Synthesis of Macrocyclic Amides and Their Intermediate 2 : 1 and 3 : 2 Reaction Compounds from Diethyl Oxalate and Ethereal Oxygen-Containing Diamines

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The reaction of diethyl oxalate with ethereal oxygen-containing diamines under high-dilution conditions gave 2 : 2 reaction products, 22-, 28-, and 34-membered macrocyclic amides in good yields. From the 2 : 1-mixed reaction between diethyl oxalate and the diamines, acyclic 2 : 1 and 3 : 2 reaction products were isolated at a ratio of ca. 9 : 1. The intermediate 2 : 1 and 3 : 2 reaction products led to the 2 : 2 reaction products mentioned above and the 3 : 3 reaction products, 33-, 42-, and 51-membered macrocyclic amides, respectively, upon reaction with additional corresponding diamines. Also, other macrocyclic amides were synthesized by combining the 2 : 1 reaction products and diamines.

Many synthetic routes to 5- and 6-membered cyclic amides by the reaction between an ester group and an amino group are known.[1] The reaction of diethyl malonate (**1**) with urea in the presence of sodium methoxide under reflux for 7 h gives barbituric acid (**2**) in a 76% yield.[2,3] Also, parabanic acid (**4**) is obtained in a 61% yield from diethyl oxalate (**3**), urea, and sodium methoxide at room temperature.[2,4]

Since crown ethers appeared in 1967,[5] many azacrown ethers and macrocyclic polyamines and amides have also been synthesized. Macrocyclic amide **5** was prepared by Lehn et al. from a diamine (1,8-diamino-3,6-dioxaoctane) and a diacid dichloride (3,6-dioxaoctanedioyl dichloride).[6] Tabushi et al. obtained macrocyclic amides **6** by the reaction of ester **1** or its derivatives with a polyamine (1,9-diamino-3,7-diazanonane) in ethanol under reflux for 3 d (Fig. 1).[7] Among natural macrocyclic peptides or amides, amanitin and phalloidin isolated as well-known toxins from the poisonous mushroom *Amanita phalloides* are bicyclic oligopeptide ionophores. Valinomycin, beauvericin, and enniatin are known as depsipeptides and ionophore antibiotics.[8] Compounds containing an amide bond in the ring such as verbacenine and celacinnine belong to macrocyclic spermine and spermidine alkaloids, respectively.[9]

We have previously reported on the synthesis of macrocyclic compounds from some dithiocarboxylic acid esters and ethereal oxygen-containing diamines **7**.[10—12] In this paper, we wish to report the synthesis of macrocyclic amides and their intermediates using ester **3** and diamines **7**. The reaction of malonic ester **1** to afford compounds **2** and **6** requires a long period of heating as mentioned above. On the other hand, oxalic ester **3** reacted with diamines **7** under mild conditions similar to the preparation of compound **4**.

A solution of equimolecular amounts of **3** and 1,7-diamino-4-oxaheptane (**7a**) in ethanol under high-dilution conditions was left for 3 d at −20 °C to give white precipitates in a good yield. We at first expected the reaction to form a 1 : 1 reaction product similar to the formation of compound **4**. The mass spectra, however, indicated a 22-membered cyclic 2 : 2 reaction product, 6,7,17,18-tetraoxo-1,12-dioxa-5,8,16,19-tetraazacyclodocosane (**8a**) (Table 1) (Scheme 1). Thus, from the reaction of **3** with 1,10-diamino-4,7-dioxadecane (**7b**) and 1,13-diamino-4,7,10-trioxatridecane (**7c**), 28- and 34-membered ring compounds **8b** and **8c** were afforded, respectively. The 2 : 2 reaction may occur due to the *trans* conformation of ester **3** and the flexibility of long chain diamines **7**.

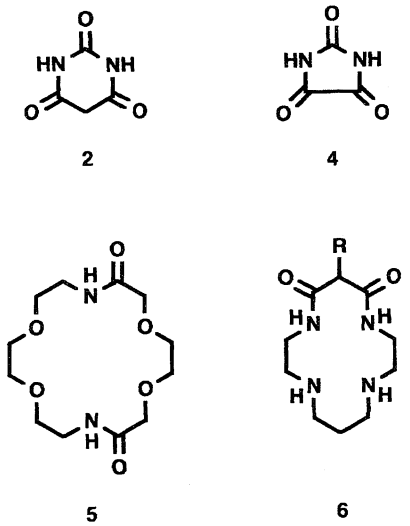


Fig. 1.

Recently, Kodama et al. synthesized a 2 : 2 cyclization product, a pyridyl-containing tetraoxo octaaza macrocycle from dicarboxylate and diethylenetriamine, and described the complexation equilibrium of the macrocyclic ligand with copper(II) ions.[13]

Table 1. Yields, Melting Points, and Mass Spectral Data of Compounds **8**—**14**

Compd	Ring member	Yield[a] %	mp °C	MS (M^+) *m/z*
8a	22	79 (85)	222—223[b]	372
8b	28	69 (87)	174—176[b]	460
8c	34	60 (71)	167—168	548
9a		64	52—53	332
9b		52	43—45	376
9c		65	oil	420
10a		7	88—90	518
10b		6	79—80	606
10c		8	52—54	694
11a	33	66	199—201[b]	558
11b	42	97	169—170	690
11c	51	76	125—126	—[c]
12	25	63	198—200[b]	416
13	31	53	153—156	504
14	28	73	174—176	460

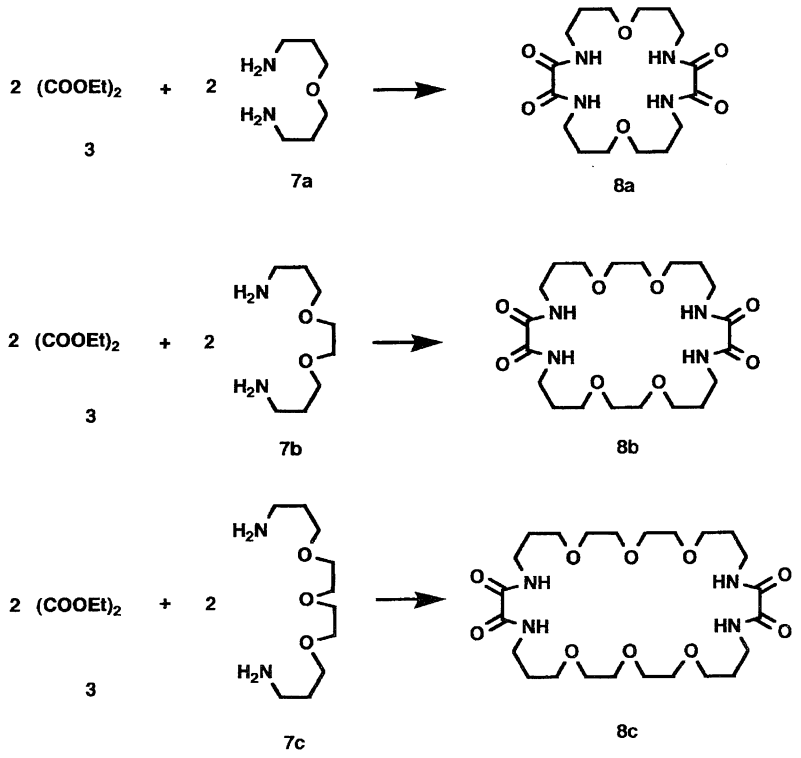
a) The yield in parenthesis refers to that given for the reaction of **9** with **7**. b) Decomposition. c) The molecular ion peak was undetectable.

For the purpose of preparing an acylic 2 : 1 reaction product, the ratio of starting materials **3** and **7a** was set at 2 : 1.[11] The reaction was conducted under high-dilution conditions similar to the 2 : 2 reaction. The resulting oily substance was chromatographed on a silica-gel column to give two major products at a ratio of ca. 9 : 1—a 2 : 1 reaction product, diethyl *N*,*N*′-(4-oxaheptamethylene)dioxamate (**9a**) and a 3 : 2 reaction product, diethyl *N*,*N*′-(9,10-dioxo-4,15-dioxa-8,11-diazaoctadecamethylene)dioxamate (**10a**) (Scheme 2). Also, from the reaction of **3** with **7b** or **7c**, compounds **9b** and **10b** or **9c** and **10c**, respectively, were obtained at ratios of ca. 9 : 1. Attempts to obtain **10** in relatively larger quantities by the 3 : 2-mixed reaction led to compounds **9**, **10**, and **8** in a ratio of ca. 3 : 1 : 1.

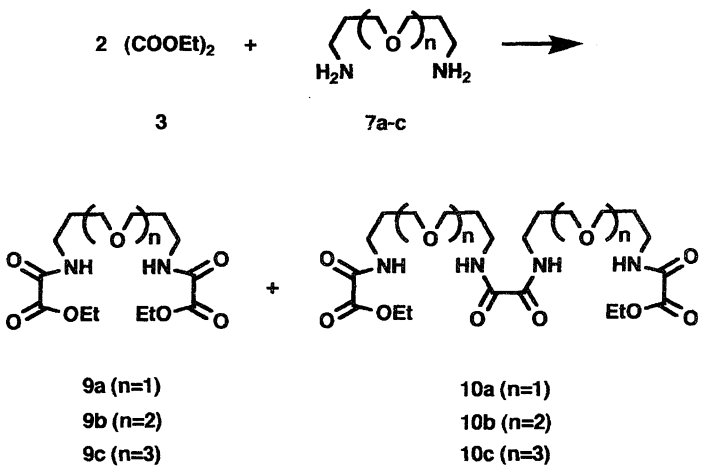
Compounds **9** are regarded as intermediates of **8**. In fact, the 1 : 1 reaction of **9a**—**c** with the corresponding amines **7a**—**c** under high-dilution conditions at room temperature for 3 d gave **8a**—**c** in good yields. Similarly, larger macrocyclic 33-, 42-, and 51-membered ring 3 : 3 reaction products **11a**—**c** were obtained by the reaction of **10a**—**c** with the corresponding amines **7a**—**c** (Scheme 3). Furthermore, macrocycles **12**—**14** could be prepared using **9** and the noncorresponding diamines **7** (Scheme 4). This method may make it possible to synthesize various macrocyclic amides.

In general, the macrocyclic amides obtained here are not very soluble in common organic solvents. And the smaller macrocycles tend to decrease in solubility. All of the new compounds were characterized by microanalysis as well as by their spectral data. The IR spectra could be used to distinguish clearly among **8** (also **11**—**14**), **9**, and **10** by observing one, two, or three kinds of carbonyl absorption bands.

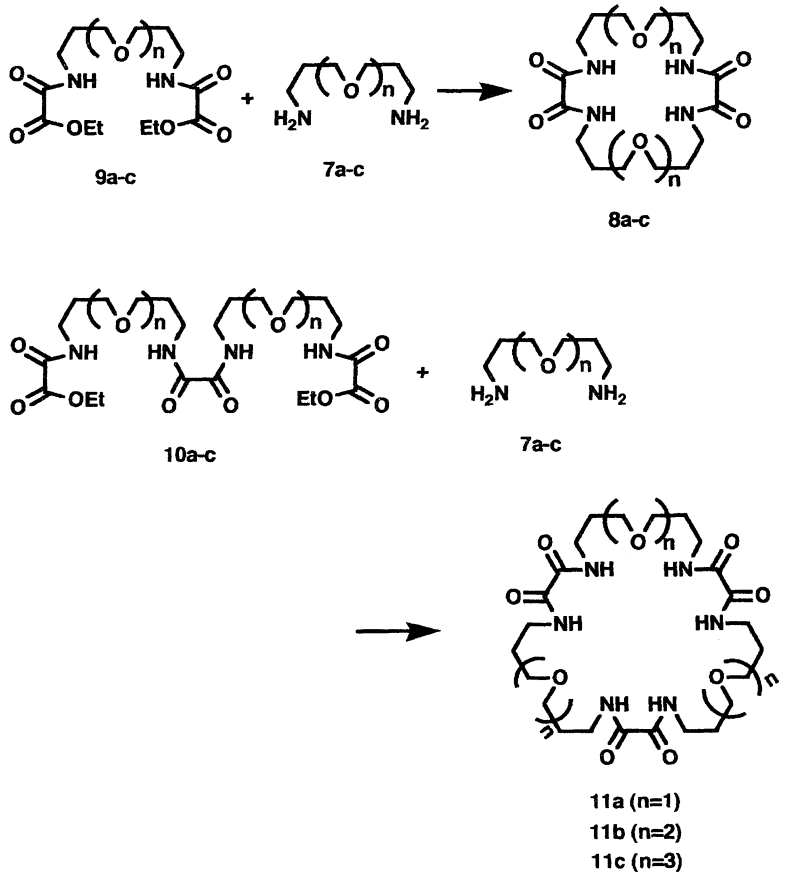
Although the 2 : 2 and 2 : 1 reactions of ester **3** with polyamines such as diethylenetriamine and triethylenetetramine instead of diamines **7** actually proceeded, purification of the products to analytical grade was difficult. Attempts to synthesize a variety of macrocycles using diethyl carbonate, succinate, maleate, fumarate, and phthalate instead of ester **3** were unsuccessful.



Scheme 1.



Scheme 2.



Scheme 3.

Experimental

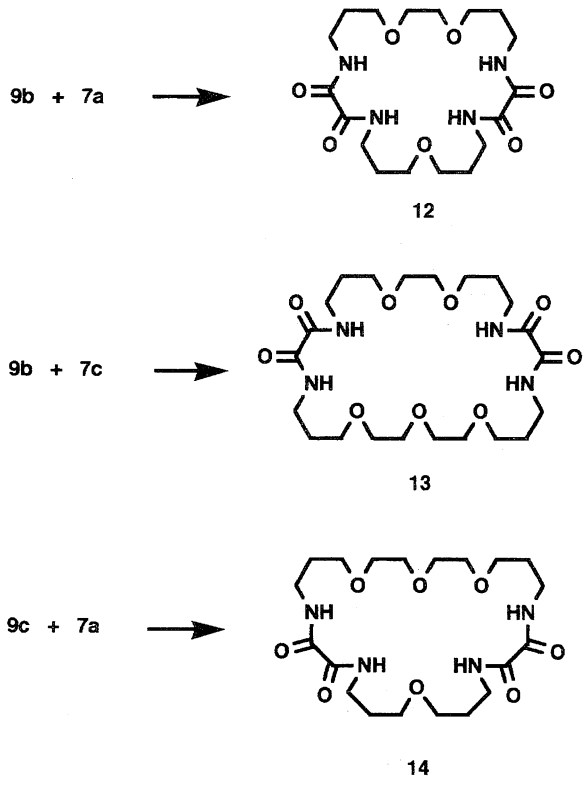
2 : 2 Reaction Products 8. General Procedure.

(A) From Ester 3. To a solution of diethyl oxalate (**3**) (0.73 g, 0.005 mol) in precooled ethanol (50 ml) was added a solution of diamine **7** (0.005 mol) in precooled ethanol (50 ml), and the clear mixture was transferred to a freezer. The mixture, becoming cloudy after 0.5—1 h, was allowed to stand for 3 d at −20 °C. The white solid which precipitated was collected and recrystallized from methanol.

(B) From Intermediate 9. To a solution of compound **9** (0.0012 mol) in ethanol (15 ml) was added a solution of the corresponding diamine **7** (0.0012 mol) in ethanol (10 ml), and the mixture was allowed to stand for 3 d at room temperature.

6, 7, 17, 18- Tetraoxo- 1, 12- dioxa- 5, 8, 16, 19- tetraazacyclodocosane (8a): IR (KBr) 3275vs and 1655vs cm^{-1}. Found: C, 51.20; H, 7.60; N, 14.83%. Calcd for $C_{16}H_{28}N_4O_6$: C, 51.60; H, 7.58; N, 15.04%.

9,10,23,24-Tetraoxo-1,4,15,18-tetraoxa-8,11,22,25-tetraazacyclooctacosane (8b): IR (KBr) 3280vs and 1645vs cm^{-1}. Found:



Scheme 4.

C, 51.84; H, 7.70; N, 11.85%. Calcd for $C_{20}H_{36}N_4O_8$: C, 52.16; H, 7.88; N, 12.17%.

12,13,29,30-Tetraoxo-1,4,7,18,21,24-hexaoxa-11,14,28,31-tetraazacyclotetratriacontane (8c): IR (KBr) 3285vs and 1650vs cm^{-1}. Found: C, 52.47; H, 8.03; N, 10.14%. Calcd for $C_{24}H_{44}N_4O_{10}$: C, 52.54; H, 8.08; N, 10.21%.

2:1 Reaction Products 9 and 3:2 Reaction Products 10. General Procedure. To a solution of ester **3** (3.51 g, 0.024 mol) in precooled ethanol (200 ml) was added a solution of diamine **7** (0.024 mol) in precooled ethanol (100 ml), and the mixture was allowed to stand for 3 d at −20 °C in a freezer. The resulting trace amount of precipitate (2:2 reaction products **8**) was removed by filtration. The filtrate was concentrated under reduced pressure without heating. The residual oil was chromatographed on a silica-gel column with acetone–chloroform–ethyl acetate (3:3:2) as an eluent to give compounds **9** and **10** which were recrystallized from ethanol.

Diethyl *N,N′*-(4-Oxaheptamethylene)dioxamate (9a): IR (KBr) 3280vs, 1735vs, and 1680vs cm^{-1}. Found: C, 50.57; H, 7.25; N, 8.39%. Calcd for $C_{14}H_{24}N_2O_7$: C, 50.59; H, 7.28; N, 8.43%.

Diethyl *N,N′*-(4,7-Dioxadecamethylene)dioxamate (9b): IR (KBr) 3290vs, 1730vs, and 1680vs cm^{-1}. Found: C, 50.74; H, 7.36; N, 7.28%. Calcd for $C_{16}H_{28}N_2O_8$: C, 51.06; H, 7.50; N, 7.44%.

Diethyl *N,N′*-(4, 7, 10-Trioxatridecamethylene)dioxamate (9c): IR (KBr) 3300vs, 1749vs, and 1690vs cm^{-1}. Found: C, 51.08; H, 7.54; N, 6.45%. Calcd for $C_{18}H_{32}N_2O_9$: C, 51.42; H, 7.67; N, 6.66%.

Diethyl *N,N′*-(9,10-Dioxo-4,15-dioxa-8,11-diazaoctadecamethylene)dioxamate (10a): IR (KBr) 3290vs, 1745s, 1685vs, and 1650vs cm^{-1}. Found: C, 50.73; H, 7.27; N, 10.74%. Calcd for $C_{22}H_{38}N_4O_{10}$: C, 50.96; H, 7.39; N, 10.80%.

Diethyl *N,N′*-(12, 13-Dioxo-4, 7, 18, 21-tetraoxa-11, 14-diazatetracosamethylene)dioxamate (10b): IR (KBr) 3290vs, 1735s, 1680vs, and 1655vs cm^{-1}. Found: C, 51.38; H, 7.52; N, 9.22%. Calcd for $C_{26}H_{46}N_4O_{12}$: C, 51.48; H, 7.64; N, 9.24%.

Diethyl *N,N′*-(15,16-Dioxo-4,7,10,21,24,27-hexaoxa-14,17-diazatriacontamethylene)dioxamate (10c): IR (KBr) 3240vs, 1740s, 1670vs, and 1640vs cm^{-1}. Found: C, 51.45; H, 7.69; N, 7.79%. Calcd for $C_{30}H_{54}N_4O_{14}$: C, 51.86; H, 7.83; N, 8.06%.

3:3 Reaction Products 11. General Procedure. To a solution of compound **10** (0.0002 mol) in ethanol (5 ml) was added a solution of the corresponding diamine **7** (0.0002 mol) in ethanol (5 ml), and the mixture was allowed to stand for 3 d at room temperature. The white solid which precipitated was collected and recrystallized from methanol.

6,7,17,18,28,29-Hexaoxo-1,12,23-trioxa-5,8,16,19,27,30-hexaazacyclotritriacontane (11a): IR (KBr) 3280vs and 1650vs cm^{-1}. Found: C, 51.26; H, 7.39; N, 14.75%. Calcd for $C_{24}H_{42}N_6O_9$: C, 51.60; H, 7.58; N, 15.04%.

9,10,23,24,37,38-Hexaoxo-1,4,15,18,29,32-hexaoxa-8,11,22,25,36,39-hexaazacyclodotetracontane (11b): IR (KBr) 3275vs and 1645vs cm^{-1}. Found: C, 52.16; H, 7.77; N, 12.11%. Calcd for $C_{30}H_{54}N_6O_{12}$: C, 52.16; H, 7.88; N, 12.17%.

12,13,29,30,46,47-Hexaoxo-1,4,7,18,21,24,35,38,41-nonaoxa-11,14,28,31,45,48-hexaazacyclohenpentacontane (11c): IR (KBr) 3280vs and 1645vs cm^{-1}. Found: C, 52.23; H, 7.99; N, 10.05%. Calcd for $C_{36}H_{66}N_6O_{15}$: C, 52.54; H, 8.08; N, 10.21%.

9,10,20,21-Tetraoxo-1,4,15-trioxa-8,11,19,22-tetraazacyclopentacosane (12) was prepared from **9b** (0.19 g, 0.0005 mol) in ethanol (10 ml) and **7a** (0.066 g, 0.0005 mol) in ethanol (10 ml) by a method similar to that described for the preparation of **8** from intermediate **9**. IR (KBr) 3265vs and 1640vs cm^{-1}. Found: C, 51.77; H, 7.70; N, 13.10%. Calcd for $C_{18}H_{32}N_4O_7$: C, 51.91; H, 7.75; N, 13.45%.

12,13,26,27-Tetraoxo-1,4,7,18,21-pentaoxa-11,14,25,28-tetraazacyclohentriacontane (13) was prepared from **9b** (0.19 g, 0.0005 mol) in ethanol (10 ml) and **7c** (0.11 g, 0.0005 mol) in ethanol (10 ml) by a method similar to that described for the preparation of **8** from intermediate **9**. IR (KBr) 3270vs and 1640vs cm^{-1}. Found: C, 52.60; H, 7.97; N, 10.81%. Calcd for $C_{22}H_{40}N_4O_9$: C, 52.37; H, 7.99; N, 11.10%.

12,13,23,24-Tetraoxo-1,4,7,18-tetraoxa-11,14,22,25-tetraazacyclooctacosane (14) was prepared from **9c** (0.28 g, 0.0007 mol) in ethanol (20 ml) and **7a** (0.092 g, 0.0007 mol) in ethanol (20 ml) by a method similar to that described for the preparation of **8** from intermediate **9**. IR (KBr) 3275vs and 1650vs cm^{-1}. Found: C, 51.83; H, 7.79; N, 11.85%. Calcd for $C_{20}H_{36}N_4O_8$: C, 52.16; H, 7.88; N, 12.17%.

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