylene bromide in ethanolic sodium ethoxide were unsuccessful. On the other hand, the dipotassium salts of **6–9** (readily obtained with ethanolic potassium hydroxide) were found to give moderate to good yields (40–90%) of the macrocycles **13–28** upon heating with the appropriate dihalo or ditosylate compounds in dimethylformamide (DMF). The structures proposed for these macrocycles are consistent with data obtained from ^{1}H NMR, ^{13}C NMR, MS and IR spectra and elemental analyses.

The second route investigated for the synthesis of these macrooxacyclams (Scheme 2) was found to give a very poor yield in the cyclization step. Thus, 1,2-bis(2-carboxyphenoxy)ethane (**11**) (obtained from potassium salicylate and ethylene bromide in DMF) was converted by the action of thionyl chloride into its diacid dichloride **12**. The latter was reacted with ethylenediamine in chloroform and triethylamine under the conditions of high dilution described by Dietrich et al.[31] to give only 3% of **13**.



10 **11** **12** **13**

Scheme 2

The exceptional good yield (40–90%) in the macrocyclization of the dipotassium salts of **6–9** in DMF can partly

Table 1. ^{1}H NMR Spectroscopic Data of Macrocyclic Oxacyclams **13–28**[a], δ

Compound[b]	NH	ArH's	CH_2N	CH_2O
13	8.00 (br s, 2H)	7.10–8.15 (m, 8H)	3.75 (m, 4H)	4.55 (s, 4H)
14	8.15 (br s, 2H)	6.85–8.15 (m, 8H)	3.70 (m, 4H)	4.35 (t, 4H)
15	8.15 (br s, 2H)	6.95–8.40 (m, 8H)	3.75 (m, 4H)	4.55 (m, 4H)
16	8.10 (br s, 2H)	6.90–8.25 (m, 8H)	3.75 (m, 4H)	4.20 (t, 4H)
17	8.15 (br s, 2H)	6.95–8.25 (m, 8H)	3.75 (m, 4H)	4.76 (s, 4H)
18	8.30 (br s, 2H)	6.95–7.80 (m, 12H)	3.30 (br s, 4H)	5.35 (s, 4H)
19	6.85–8.25 (m, 10 H)		3.72 (m, 4H)	4.26 (m, 4H)
20	8.40 (br s, 2H)	7.35–7.85 (m, 6H)	3.50 (br s, 4H)	4.55 (s, 4H)
21	8.50 (br s, 2H)	7.20–7.70 (m, 6H)	3.50 (m, 4H)	4.30 (t, 4H)
22	8.35 (br s, 2H)	7.20–7.80 (m, 6H)	3.55 (br s, 4H)	4.20 (br s, 4H)
23	8.00 (br s, 2H)	6.85–8.20 (m, 6H)	3.70 (m, 4H)	4.75 (s, 4H)
24	6.85–8.15 (m, 8 H)		3.70 (m, 4H)	4.24 (m, 4H)
25	9.43 (br s, 2H)	7.00–8.20 (m, 12H)	–	4.60 (s, 4H)
26	9.80 (br s, 2H)	7.00–8.40 (m, 12H)	–	4.40 (t, 4H)
27	9.30 (br s, 2H)	7.00–8.20 (m, 10H)	–	4.60 (s, 4H)
28	9.60 (br s, 2H)	6.90–8.30 (m, 10H)	–	4.40 (t, 4H)

[a] ^{1}H NMR spectra of **13–19** and **23–28** were measured in $CDCl_3$ and of **20–22** in DMSO-d_6.

[b] Special additional signals for each compound: compound **14**, 2.45 (quint, 2H); compound **15**, 2.10 (br s, 4H); compound **16**, 1.95 (q, 6H); compound **17**, 5.63 (s, 2H); compound **19**, 3.96 (m, 4H); compound **21**, 2.38 (quint, 2H); compound **22**, 1.98 (br s, 4H); compound **23**, 5.66 (s, 2H); compound **24**, 3.96 (m, 4H); compound **26**, 2.39 (quint, 2H); compound **28**, 2.4 (quint, 2H).

Table 2. ^{1}H NMR Spectroscopic Data of *N,N'*-Dialkylmacrooxacyclams **29–33** ($CDCl_3$) δ, J (Hz)

Compound[a]	**29**	**30**	**31**	**32**	**33**
ArH's	6.95–7.37 (m, 8H)	6.90–7.40 (m, 8H)	6.85–7.38 (m, 8H)	7.00–7.50 (m, 18H)	6.70–7.68 (m, 22H)
NCH_2CH_2N	3.00 (d, 2H, J = 10), 5.04 (d, 2H, J = 10)	3.15 (d, 2H, J = 10.8), 4.87 (d, 2H, J = 10.8)	3.15 (d, 2H, J = 10.3), 4.88 (d, 2H, J = 10.3)	2.81 (d, 2H, J = 10.5), 4.79 (d, 2H, J = 10.5)	–
OCH_2CH_2O	4.18 (d, 2H, J = 7), 4.44 (d, 2H, J = 7)	4.17 (d, 2H, J = 7.2), 4.43 (d, 2H, J = 7.2)	4.10 (d, 2H, J = 7.32), 4.40 (d, 2H, J = 7.24)	4.20 (d, 2H, J = 7.3), 4.54 (d, 2H, J = 7.2)	4.36 (d, 2H, J = 7.2), 4.67 (d, 2H, J = 7.2)
NCH_2R	2.88, 2.89 (2s, 6H)	3.18 (dt, 2H), 3.46 (dt, 2H), ^2J = 15, ^3J = 7.5	3.12 (dt, 2H), 3.86 (dt, 2H), ^2J = 14.85, ^3J = 7.6	4.51 (d, 2H), 4.61 (d, 2H), ^2J = 15.8	4.75 (d, 2H), 4.90 (d, 2H), ^2J = 14.6

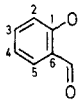
[a] Special additional signals for each compound: compound **30**, 0.98 (t, 3H, ^3J = 7.5, $C\underline{H}_3CH_2N$); compound **31**, 1.20–1.50 (m, 4H, $NCH_2C\underline{H}_2CH_2CH_3$), 1.04 (sextet, 4H, $NCH_2CH_2C\underline{H}_2CH_3$), 0.7 (q, 6H, $NCH_2CH_2CH_2C\underline{H}_3$).

Table 3. ^{13}C NMR Spectroscopic Data of Compounds **13**, **14**, **17–21**, **23**, **25**, δ

Compound[a]		13	14	17	18	19	20	21	23	25
NCH_2		41.10	42.45	40.58	40.04	40.05	39.93	40.18	41.00	–
OCH_2		70.30	70.14	70.18	70.50	69.48	69.02	71.50	71.90	68.39
	C1	157.89	159.05	157.90	157.50	158.25	156.29	157.00	156.00	156.39
	C2	116.40	113.94	114.43	114.50	114.58	118.60	117.00	115.90	115.10
	C3	134.76	134.90	134.55	132.20	134.51	133.34	133.50	133.90	135.22
	C4	124.98	123.44	123.95	122.20	122.67	127.12	127.00	129.60	127.53
	C5	134.29	134.46	124.06	130.50	132.76	131.33	131.50	134.00	135.02
	C6	125.78	123.54	124.15	125.40	123.66	127.99	126.50	125.90	125.68
C=O		167.48	167.92	167.46	166.50	166.75	165.73	166.00	166.60	165.93

[a] Special additional signals for each compound: compound **14**, 29.00 ($\underline{C}H_2CH_2O$); compound **17**, 122.60 ($\underline{C}H_2$=C), 141.90 (CH_2=$\underline{C}$); compound **18**, 136.20, 132.50, 131.50 (C1, C2, C3 of *o*-phenylene group respectively); compound **19**, 70.13 ($CH_2O\underline{C}H_2$); compound **21**, 30.0 ($\underline{C}H_2CH_2O$); compound **23**, 123.50 ($\underline{C}H_2$=C), 141.0 (CH_2=C); compound **25**, 131.21, 126.20, 124.78 (C1, C2, C3 of *o*-phenylene group respectively).

Table 4. ^{13}C NMR Spectroscopic Data of Compounds **29–33**, δ

Compound		29	30	31	32	33
R		H	Me	Pr	Ph	Ph
NCH_2CH_2N		44.00	39.40	39.83	39.54	–
NCH_2R		37.00	42.00	47.77	52.10	56.44
R		–	14.50	31.17 CH_2	138.06 C1	139.85 C1
				21.27 CH_2	129.00 *o*-C	129.61 *o*-C
				15.31 CH_3	130.00 *m*-C	130.19 *m*-C
					131.00 *p*-C	131.45 *p*-C
OCH_2CH_2O		68.50	68.40	68.31	68.44	68.18
	C1	156.00	155.70	155.69	156.0	156.09
	C2	115.00	114.60	114.50	114.63	114.48
	C3	133.00	132.10	132.18	138.00	134.57
	C4	124.00	123.80	123.87	124.30	124.59
	C5	131.00	129.83	130.36	132.00	133.14
	C6	130.00	129.80	129.58	130.00	128.96
C=O		172.60	172.00	172.02	172.44	171.87
	C1	–	–	–	–	138.45
	C2	–	–	–	–	131.89
	C3	–	–	–	–	134.47

be explained as a result of the restricted rotational freedom in the dianions **34** (caused by the high resonance stabilization and hydrogen bonding). As a result of the restricted rotation, there is a relatively small loss in entropy on cyclization, allowing ring closure to occur in high yield without a need for a preorganization of the starting materials.[32] Clearly, the diacid dichloride **12** has more degrees of rotational freedom than the dipotassium salts **34** (which means less conjugation, more single bond characters and no hydrogen bonding in case of **12**).

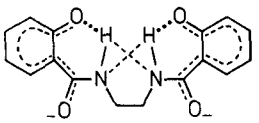


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Figure 2

It is worth mentioning that cyclization of potassium salts of **7**, **9** goes slower than that of **6**, **8**. This could be due to the decreased nucleophilicity of the dianion caused by the stabilizing effect of the chlorine substituents in the former.

Compounds **13** and **25** were readily alkylated to the corresponding *N,N'*-dialkyl derivatives **29–32** and **33** respectively by the action of the appropriate halo compound in tetrahydrofuran (THF) in the presence of sodium hydride. On the other hand, compound **13** was recovered completely unchanged during an attempt for its conversion to the corresponding *N,N'*-dimethyl derivative **29** by the action of diazomethane.

From the ^1H and ^{13}C NMR data of the new macrocyclic oxycyclams listed in Tables 1–4, the following conclusions were derived.

1) The magnetic equivalence of the OCH_2 and NCH_2 protons indicates rapid conformational change in all NH macrooxycyclams **13–28**.

2) Contrary to compounds **13–28**, the *N*-alkylated derivatives **29–33** are evidently present in one stable conformer or in slowly (on the time scale of NMR) interconvertible conformers. This is indicated by the presence of geminal coupling and nonequivalence of all OCH_2 and NCH_2 protons.

3) Evidence from ^{13}C NMR data indicates that all *N*-alkylated macrooxycyclams **29–33** exist entirely as one stable nonconvertible conformer. Comparison of such data with reported[33] ^{13}C NMR of 10-16-macrocyclic dilactams and tetralactams reveals the existence of compounds **29–33** as the *trans, trans* conformers **A** and not the *cis, cis* **B** or *cis,trans* **C** conformers. Such conformers of cyclic *N*-alkylated lactams have been reviewed.[34]

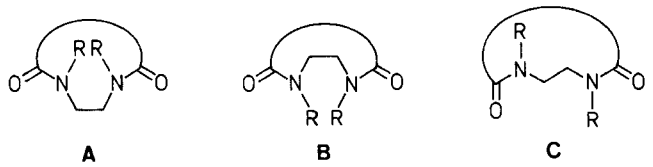

Figure 3

All melting points are uncorrected. IR spectra (KBr) were recorded with a Unicam SP 1200 infrared spectrophotometer. NMR spectra were determined with a Varian Gemini 200 spectrometer (200 MHz ^1H NMR; 50 MHz ^{13}C NMR). Mass spectra were measured (70 ev) on a Finnigan MAT 312 or GCMS-QP 1000 EX spectrometer. Elemental analyses were carried out at the Microanalytical Centre, Cairo University. 1,2-Dibromoethane, 2-chloromethyl-3-chloropropene, and α,α'-dibromo-*o*-xylene were used as purchased from Aldrich. The following starting materials were prepared as reported: 1,3-dibromopropane,[35] 1,4-dibromobutane,[35] 1,5-dibromopentane,[35] 2-hydroxybenzoyl chloride[36] and 5-chloro-2-hydroxybenzoyl chloride.[36]

Satisfactory microanalyses were obtained for compounds **6–9, 13–19, 25, 26, 29–33**. C ± 0.25, H ± 0.25, N ± 0.21; compound **11**: C + 0.13, H + 0.13; compounds **20–24, 27, 28**: C ± 0.29, H ± 0.13, N ± 0.16, Cl ± 0.20.

1,2-Bis(2-hydroxybenzoylamino)ethane (6):
A mixture of ethylenediamine (0.6 g, 10 mmol) and methyl 2-hydroxybenzoate (**1**; 3.04 g, 20 mmol) was heated on a steam bath for 30 min. The solid obtained upon cooling was collected and recrystallized from dilute EtOH to give colorless crystals of **6**; yield: 2.85 g (95%), mp 181 °C.

IR: ν = 3400–3250 (NH, OH), 1640 cm^{-1} (C=O).

^1H NMR (DMSO-d_6): δ = 3.90 (s, 4H, NCH_2), 6.80–7.90 (m, 10H, Ar's, NH), 9.10 (s, 2H, OH).

1,2-Bis(2-hydroxy-5-chlorobenzoylamino)ethane (7):
A solution of 5-chloro-2-hydroxybenzoyl chloride (**3**; 3.13 g, 20 mmol) in dry benzene (20 mL) was added portionwise with stirring and cooling over a period of 10 min to a solution of ethylenediamine (0.6 g, 10 mmol) and Et_3N (3.5 mL) in dry benzene (10 mL). The mixture was then heated at 40–50 °C for 15 min. The solid obtained was collected and recrystallized from EtOH to give yellow crystals of **7**; yield: 2.78 g (75%), mp 247–249 °C.

^1H NMR (DMSO-d_6): δ = 3.65 (s, 4H, NCH_2), 7.00–8.10 (m, 6H, Ar's), 9.18 (s, 2H, NH), 12.50 (s, 2H, OH).

1,2-Bis(2-hydroxybenzoylamino)benzene (8):
A mixture of 1,2-phenylenediamine (1.08 g, 10 mmol) and 2-hydroxybenzoyl chloride (**2**; 3.13 g, 20 mmol) was heated on a steam bath for 10 min. After cooling, the mixture was dissolved in EtOH (20 mL) and diluted with H_2O (50 mL). The precipitated was collected and purified by dissolving in 10% NaOH (50 mL), filtered and repricipitated with conc. HCl to give a grey precipitate of **8**; yield: 2.74 g (79%), mp 145 °C.

^1H NMR ($CDCl_3$): δ = 6.90–7.90 (m, 12H, Ar's), 9.18 (s, 2H, NH), 10.20 (br s, 2H, OH).

1,2-Bis(2-hydroxy-5-chlorobenzoylamino)benzene (9):
This compound was prepared exactly as described for **8** using **3** to afford a grey precipitate; yield: 72%, mp 226 °C.

^1H NMR (DMSO-d_6): δ = 7.00–8.30 (m, 10H, ArH's), 10.50 (s, 2H, NH), 11.90 (s, 2H, OH).

Preparation of Potassium Salts of 6–9:
A solution of each of compounds **6–9** (10 mmol) and KOH (1.14 g, 20 mmol) in EtOH (10 mL) was stirred at r. t. for 10 min. The solvent was removed in vacuo and the remaining solid was triturated with dry Et_2O, collected and dried. It was then used in the next steps without further purification.

1,2-Bis(2-carboxyphenoxy)ethane (11):
A solution of potassium 2-hydroxybenzoate (3.52 g, 20 mmol) and 1,2-dibromoethane (1.86 g, 10 mmol) in DMF (20 mL) was heated under reflux for 15 min (during which KBr precipitated). The solvent was then removed in vacuo and the remaining material was washed with H_2O (20 mL) and recrystallized from dilute EtOH to give colorless crystals of **11**; yield: 2.1 g (72%), mp 103–105 °C.

1,2-Bis[2-(chloroformyl)phenoxy]ethane (12):
A solution of **11** (3.02 g, 10 mmol) in $SOCl_2$ (10 mL) was heated under reflux for 2 h. The solvent was then removed in vacuo and the remaining material was used in the next step without further purification.

5,6,7,8,9,10,16,17-Octahydrodibenzo[*e,m*][1,4,8,11]dioxadiazatetradecine-5,10-dione (13):
To a solution of Et_3N (25 mL) in CH_2Cl_2 (100 mL) was added with stirring and cooling (ice-bath) at the same rate over a period of 2 h each of a solution of **12** (3.4 g, 10 mmol) and a solution of ethylenediamine (0.6 g, 10 mmol) in CH_2Cl_2 (25 mL). The mixture was then heated under reflux while stirring for 3 h. The solvent was removed in vacuo and the residue was crystallized from EtOH to give colorless crystals of **13**; yield: 0.097 g (3%); mp 246–248 °C.

IR: ν = 3350, 3275 (NH), 1625 cm^{-1} (C=O).

MS: *m/z* (%) = 326 (M^+, 8).

Preparation of the Cyclic Diamides 13–28 from Potassium Salts of 6–9; General Procedure:
A solution of the potassium salt of each of compounds **6–9** (10 mmol) and the appropriate dihalo compound or ditosylate (10 mmol) in DMF (20 mL) was heated under reflux for 15 min (during which time potassium halide precipitate when a dihalo compound is used but no precipitation is observed when a ditosylate is used). The solvent was then removed in vacuo and the remaining material was washed with H_2O (50 mL) and recrystallized from the appropriate solvent to give compounds **13–28**.

5,6,7,8,9,10,16,17-Octahydrodibenzo[e,m][1,4,8,11]dioxadiazacyclotetradecine-5,10-dione **(13)**:

Potassium salt of **6** and 1,2-dibromoethane gave crude **13** which was recrystallized from EtOH to give colorless crystals; yield: 95%; identical with compound **13** obtained previously (mmp and IR).

5,6,7,8,9,10,17,18-Octahydro-16H-dibenzo[b,j][1,12,5,8]dioxadiazacyclopentadecine-5,10-dione **(14)**:

Potassium salt of **6** and 1,3-dibromopropane gave crude **14** which was recrystallized from EtOH to give colorless crystals; yield: 93%; mp 208–210 °C.

IR: ν = 3400, 3300 (NH), 1640 cm^{-1} (C=O).

MS: *m/z* (%) = 340 (M^+, 19.3).

6,7,8,9,15,16,17,18,19,20-Decahydrodibenzo[b,j][1,12,5,8]dioxadiazacyclohexadecine-15,20-dione **(15)**:

Potassium salt of **6** and 1,4-dibromobutane gave crude **15** which was recrystallized from EtOH to afford colorless crystals; yield: 94%; mp 226–228 °C.

MS: *m/z* (%) = 354 (M^+, 15.3).

7,8,9,10,16,17,18,19,20,21-Decahydro-6H-dibenzo[b,j][1,12,5,8]dioxadiazacyclohexadecine-16,21-dione **(16)**:

Potassium salt of **6** and 1,5-dibromopentane gave crude **16** which was recrystallized from EtOH to afford colorless crystals; yield: 94%; mp 244–245 °C;

MS: *m/z* (%) = 368 (M^+, 6).

17-Methylene-5,6,7,8,9,10,17,18-octahydro-16H-dibenzo[b,j][1,12,5,8]dioxadiazacyclopentadecine-5,10-dione (17):

Potassium salt of **6** and 2-chloromethyl-3-chloropropene gave crude **17** which was recrystallized from dilute EtOH to give colorless crystals; yield: 77%; mp 179–180°C.

MS: *m/z* (%) = 352 (M^+, 14).

IR: ν = 3400, 3325 (NH), 1635 cm^{-1} (C=O).

5,11,12,13,14,15,16,22-Octahydrotribenzo[b,j,n][1,12,5,8]dioxadiazacyclohexadecine-11,16-dione **(18)**:

Potassium salt **6** and α,α'-dibromo-*o*-xylene gave crude **18** which was recrystallized from EtOH to give pale yellow crystals; yield: 91%; mp 278–279°C.

MS: *m/z* (%) = 402 (M^+, 4).

6,7,9,10,16,17,18,19,20,21-Decahydrodibenzo[h,p][1,4,7,11,14]trioxadiazacycloheptadecine-16,21-dione **(19)**:

Potassium salt of **6** and diethylene glycol ditosylate gave crude **19** which was recrystallized from EtOH to give colorless crystals; yield: 84%; mp 258–259°C.

MS: *m/z* (%) = 370 (M^+, 6%).

3,12-Dichloro-5,6,7,8,9,10,16,17-octahydrodibenzo[e,m][1,4,8,11]dioxadiazacyclotetradecine-11,16-dione **(20)**:

Potassium salt of **7** and 1,2-dibromoethane gave crude **20** which was recrystallized from AcOH to give pale yellow crystals; yield: 72%; mp 302–303°C.

IR: ν = 3350, 3275 (NH), 1630 cm^{-1} (C=O).

3,12-Dichloro-5,6,7,8,9,10,17,18-octahydro-16H-dibenzo[b,j][1,12,5,8]dioxadiazacyclopentadecine-5,10-dione **(21)**:

Potassium salt of **7** and 1,3-dibromopropane gave crude **21** which was recrystallized from AcOH to give colorless crystals; yield: 75%; mp 315–317°C.

IR: ν = 3400, 3275 (NH), 1650 cm^{-1} (C=O).

MS: *m/z* (%) = 408 (M^+, 26.6), 410 (M + 2, 19), 412 (M + 4, 4).

2,13-Dichloro-6,7,8,9,15,16,17,18,19,20-decahydrodibenzo[b,j][1,12,5,8]dioxadiazacyclohexadecine-15,20-dione **(22)**:

Potassium salt of **7** and 1,4-dibromobutane gave crude **22** which was recrystallized from AcOH to give colorless crystals; yield: 79%; mp 297–298°C.

3,12-Dichloro-5,6,7,8,9,10,17,18-octahydro-17-methylene-16H-dibenzo[b,j][1,12,5,8]dioxadiazacyclopentadecine-5,10-dione **(23)**:

Potassium salt of **7** and 2-chloromethyl-3-chloropropene gave crude **23** which was recrystallized from AcOH to give colorless crystals; yield: 61%; mp 195–197°C.

MS: *m/z* (%) = 420 (M^+, 7.75), 422 (M + 2, 2).

IR: ν = 3400 (NH), 1640 cm^{-1} (C=O).

2,14-Dichloro-6,7,9,10,16,17,18,19,20,21-decahydrodibenzo[h,p][1,4,7,11,14]trioxadiazacycloheptadecine-16,21-dione **(24)**:

Potassium salt of **7** and diethylene glycol ditosylate gave crude **24** which was recrystallized from EtOH to give colorless crystals; yield: 76%; mp 230–232°C.

6,7,13,14,19,20-Hexahydrotribenzo[e,i,m][1,4,8,11]dioxadiazacyclotetradecine-13,20-dione **(25)**:

Potassium salt of **8** and 1,2-dibromoethane gave crude **25** with was recrystallized from DMF/EtOH to give buff crystals; yield: 42%; mp 262–264°C.

IR: ν = 3340, 3275 (NH), 1650 cm^{-1} (C=O).

MS: *m/z* (%) = 374 (M^+, 56).

5,6,13,14,20,21-Hexahydro-12H-tribenzo[b,f,j][1,12,5,8]dioxadiazacyclopentadecine-6,20-dione **(26)**:

Potassium salt of **8** and 1,3-dibromopropane gave crude **26** which was recrystallized from EtOH to give grey crystals; yield 45%; mp 213–214°C.

2,11-Dichloro-6,7,13,14,19,20-hexahydrotribenzo[e,i,m][1,4,8,11]dioxadiazacyclotetradecine-13,20-dione **(27)**:

Potassium salt of **9** and 1,2-dibromoethane gave crude **27** which was recrystallized from AcOH to give grey crystals, yield: 44%; mp 292–293°C.

IR: ν = 3350 (NH), 1660 cm^{-1} (C=O).

8,18-Dichloro-5,6,13,14,20,21-hexahydro-12H-tribenzo[b,f,j][1,12,5,8]dioxadiazacyclopentadecine-6,20-dione **(28)**:

Potassium salt of **9** and 1,3-dibromopropane gave crude **28** which was recrystallized from dilute EtOH to give grey crystals; yield: 42%; mp 285–286°C.

IR: ν = 3350 (NH), 1660 cm^{-1} (C=O).

MS: *m/z* (%) = 456 (M^+, 64.6), 458 (M + 2, 42), 460 (M + 4, 13).

Synthesis of *N,N'*-Dialkyl Cyclic Diamides 29–33 by Alkylation of the Secondary Cyclic Diamides 13, 25; General Procedure:

NaH (1.25 g, 50% suspension in mineral oil, ca. 25 mmol) was washed with pentane and suspended in THF (10 mL). To this suspension was added a solution of **13** or **25** (10 mmol) in THF (10 mL) dropwise under N_2. After stirring for 1 h at 50°C, a solution of the appropriate alkyl halide (20 mmol) was added and the mixture was heated under reflux for 24 h. The solvent was then removed in vacuo, and the residue was extracted with CH_2Cl_2 (50 mL), washed with H_2O (100 mL) and then dried ($MgSO_4$). After removal of the solvent in vacuo the residue was recrystallized from EtOH/H_2O to give colorless crystals of **29–33**.

5,6,7,8,9,10,16,17-Octahydro-8,11-dimethyldibenzo[e,m][1,4,8,11]dioxadiazacyclotetradecine-5,10-dione **(29)**:

Compound **13** and MeI gave 50% yield of crystallized **29**, mp 212–213°C.

IR: ν = 1630 cm^{-1} (C=O).

8,11-Diethyl-5,6,7,8,9,10,16,17-octahydrodibenzo[e,m][1,4,8,11]dioxadiazacyclotetradecine-5,10-dione **(30)**:

Compound **13** and EtI gave 47% yield of crystallized **30**; mp 216–217°C.

IR: ν = 1635 cm^{-1} (C=O).

8,11-Dibutyl-5,6,7,8,9,10,16,17-octahydrodibenzo[e,m][1,4,8,11]dioxadiazacyclotetradecine-5,10-dione **(31)**:

Compound **13** and BuBr gave 40% yield of crystallized **31**; mp 202–203°C.

8,11-Dibenzyl-5,6,7,8,9,10,16,17-octahydrodibenzo[e,m][1,4,8,11]dioxadiazacyclotetradecine-5,10-dione **(32)**:

Compound **13** and BnCl gave 42% yield of crystallized **32**; mp 254–256°C.

IR: ν = 1630 cm^{-1} (C=O).

MS: *m/z* (%) = 506 (M^+, 4.2).

8,11-Dibenzyl-6,7,13,14,19,20-hexahydrotribenzo[e,i,m][1,4,8,11]dioxadiazacyclotetradecine-13,20-dione **(33)**:

Compound **25** and BnCl gave 31% yield of crystallized **33**, mp 318–320°C.

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