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Synthesis of Macrocyclic Amides. Formation of a New Symmetric 36-Membered Tetramide Ring

YOHMEI OKUNO,* KIYOSHI HORITA and OSAMU YONEMITSU

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

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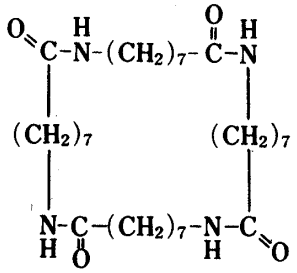
The preparation of a new macro-ring compound, 9,18,27-triaza-10,19,28-trioxo-35-pentatriacontanelactam, is described. A simple azide method in a mixed solvent system (water: dimethylformamide (DMF)=1:3) gave a good cyclization result, and the use of sodium or potassium cations as a template produced a 30% augmentation in the yield.

Keywords——9,18,27-triaza-10,19,28-trioxo-35-pentatriacontane lactam; intramolecular cyclization; metal template; flexible conformation; hydrophilic and hydrophobic cavities

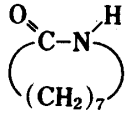
In recent years, a number of polyamines and alkaloids which contain amide or macrocyclic lactam groups have been isolated,[1] and it has been shown that many of them possess a broad spectrum of biological activity, including anti-tumor,[2] anti-viral[3] and hypotensive[4] activities. The chemical behavior of macrocyclic polyamines is also of interest because of their ability to trap selectively soft metal cations and protons;[5] these compounds differ in this respect from the crown-ethers, [6] in which oxygen atoms serve as ligands. While numerous studies on crown-ethers have been reported, comparatively little work has been done in the field of cyclic amines and amides, especially those with large macro rings. It thus seems to be of interest to examine the effects of various features of macrocyclic amines and amides as big as valinomycin, such as ring size, flexibility and conformation, on the complexation properties, as has been done extensively for crown-ethers and cryptates.[7,8]

In addition, during our extensive studies[9] on nonheme iron-sulfur proteins,[10] we required simple preparation methods for a series of cyclic tetramides consisting of a 36-membered ring or so as key intermediates. In this context, we present here some results on cyclic amide (**1**) formation.

The synthesis of ring compounds through amide bond formation is usually not readily achieved. Earlier investigators have developed various procedures,[11-14] but these seemed to be



1



2

Z-[NH-$(CH_2)_7$-CO]$_n$-R

3: n=1, R=OH
5: n=2, R=OEt
7: n=2, R=OH
8: n=4, R=OEt
9: n=4, R=$NHNH_2$

HCl·H-[NH-$(CH_2)_7$-CO]$_m$-OEt
4: m=1, **6**: m=2

H-[NH-$(CH_2)_7$-CO]$_4$-$NHNH_2$·2HBr
10

Fig. 1

inappropriate for the preparation of **1** because of their inherent unfavorable dispositions of nitrogen atoms in the carbon framework, and the comparatively poor yield. Zahn and Determann reported[15] the synthesis of cyclic oligoamides of ω-aminohexanoic acid in good yield (50%) *via* the corresponding azides. Consequently, starting from 2-azacyclononanone [16] (**2**), We investigated intramolecular cyclizations of tetrapeptide.

Acid hydrolysis of **2**, followed by carbobenzoxylation gave **3**. Esterification of the amino acid intermediate afforded the amino ester **4**. Condensation of the two components with dicyclohexylcarbodiimide (DCC)-dimethylamino pyridine (DMAP)[17] yielded the dipeptide **5**, which was converted into **6** by H_2-Pd/C treatment, and then into the acid **7**. Compound **7** was condensed with **6** in dimethylformamide (DMF)–tetrahydrofuran (THF) (1:1) at −18 °C by a mixed anhydride method, affording the linear tetrapeptide **8**, which was treated with hydrazine hydrate in boiling MeOH to give **9**. Removal of the Z-group of **9** with 25% HBr/AcOH gave 35-amino-9,18,27-triaza-10,19,28-trioxopentatriacontanohydrazide dihydrobromide **10** in 98% yield.[18]

Cyclization reactions via the azide were examined under various conditions. The corresponding azide generated [19] by treatment of **9** with equimolar $NaNO_2$/HCl at 0 °C was dissolved in a solvent (see Table I). After addition of $NaHCO_3$(solid) the mixture was permitted to react at 0 °C.

TABLE I

Run	Solvent system	Concentration of **10** (mM)	Yield of **1** (%)
1	H_2O	0.31	1
2	H_2O:DMF=1:3	0.31	40
3	H_2O:DMF=1:3	1.8	14
4	H_2O:DMF=1:20	0.93	1
5	H_2O:DMF:DMSO=1:10:20	0.93	Trace

The yield of **1** was influenced greatly by the solvent system used. When water was employed the yield amounted to only 1% (run 1 in Table I), probably due to slight solubility of the substrate. When the reaction was carried out in H_2O–DMF (1:3), a great improvement in yield (40%) was observed. An increase in the concentration of **10** by a factor of 6 decreased the yield to 14%, and neither increased ratio of DMF nor employment of dimethyl sulfoxide (DMSO) resulted in better yields (runs 4 and 5).

Since noticeable template effects of metal ions have been reported in the synthesis of phthalocyanines,[20] porphyrins[21] and crownethers,[22-24] experiments were carried out with K^+, Cu^{2+}, Mg^{2+}, and Na^+. The results are summarized in Table II.[25]

This newly prepared cyclic tetramide is poorly soluble in both protic and aprotic polar solvents as well as in non-polar solvents, but is soluble without difficulty in $CHCl_3$ in the presence of several drops of MeOH or *vice versa* at room temperature. An additional feature of interest arose from the Corey-Pauling-Koltun (CPK) model examination. If the four carbonyl groups are oriented outside the ring, it is possible to form a large hydrophobic cavity (approximate size of 7Å×7Å) in which $CHCl_3$ can fit well.[29] Conversely, because of the flexible conformation of the molecule, the formation of a much smaller hydrophilic cavity which may accommodate the methanol molecule is also feasible by the disposition of the carbonyl groups

TABLE II

Metal salts	—	KCl	$MgCl_2$	$CuCl_2$	NaCl
mM	—	5.8	5.8	0.35	5.8
Relative ratio of **1**	1.0	1.26	0.41	1.11	1.33

inside the carbon skeleton. The unique apparent ability to form both hydro- and lipophilic cavities depending on the environment is of interest in connection with problems of molecular recognition. Further work is in progress.

Experimental[26]

8-Benzyloxycarbonylaminooctanoic Acid 3———**3** was synthesized in a manner similar to that described for benzoylaminohexanoic acid,[27] starting from 10g of cyclooctanone oxime,[28] and 11.2g of carbobenzoxy chloride. mp 63—64°C (AcOEt-pet. ether), 82%. IR (Nujol): 1680—1700. Mass spectra (MS) (*m/e*, %): 295(M^+, 25), 91 (100). PMR ($CDCl_3$) δ: 1.32—1.61 (m, 10H), 2.33 (t,2H, J=7 Hz), 3.12—3.17 (m, 2H), 4.79 (br s, 1H), 5.10 (s, 2H), 7.35 (s, 5H), 10.25 (br s, 1H).

TABLE III. Elemental Analyses Results

No.	Formula	Calcd (%)				Found (%)			
		C	H	N	Cl	C	H	N	Cl
3	$C_{16}H_{23}NO_4$	65.51	7.90	4.78		65.31	7.93	4.69	
4	$C_{10}H_{22}ClNO_2$	53.68	9.91	6.26	15.84	53.43	10.04	6.19	15.94
5	$C_{26}H_{42}N_2O_5$	67.50	9.15	6.06		67.26	9.19	5.96	
6	$C_{18}H_{37}ClN_2O_3$	59.24	10.22	7.68	9.71	58.71	10.34	7.56	9.99
7	$C_{24}H_{38}N_2O_5$	66.33	8.81	6.45		66.17	8.89	6.49	
8	$C_{42}H_{72}N_4O_7$	67.71	9.76	7.52		67.43	9.84	7.43	
9	$C_{40}H_{70}N_6O_6$	65.72	9.65	11.50		65.55	9.60	11.27	
1	$C_{32}H_{60}N_4 \cdot CH_3OH$	66.40	10.81	9.39		66.20	10.35	9.38	

Ethyl 8-Aminooctanoate 4———The hydrolyzed product of 3.5 g of **2** obtained under reflux for 8h in const. boiling HCl (35 ml) was esterified with EtOH-$SOCl_2$. mp 118.5—120°C, 4.6 g (89%). IR (Nujol); 1730 cm^{-1}. PMR(D_2O) δ: 1.24 (t, 3H, J=7 Hz), 1.35 (s, 6H), 1.59—1.70 (m, 4H), 2.37 (t, 2H, J=7.3 Hz), 2.94 (t, 2H, J=7.3 Hz), 4.14 (q, 2H, J=7 Hz).

Ethyl 17-Benzyloxycarbonylamino-10-oxo-9-azaheptadecanoate 5———A solution of **4** (8.6 g) and Et_3N (3.9 g) in CH_2Cl_2 (100 ml) was added to a mixture of **3** (11.3 g), DCC (8.7 g) and DMAP[17] (502 mg) in CH_2Cl_2 (100 ml) at 0°C. After 24 h with stirring at room temperature, excess DCC was deactivated with AcOH, the solvent was replaced by AcOEt and then the urea was removed by filtration. Recrystallization from EtOH-ether gave 15.8 g (89 %) of colorless leaflets. mp 80—82°C. IR (Nujol): 1730, 1690, 1630 cm^{-1}. PMR($CDCl_3$) δ: 1.25 (t, 3H, J=7 Hz), 1.31—1.66 (m, 20H), 2.14 (t,2H, J=7.3 Hz), 2.28 (t, 2H, J=7.3 Hz), 3.13—3.27 (m, 4H), 4.14 (q, 2H, J=7 Hz), 4.75 (br s, 1H), 5.09 (s, 2H), 5.45 (br s, 1H), 7.37 (s, 5H).

17-Amino-10-oxo-9-azaoctadecanoic Acid Ethyl Ester Hydrochloride 6———Deprotection was carried out by catalytic reduction of **5** (7.68 g) in 1.2N HCl-EtOH (100 ml) in the presence of 10% Pd/C (1.9 g) for 2 h. yield 5.4 g (90%). mp 129—132°C (EtOH-ether). IR (Nujol): 1730, 1630 cm^{-1}. PMR (D_2O) δ: 1.24 (t, 3H, J=7 Hz), 1.30—1.32 (m, 12H), 1.43—1.67 (m, 8H), 2.22 (t, 2H, J=7.3 Hz), 2.36 (t, 2H, J=7.3 Hz), 2.97 (t, 2H, J=7.3 Hz), 3.16 (t, 2H, J=7.3 Hz), 4.14 (q, 2H, J=7 Hz).

17-Benzyloxycarbonylamino-10-oxo-9-azaheptadecanoic Acid 7———A solution of **5** (821 mg) in acetone-water (19—10 ml) was treated with 0.5N NaOH (5 ml) and the mixture was stirred for 24 h at room temperature. After evaporation of the acetone, followed by acidification of the solution with 10% HCl, the precipitate was collected by filtration and recrystallized from $CHCl_3$-pet. ether to give 644 mg (84%) of a colorless solid. mp 105—106°C. IR (Nujol): 1690—1700, 1630 cm^{-1}. PMR ($CDCl_3$) δ: 1.32—1.61 (m, 20H), 2.16 (t, 2H, J=7.3 Hz), 2.33 (t, 2H, J=7.3 Hz), 3.12—3.25(m, 4H), 4.86 (br, 1H), 5.09 (s, 2H), 5.65 (br s, 1H), 7.34 (s, 5H).

Ethyl 35-Benzyloxycarbonylamino-10,19,28-trioxo-9,18,27-triazapentatriacontanoate 8———**7** (65.1 mg) and Et_3N (15.2 mg) were dissolved in DMF:THF=1:1 (10 ml) and isobutyl chlorocarbonate (20.5 mg) was added at −18°C with vigorous stirring. Seven min later a solution of **6** (54.8 mg) and Et_3N (15.2 mg) in $CHCl_3$ (10 ml) was added dropwise to the mixture at −10°C and the whole was kept for 30 min at this temperature, then stirred overnight at 25°C. The solvent was removed by evaporation and then the residue was washed with sat. $NaHCO_3$, 5% HCl and water. Recrystallization of the product from EtOH afforded 94.1 mg (84%) of a colorless solid. mp 149—150.5°C. IR (Nujol): 1730, 1690, 1630 cm^{-1}. PMR (DMSO-d_6 at 80°C) δ: 1.17 (t, 3H, J=7 Hz), 1.24—1.47 (m, 40H), 2.03 (t, 6H, J=7.3 Hz), 2.21 (t, 2H, J=7.3 Hz), 2.96—3.06 (m, 8H), 4.05 (q, 2H, J=7 Hz), 5.01 (s, 2H), 6.95 (br, 1H), 7.33 (s, 5H), 7.47 (br, 3H).

35-Benzyloxycaronylamino-10,19,28-trioxo-9,18,27-triazapentatriacontanohydrazide 9———Hydrazine hydrate (1.3 ml) was added to a hot solution (50°C) of **8** (100 mg) in MeOH (13 ml) and the mixture was refluxed overnight. The resultant solid was collected and washed with ether and MeOH. mp 164—166°C, 97 mg (quant.). IR(Nujol): 1690, 1670, 1630 cm^{-1}. PMR (DMSO-d_6 at 80°C) δ: 1.24—1.48 (m, 40H), 1.99 (t, 6H, J=7.3 Hz), 2.02 (t, 2H, J=7.3 Hz), 2.90—3.02 (m, 8H), 4.03 (br s, 2H), 5.00 (s, 2H), 6.92 (br, 1H), 7.33 (s, 5H), 7.47 (br,

3H), 8.72 (br, 1H).

35-Amino-10,19,28-trioxo-9,18,27-triazapentatriacontanohydrazide Dihydrobromide 10——A suspension of **9** (706 mg) in AcOH (10 ml) was treated with 25% HBr/AcOH (19 ml) for 2 h. The gel formed upon addition of ether after evaporation of the solvent was washed repeatedly with abs. ether, and reprecipitated from abs. EtOH–ether, giving a colorless solid (680 mg, 98%).[18]

10,19,28-Trioxo-9-18,27-triaza-35-pentatriacontanelactam 1——A mixture of **10** (50 mg), $NaNO_2$ (4.7 mg) and 0.1 N HCl (0.7 ml) in 10 ml of H_2O: DMF=1:3 was stirred vigorously at 0 °C for 20 min. The mixture was then diluted with 200 ml of H_2O: DMF=1:3, followed by addition of $NaHCO_3$ (solid, 130 mg), and the whole was stirred at 0 °C for 3d, then concentrated by evaporation. The residue was extracted with hot MeOH and recrystallized from MeOH to afford 15 mg (40%) of a colorless solid.

Samples were prepared in a similar manner but in various solvent systems or in the presence of template metal salts. mp 213—216 °C. MS (*m/e*, %): 564.4626(M^+, 100); Calcd 564.4618. IR (Nujol): 3270, 3070, 1640, 1560 cm^{-1}. PMR (DMSO-d_6 at 80 °C) δ: 1.24—1.49 (m, 40H), 2.30 (t, 8H, J=7 Hz), 2.97—3.10 (m, 8H), 7.65 (br, 4H).

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