SYNTHESIS OF AZA-CROWN COMPOUNDS BY INTRAMOLECULAR CYCLIZATION OF ω-AMINO ACIDS

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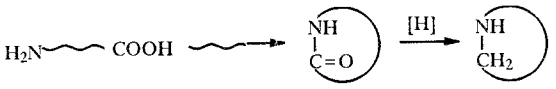
A method for the synthesis of aza-crown compounds by the intramolecular cyclization of ω-amino acids with subsequent reduction of the lactam to a macrocyclic amine was developed. 1,8-Diazacyclotetradecane and 1,8-dioxa-4,11-diazacyclotetradecane were synthesized in preparative yields. The structural assignments were made using the IR, ^1H and ^{13}C NMR, and mass spectra.

A significant number of the heretofore described methods for the synthesis of macroheterocyclic compounds make it possible to construct molecules, the structural formulas of which have relatively high symmetry (no lower than C_{2v}). "Symmetrical" reagents, i.e., reagents, the structural formulas of which have a plane of symmetry, are commonly used for unambiguous macrocyclization. Attempts to use "unsymmetrical" reagents lead to difficult-to-separate mixtures of isomers.

The method that we propose to synthesize macroheterocycles does not have the indicated drawbacks. It makes it possible to obtain aza-crown compounds with any symmetry (also including those with rather low symmetries — C_2 and lower) with arbitrary ring sizes, sets of heteroatoms, and side groups. The method consists in the realization of the intramolecular cyclization of ω-amino acids to the corresponding lactams with subsequent reduction of the amide to a macrocyclic amine [1].



The use of ω-amino acids for the synthesis of terminal diamines, which are converted to macrocyclic tetraamides by reaction with activated dicarboxylic acid esters, has been described [2].

We used our method to synthesize two cyclam analogs — 1,8-diazacyclotetradecane (XIV) and 1,8-dioxa-4,11-diazacyclotetradecane (XXIII). In the course of the synthesis of XIV we tested various protective and activating groups and varied the cyclization and reduction conditions. These experiments made it possible to select the optimum conditions for the reactions presented in the scheme.

For the construction of diaza-crown compounds by the proposed method one must have a sufficiently long ω-amino acid with a protected amino group and an activated COOH group.

The desired 13-aminotridecanoic acid derivatives were obtained by condensation of $N_{(6)}$-protected derivatives of 6-aminohexanoic acid with 6-aminohexanoic acid and its benzyl ester.

The methyl (I) and benzyl (II) esters of 6-aminohexanoic acid were synthesized in 95% and 98% yields, respectively. The reaction of tert-butyloxycarbonyl azide (Boc azide) with 6-aminohexanoic acid in the presence of magnesium oxide gave Boc-aminohexanoic acid (III) in high yield. Treatment of 6-aminohexanoic acid with benzyloxycarbonyl chloride (ZCl) under the conditions of the Schotten—Baumann reaction gives Z-aminohexanoic acid (IV) in 83% yield. Compound III was converted to N-hydroxysuccinimidyl ester V [by reaction with N-hydroxysuccinimide in the presence of N,N^1-dicyclohexylcarbodiimide (DCC)], the condensation of which with 6-aminohexanoic acid led to Boc-protected amino acid VII. An alternative pathway to VII included acylation of benzyl ester II by V and removal of the protective benzyl group by catalytic hydrogenolysis.

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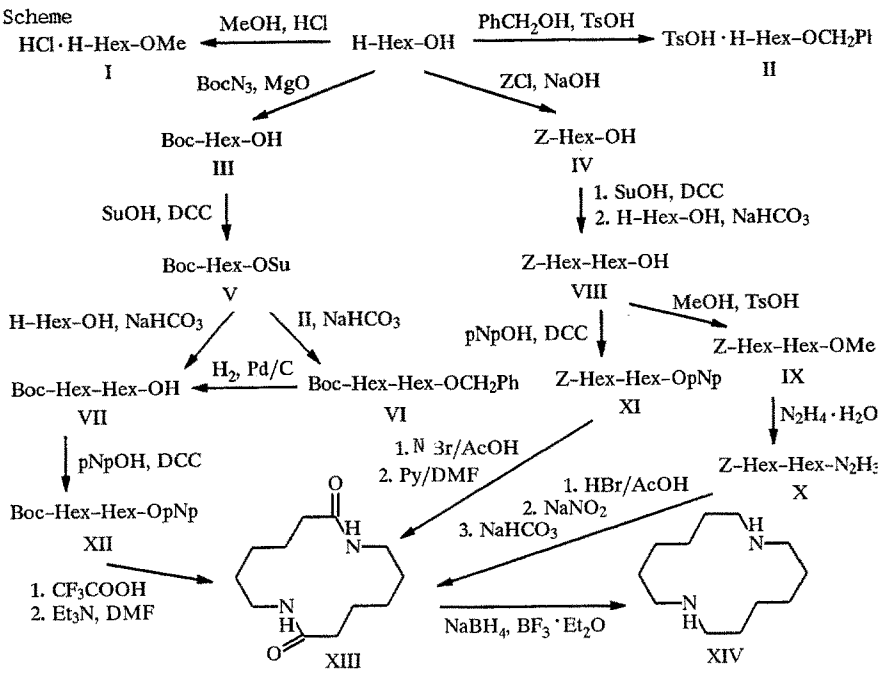


Hex = $NH(CH_2)_5C{=}O$; Boc = $(CH_3)_3OCO$; SuOH = N-hydroxysuccinimidyl Z = $C_6H_5CH_2OCO$;
DCC = C_6H_{11}-N=C=N-C_6H_{11}; pNpOH = 4-NO_2-C_6H_4-OH

Z-Aminohexanoic acid (IV) was converted to the N-hydroxysuccinimidyl ester (N-hydroxysuccinimide, DCC), which was used without isolation for the acylation of 6-aminohexanoic acid. The Z-protected amino acid VIII obtained in this way was converted to the methyl ester (IX). Attempts to obtain Z-aminohexanoic acid chloride (by reaction with PCl_5 in benzene or with $SOCl_2$ in the presence of DMF) and to subject it to reaction with 6-aminohexanoic acid under the conditions of the Schotten—Baumann reaction were unsuccessful in view of the low yields of VIII. Treatment of methyl ester IX with hydrazine hydrate led to hydrazide X in high yield.

p-Nitrophenyl ester XII was obtained from VII in ≈90% yield (pNpOH, DCC). Compound XI was also similarly obtained.

Treatment of XII with trifluoroacetic acid leads to quantitative splitting out of the Boc protective group. Attempts to cyclize the p-nitrophenyl ester trifluoroacetate obtained in this way in warm DMF in the presence of triethylamine lead to macrocyclic lactam XIII in only 9% yield.

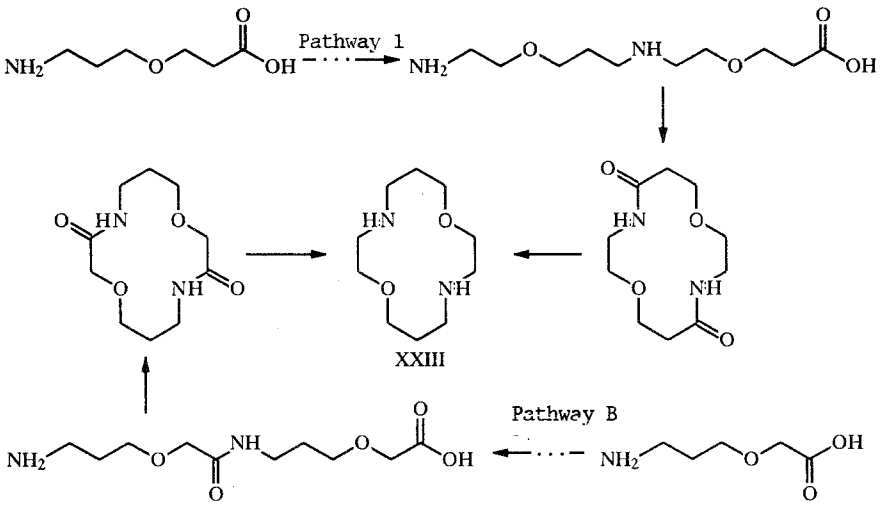
Splitting out of the protective group in XI was carried out with a solution of hydrogen bromide in acetic acid. An attempt to cyclize the p-nitrophenyl ester hydrobromide obtained in this way in DMF in the presence of pyridine leads to macrocyclic compound XIII in even lower yield — ≈7%.

Thus under the selected conditions the cyclization of p-nitrophenyl esters of ω-amino acids proceeds in low yields; this is evidently associated with the relatively slow rate at which the acylation takes place.

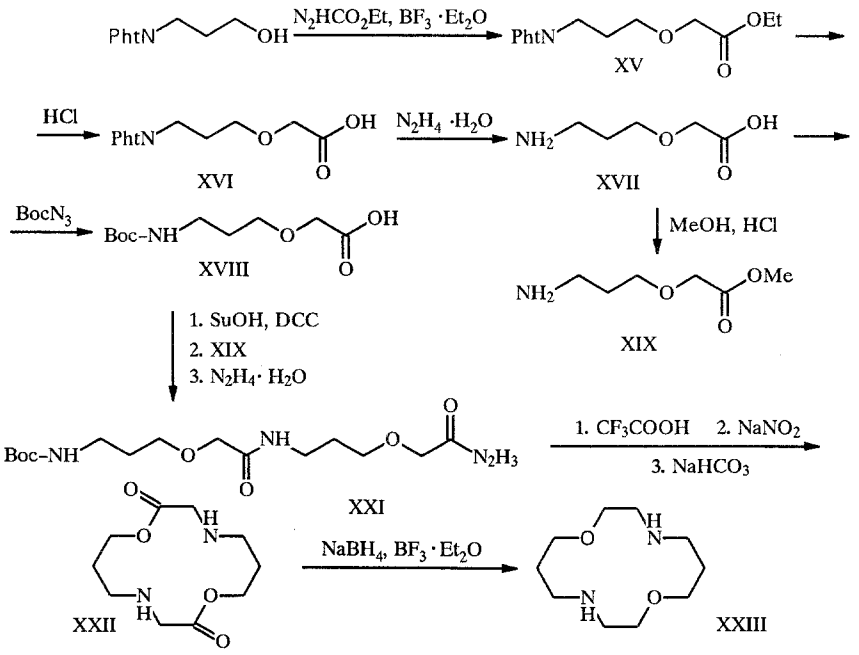
The azide method is frequently used in addition to the method of activated esters for the construction of an amide bond. In this case it proved to be more suitable. Thus splitting out of the protective group in hydrazide X with a solution of hydrogen bromide in acetic acid leads to the amino hydrazide hydrobromide, the diazotization of which with sodium nitrite solution gives the amino acyl azide hydrobromide. Cyclization of the latter in dilute aqueous sodium bicarbonate solution leads to macrocyclic compound XIII in high yield. The desired 1,8-diazacyclotetradecane (XIV) was obtained in 64% yield by the reduction of XIII with boron hydride.

The structures of the synthesized compounds were confirmed by data from the IR and PMR spectra. Compound XIV was also characterized by data from the ^{13}C NMR and mass spectra. Thus, within the framework of the given scheme, it was established that, first, the highest yields in the cyclization step are obtained when the azide rather than the activated ester is used. Second, a benzyloxycarbonyl group (Z) rather than a tert-butyloxycarbonyl group (Boc) is more suitable as protection for the $N_{(\omega)}$-amino group, since, despite the fact that the Z group is removed under somewhat more severe conditions than the Boc group and the fact that prolonged and thorough washing away of the amino acid salt from the resulting benzyl bromide is required after removal of the Z group, all of the Z-protected amino acids are solid substances that are easily separable and purifiable by recrystallization.

Oxa analogs of cyclam have heretofore been unknown. One of them — 1,8-diaza-4,11-dioxacyclotetradecane (XXIII) — was of particular interest to us. Within the framework of the developed general approach, one may contemplate two pathways to the synthesis of this compound:



6-Amino-4-oxahexanoic acid serves as the starting compound in pathway A. However, attempts to synthesize it were unsuccessful. The alkylation of 2-phthalimidoethanol with ethyl 3-bromopropionate in the presence of bases gives primarily a product of an elimination reaction — ethyl acrylate. Attempts to alkylate (under various conditions) ethyl 3-hydroxypropionate with 2-bromoethylphthalimide with the formation of a $C_{(5)}$—O ether bond were also unsuccessful. We therefore selected pathway B for the synthesis of XXIII.



Ethyl 6-phthalimido-3-oxahexanoate (XV) was obtained in good yield by the reaction of 3-phthalimidopropanol with diazoacetic ester in the presence of boron trifluoride etherate. Compound XV is formed in low yields (15-20%) when other alkylating agents — chloro- and bromoacetic acid esters — are used. The acidic hydrolysis of the ester group in XV gives the corresponding phthalimido acid XVI in good yield, treatment of which with excess hydrazine hydrate leads to the desired 6-

amino-3-oxahexanoic acid (XVII). The subsequent sequence of the reactions is similar to that described above for 6-aminohexanoic acid.

The cyclization of 13-amino-8-oxo-3,10-dioxa-7-azatridecanoyl azide in sodium bicarbonate solution gives macrocycle XXII in 70% yield, the reduction of which with boron hydride leads to the desired XXIII.

Absorption bands at 3140-3260 cm^{-1}, which are characteristic for the stretching vibrations of free and associated NH groups of secondary amides, and intense absorption bands of a carbonyl group at 1630-1640 cm^{-1} are present in the IR spectra of the synthesized macrocyclic compounds XIII and XXII. Bands of stretching vibrations of NH groups of secondary amines at 3040-3070 cm^{-1} are observed in the IR spectra of macrocyclic amines XIV and XXIII, and there are no absorption bands at 1630-1640 cm^{-1}.

An analysis of the ^{13}C and ^{1}H NMR spectra of XIV and XXIII confirms the sequence of the location of the groups of atoms in the chains of the synthesized macrocycles. Thus the weakest-field signals with chemical shifts of 72.5 and 66.3 ppm in the ^{13}C NMR spectra of XXIII were assigned to the carbon atoms bonded to an oxygen atom. The less electronegative nitrogen atom gives rise to smaller chemical shifts of the ^{13}C atoms bonded to it — 46.3-57.3 ppm (XIV and XXIII). The chemical shifts of the signals of the carbon atoms that are most remote from the heteroatoms (C_{3-6} and C_{10-13} in XIV and C_6 and C_{13} in XXIII) are located at strong field — 22.5-27.3 ppm. The relative intensities of the signals and their location in regions that are typical for analogous systems [3] confirm the structures of the synthesized XIV and XXIII.

The presence of molecular ions (M^+) with m/z 198 and 202 in the mass spectra of XIV and XXIII and the absence of molecular ions with greater masses provide evidence that the cyclization of protected ω-amino acids X, XII, and XXI under the selected conditions proceeds primarily intramolecularly.

Thus we have shown that the intramolecular cyclization of ω-amino acids is a convenient and preparative method for the synthesis of aza-crown compounds that makes it possible to synthesize macroheterocyclic compounds that are difficult to obtain by known methods.

EXPERIMENTAL

The IR spectra of solutions in $CHCl_3$ in 0.288-μ thick NaCl cuvettes or suspensions in mineral oil were recorded with a Specord IR-71 spectrometer. The PMR spectra were recorded with Tesla BS-467 (60 MHz) and Bruker HX-270 (270 MHz) spectrometers with tetramethylsilane (TMS) as the internal standard. The ^{13}C NMR spectra of solutions in $CDCl_3$ were obtained with an NKh-270 spectrometer. The mass spectra were obtained with an MKh-1303 spectrometer. Thin-layer chromatography was carried out on Silufol plates, while preparative chromatography was carried out on Brockmann activity II aluminum oxide.

Methyl 6-Aminohexanoate Hydrochloride (I). A 22-ml (0.31 mole() sample of thionyl chloride was added slowly dropwise at 0°C to a vigorously stirred suspension of 26.2 g (0.2 mole) of 6-aminohexanoic acid in 200 ml of dry methanol. At the end of the addition the reaction mixture was refluxed for 2 h on a water bath. It was then cooled, the solvent was evaporated to dryness in vacuo, and the crystals were washed with dry ether and dried in vacuo over potassium hydroxide to give 34.5 g (95%) of I with mp 116°C. PMR spectrum (D_2O, δ): 3.82 (s, 3H, OCH_3), 2.73-3.18 [m, 2H, $C_{(6)}H_2$], 2.17-2.57 [m, 2H, $C_{(2)}H_2$], 1.20-2.00 [m, 6H, $C_{(3-5)}H_2$].

Benzyl 6-Aminohexanoate Hydrotoluenesulfonate (II). A suspension of 10.0 g (76.3 mmole) of 6-aminohexanoic acid and 17.0 g (89.5 mmole) of p-toluenesulfonic acid monohydrate in a mixture of 34 ml of benzyl alcohol and 40 ml of benzene was refluxed with a Dean—Stark water separator for 2 h until water separation was complete (≈3 ml). The solution crystallized when it was cooled. The crystals were separated, washed with dry ether (3 × 100 ml), and dried in vacuo over potassium hydroxide to give 29.4 g (98%) of II with mp 105-106°C. PMR spectrum (D_2O, δ): 7.82 (d, 2H, J = 8 Hz, Ts), 7.20 (s, 5H, Ph), 7.10 (d, 2H, J = 8 Hz, Ts), 5.08 (s, 2H, CH_2O), 2.75-3.20 [m, 2H, $C_{(6)}H_2$], 2.20-2.60 [m, 2H, $C_{(2)}H_2$], 2.30 (s, 3H, CH_3), 1.20-2.00 [m, 6H, $C_{(3-5)}H_2$].

6-tert-Butyloxycarbonylaminohexanoic Acid (III). A solution of 20.1 g (0.14 mole) of tert-butyloxycarbonyl azide [4] in 150 ml of dioxane was added to a stirred suspension of 13.1 g (0.1 mole) of 6-aminohexanoic acid and 8.0 g (0.2 mole) of magnesium oxide in 120 ml of water, and the reaction mixture was stirred at 50°C for 26 h. The dioxane was then evaporated in vacuo, the residue was diluted with 100 ml of water, and the aqueous mixture was filtered. The precipitate was washed with 50 ml of water, and the combined filtrates were saturated with sodium chloride and citric acid and extracted with ethyl acetate (3 × 70 ml). The extract was dried with sodium sulfate, and the solvent was evaporated in vacuo to give a colorless oil that crystallized slowly in air to give 22.2 g (96%) of III with mp 48-49°C. PMR spectrum ($CDCl_3$, δ): 4.71

(broad m, 1H, NH), 2.90-3.28 [m, 2H, $C_{(6)}H_2$], 2.17-2.53 [m, 2H, $C_{(2)}H_2$], 1.25-1.75 [m, 6H, $C_{(3\text{-}5)}H_2$], 1.47 (s, 9H, tert-Bu).

6-Benzyloxycarbonylaminohexanoic Acid (IV). A 17.0-g (0.1 mole) sample of benzyloxycarbonyl chloride and 25 ml of 4 M sodium hydroxide solution were added dropwise simultaneously from two dropping funnels to a cooled (to 0°C) solution of 13.1 g (0.1 mole) of 6-aminohexanoic acid in 25 ml of 4 M sodium hydroxide solution. At the end of the addition the reaction mixture was stirred for 1 h at 0°C and for 3 h at 20°C, after which 30 ml of water was added, and the mixture was extracted with toluene (2 × 25 ml). The cooled aqueous layer was acidified with concentrated HCl, and the crystals were separated, washed on the filter with ice water, and dried in vacuo over potassium hydroxide to give 22.0 g (83%) of IV with mp 56°C. PMR spectrum* ($CDCl_3$, δ): 7.33 (s, 5H, Ph), 5.08 (s, 2H, CH_2O), 4.70 (broad m, 1H, NH), 3.16 [m, 2H, $C_{(6)}H_2$], 2.33 [m, 2H, $C_{(2)}H_2$], 1.63 [m, 2H, $C_{(5)}H_2$], 1.50 [m, 2H, $C_{(3)}H_2$], 1.37 [m, 2H, $C_{(4)}H_2$].

N-Hydroxysuccinimidyl 6-tert-Butyloxycarbonylaminohexanoate (V). A 13.6-g (66 mmole) sample of DCC was added at −20°C in a nitrogen atmosphere to a solution of 13.8 g (60 mmole) of III and 6.9 g (60 mmole) of N-hydroxysuccinimide in 85 ml of dry dimethoxyethane (DME), and the mixture was allowed to stand at 0°C for 20 h. The precipitate was then removed by filtration and washed on the filter with 40 ml of DME. The combined filtrates were evaporated to dryness, and the residue was recrystallized from ether—hexane (1:2) to give 10.8 g (55%) of V with mp 83°C.

Benzyl 13-tert-Butyloxycarbonylamino-8-oxo-7-azatridecanoate (VI). A 1.4-ml (10 mmole) sample of triethylamine was added to a stirred suspension of 3.93 g (10 mmole) of II in 50 ml of dry DME, and the mixture was stirred for 30 min and then treated with a solution of 3.28 g (10 mmole) of V in 20 ml of dry DME. The reaction mixture was stirred for 3 h, after which 70 ml of water was added. The solution was saturated with sodium chloride and citric acid and extracted with ethyl acetate (4 × 50 ml). The combined extracts were washed successively with 5% $NaHCO_3$ solution (2 × 100 ml), saturated NaCl solution (2 × 100 ml), 0.1 M HCl (2 × 100 ml), and again with saturated NaCl solution (2 × 100 ml) and dried with sodium sulfate. The solvent was evaporated in vacuo, and the residue was dried in vacuo to give 4.08 g (94%) of VI with mp 59°C. PMR spectrum* ($CDCl_3$, δ): 7.32 (s, 5H, Ph), 6.58 [broad s, 1H, $N_{(7)}H$], 5.09 (s, 2H, CH_2O), 4.67 (broad s, 1H, NH), 3.18 [m, 2H, $C_{(13)}H_2$], 3.06 [m, 2H, $C_{(6)}H_2$], 2.34 [t, 2H, J = 7.4 Hz, $C_{(9)}H_2$], 2.15 [t, 2H, J = 7.4 Hz, $C_{(2)}H_2$], 1.61 [m, 4H, $C_{(5,12)}H_2$], 1.43 [m, 4H, $C_{(3,10)}H_2$], 1.42 (s, 9H, tert-Bu), 1.33 [m, 4H, $C_{(4,11)}H_2$].

13-tert-Butyloxycarbonylamino-8-oxo-7-azatridecanoic Acid (VII). A. A 1.73-g (15 mmole) sample of sodium bicarbonate and a solution of 3.28 g (10 mmole) of V in 20 ml of DME were added to a stirred solution of 1.97 g (15 mmole) of 6-aminohexanoic acid in 15 ml of water, and the reaction mixture was stirred at room temperature. After 3 h, it was saturated with sodium chloride and citric acid and extracted with ethyl acetate (3 × 30 ml). The extract was dried with sodium sulfate, the solvent was evaporated, and the residue was dried in vacuo to give 3.27 g (95%) of VII with mp 68°C. PMR spectrum* ($CDCl_3$, δ): 10.08 (s, 1H, COOH), 6.61 [m, 1H, $N_{(7)}H$], 4.02 (m, 1H, NH), 3.21 [m, 2H, $C_{(13)}H_2$], 3.07 [m, 2H, $C_{(6)}H_2$], 2.29 [t, 2H, J = 7.4 Hz, $C_{(9)}H_2$], 2.19 [t, 2H, J = 7.4 Hz, $C_{(2)}H_2$], 1.62 [m, 4H, $C_{(5,12)}H_2$], 1.47 [m, 4H, $C_{(3,10)}H_2$], 1.43 (s, 9H, tert-Bu), 1.35 [m, 4H, $C_{(4,11)}H_2$].

B. A 0.5-g sample of 10% palladium on carbon and 0.5 ml of acetic acid were added to a solution of 2.5 g (5.76 mmole) of VI in 50 ml of methanol, and hydrogenation was carried out with hydrogen at atmospheric pressure with vigorous stirring. After 1 h, 130 ml of hydrogen was absorbed. The hydrogen residues were displaced with nitrogen, the catalyst was removed by filtration, the filtrate was evaporated, and the residue was dried in vacuo to give 1.98 g (quantitative yield) of VII.

13-Benzyloxycarbonylamino-8-oxo-7-azatridecanoic Acid (VIII). An 18.2-g (88 mmole) sample of DCC was added with stirring and cooling to 0°C to a solution of 21.2 g (80 mmole) of IV and 9.2 g (80 mmole) of N-hydroxysuccinimide in 150 ml of dry dioxane, and the mixture was allowed to stand for 24 h in a refrigerator at 0°C. The precipitate was then removed by filtration and washed with 30 ml of dioxane, and the combined filtrates were evaporated in vacuo at 20°C. The resulting colorless oil was dissolved in 200 ml of DME, and this solution was added with vigorous stirring to a solution of 13.1 g (0.1 mole) of 6-aminohexanoic acid and 8.4 g (0.1 mole) of $NaHCO_3$ in 160 ml of water. The reaction mixture was stirred at 20°C for 5 h and allowed to stand overnight. The next morning, 100 ml of water was added, and the mixture was acidified to pH 1 with concentrated HCl. The resulting precipitate was removed by filtration, washed with cold water (100 ml), and dried in vacuo over potassium hydroxide to give 26.3 g (87%) of VIII with mp 104-105°C. PMR spectrum* (DMSO-D_6, δ): 7.34 (s, 5H, Ph), 5.00 (s, 2H, CH_2O), 3.40 [m, 4H, $C_{(6,13)}H_2$], 2.33 [m, 2H, $C_{(2)}H_2$], 2.16 [m, 2H, $C_{(9)}H_2$], 1.23-1.56 [m, 12H, $C_{(3\text{-}5,10\text{-}12)}H_2$].

*270 MHz.

Methyl 13-Benzyloxycarbonylamino-8-oxo-7-azatridecanoate (IX). A solution of 3.44 g (9.1 mmole) of VIII and 0.2 g of p-toluenesulfonic acid in a mixture of 100 ml of dichloroethane and 10 ml of methanol was refluxed for 15 h, after which it was cooled, washed successively with water (50 ml), 5% Na_2CO_3 solution (2 × 50 ml), and water (50 ml), and dried with sodium sulfate. Removal of the solvent by distillation in vacuo gave 3.28 g (92%) of IX with mp 66°C. The melting point remained unchanged after recrystallization from 70% aqueous methanol. PMR spectrum ($CDCl_3$, δ): 7.27 (s, 5H, Ph), 5.77 (m, 1H, NH), 5.03 (s, 2H, CH_2O), 5.00 [m, 1H, $N_{(7)}H$], 3.57 (s, 3H, OCH_3), 3.13 [m, 4H, $C_{(6,13)}H_2$], 2.17 [m, 4H, $C_{(2,9)}H_2$], 1.17-1.93 [m, 12H, $C_{(3\text{-}5,10\text{-}12)}H_2$].

13-Benzyloxycarbonylamino-8-oxo-7-azatridecanoic Acid Hydrazide (X). A 2-ml sample of 85% hydrazine hydrate was added to a solution of 2.57 g (6.56 mmole) of IX in 10 ml of methanol, and the mixture was allowed to stand at 20°C for 24 h. Water (25 ml) was then added, and the mixture was heated until a homogeneous solution formed. The solution was cooled, and the resulting precipitate was separated, washed with ice water (5 ml), and dried in vacuo over P_2O_5 to give 2.39 g (93%) of X with mp 127°C.

p-Nitrophenyl 13-Benzyloxycarbonylamino-8-oxo-7-azatridecanoate (XI). A 3.66-g (26.5 mmole) sample of p-nitrophenol was added with stirring and cooling to 0°C to a solution of 8.29 g (21.9 mmole) of VIII in 100 ml of dry DMF, and 4.52 g (21.9 mmole) of DCC was then added after the p-nitrophenol had dissolved. The reaction mixture was stirred for 1 h at 0°C and for 2 h at 20°C, after which the DMF was removed by distillation in vacuo. Ethyl acetate (80 ml) was added to the residue, and the precipitate was removed by filtration and washed with 20 ml of ethyl acetate. The combined filtrates were washed with saturated sodium bicarbonate solution (5 × 50 ml) and dried with sodium sulfate, and the solvent was evaporated in vacuo. The residue was recrystallized from ethanol to give 9.83 g (90%) of XI with mp 57°C.

p-Nitrophenyl 13-tert-Butyloxycarbonylamino-8-oxo-7-azatridecanoate (XII). A 2.06-g (10 mmole) sample of DCC was added at 0°C to a stirred solution of 3.44 g (10 mmole) of VII and 1.67 g (12 mmole) of p-nitrophenol in 40 ml of dry ethyl acetate, after which the reaction mixture was stirred for 1 h at 0°C and for 2 h at 20°C. The precipitate was separated and washed with 20 ml of ethyl acetate, and the combined filtrates were washed with saturated $NaHCO_3$ solution (4 × 50 ml) and dried with sodium sulfate. The solvent was evaporated, and the residue was dried in vacuo to give 4.18 g (90%) of XII in the form of a yellow oil. PMR spectrum* ($CDCl_3$, δ): 8.15 (d, 2H, J = 8 Hz, Ar), 6.90 (d, 2H, J = 8 Hz, Ar), 6.40 [broad s, 1H, $N_{(7)}H$], 4.55 (m, 1H, NH), 3.19 [m, 2H, $C_{(13)}H_2$], 3.08 [m, 2H, $C_{(6)}H_2$], 2.35 [t, 2H, J = 7.5 Hz, $C_{(9)}H_2$], 2.25 [t, 2H, J = 7.5 Hz, $C_{(2)}H_2$], 1.62 [m, 4H, $C_{(5,12)}H_2$], 1.43 [m, 4H, $C_{(3,10)}H_2$], 1.41 (s, 9H, tert-Bu), 1.34 [m, 4H, $C_{(4,11)}H_2$].

1,8-Diazacyclotetradecane-2,9-dione (XIII). A. Cyclization of nitrophenyl ester XII. A solution of 2.8 g (6 mmole) of XII in 30 ml of trifluoroacetic acid was heated to 50°C and maintained at this temperature for 15 min, after which it was evaporated to dryness in vacuo. The residue was dissolved in 80 ml of dry DMF, and the solution was added in the course of 4 h to a heated (to 60°C) solution of 10 ml of triethylamine in 1 liter of dry DMF. The reaction mixture was stirred for another 4 h at 60°C, and the solvent was evaporated to dryness in vacuo. The residue was dissolved in 100 ml of chloroform and worked up as described below (example B). Chromatographic purification on aluminum oxide gave 0.12 g (8.8%) of XIII.

B. Cyclization of nitrophenyl ester XI. A 30-ml sample of a 33% solution of hydrogen bromide in acetic acid was added to a solution of 5.60 g (11.22 mmole) of XI in 30 ml of acetic acid, and the mixture was maintained for 2 h at 20°C, after which it was evaporated to dryness in vacuo. The residue was washed with dry ether (3 × 50 ml), the ether was decanted, and the residue was dissolved in 150 ml of DMF. This solution was added in the course of 6 h to a heated (to 60°C) solution of 15 ml of dry pyridine in 1 liter of dry DMF, and the reaction mixture was stirred at 60°C for another 4 h. The solvent was then removed by distillation in vacuo, the residue was dissolved in 200 ml of chloroform, and the solution was washed with 1 M NH_4OH until it was colorless and then with 1 M HCl (2 × 100 ml) and water (2 × 100 ml) and dried with sodium sulfate. After evaporation of the solvent, the residue was chromatographed on aluminum oxide by elution with chloroform to give a substance with R_f 0.53. This procedure gave 0.18 g (7.1%) of XIII.

C. Cyclization of X. A solution of 2.39 g (6.1 mmole) of X in 100 ml of a 33% solution of HBr in acetic acid was stirred at 20°C for 1 h, after which it was added dropwise to 100 ml of dry ether. The liberated oil was washed with dry ether (3 × 50 ml), the ether was decanted, and the oil was dissolved in 50 ml of water. A 6.1-ml sample of 1 M HCl was added to this solution, a solution of 0.42 g (6.1 mmole) of sodium nitrite in 4 ml of water was added with cooling, and the reaction mixture was stirred at 0°C for 15 min, and the cooled (to 0°C) solution was added in the course of 2 h to a solution of 8.0 g of sodium bicarbonate in 900 ml of water at 20°C. At the end of the addition the reaction mixture was stirred for another 4 h at 20°C and allowed to stand overnight. The next morning, the water was evaporated to dryness in vacuo, and the dry residue was extracted with chloroform (8 × 30 ml). The chloroform was removed by distillation, and the residue was

recrystallized from water to give 1.17 g (85%) of XIII with mp 280°C. IR spectrum ($CHCl_3$, cm^{-1}): 3260, 3150 (NH); 1630 (C=O). PMR spectrum ($CDCl_3$, δ): 3.25 (m, 4H, CH_2N), 2.20 (m, 4H, CH_2CO), 1.20-1.80 [m, 12H, $C_{(4\text{-}6,11\text{-}13)}H_2$].

1,8-Diazacyclotetradecane (XIV). A 2.6-ml sample of boron trifluoride etherate was added dropwise in the course of 40 min to a stirred suspension of 0.25 g (1.1 mmole) of XIII and 0.5 g (13.2 mmole) of sodium borohydride in 40 ml of dry THF. At the end of the addition the reaction mixture was refluxed for 4 h, after which it was cooled and poured into 100 ml of water. The aqueous mixture was acidified with 30 ml of concentrated HCl and stirred for 2 h, after which it was made alkaline to pH $\approx$10 with solid sodium hydroxide and extracted with ether (5 × 50 ml). The combined extracts were dried with Na_2SO_4, and the solvent was evaporated in vacuo to give 0.14 g (64%) of XIV in the form of a colorless oil that crystallized rapidly on standing to give a product with mp 68°C. IR spectrum ($CHCl_3$, cm^{-1}): 3070 (NH). PMR spectrum ($CDCl_3$, δ): 2.63 (m, 8H, CH_2N), 1.20-1.80 (m, 16H, CH_2). ^{13}C NMR spectrum ($CDCl_3$, δ relative to TMS): 46.3 [$C_{(2,7)}$], 27.3 [$C_{(3,6)}$], 22.5 [$C_{(4,5)}$]. M^+ 198. $C_{12}H_{26}N_2$. M^+_{calc} 198.

Ethyl 6-phthalimido-3-oxahexanoate (XV). A solution of diazoacetic ester* in 200 ml of methylene chloride was treated at 0°C with 37.5 g (0.183 mole) of 3-phthalimidopropanol,† and the mixture was stirred until the solid had dissolved completely. A 1.0-ml sample of boron trifluoride etherate was then added in three portions with monitoring of the disappearance of the 3-phthalimidopropanol by means of TLC [Silufol, toluene—acetone (4:1)], and the solution was washed with 2 M HCl (2 × 100 ml), 2% sodium carbonate solution (100 ml), and water (2 × 100 ml) and dried with sodium sulfate. After evaporation of the solvent, the residue was dissolved in chloroform and chromatographed on 250 g of silica gel L 40/250 to give 48.4 g (91%) of XV with mp 55-57°C. PMR spectrum ($CDCl_3$, δ): 7.67 (m, 4H, Ar), 4.11 [q, J = 7 Hz, 2H, CH_2(Et)], 4.00 [s, 2H, $C_{(2)}H_2$], 3.57 [t, 2H, J = 6.5 Hz, $C_{(6)}H_2$], 1.96 [quintet, 2H, J = 6.5 Hz, $C_{(5)}H_2$].

6-Phthalimido-3-oxahexanoic Acid (XVI). Water (450 ml) and 400 ml of concentrated HCl were added to a solution of 48.4 g (0.166 mole) of XV in 1 liter of acetone, and the mixture was refluxed for 5 h. It was then evaporated in vacuo to a volume of 250 ml and extracted with ethyl acetate (5 × 50 ml), and the combined extracts were washed with saturated sodium bicarbonate solution (5 × 100 ml). The aqueous phase was separated and acidified to pH 1 with concentrated HCl, and the resulting precipitate was separated, washed with ice water, and dried in vacuo over potassium hydroxide to give 32.5 g of XVI. The combined filtrates were extracted with ethyl acetate (2 × 100 ml), and the extract was dried with sodium sulfate. Removal of the solvent by distillation gave another 5.0 g (86%) of XVI with mp 51-52°C. PMR spectrum ($CDCl_3$, δ): 9.90 (s, 2H, COOH), 7.70 (m, 4H, Ar), 4.00 [s, 2H, $C_{(2)}H_2$], 3.73 [t, 2H, J = 6.5 Hz, $C_{(4)}H_2$], 3.53 [t, 2H, J = 6.5 Hz, $C_{(6)}H_2$], 1.93 [quintet, 2H, J = 6.5 Hz, $C_{(5)}H_2$].

6-Amino-3-oxahexanoic Acid (XVII) Hydrochloride. A 5.8-ml sample of 90% hydrazine hydrate was added to a solution of 27.0 g (102.7 mmole) of XVI in 300 ml of ethanol, and the mixture was refluxed for 6 h. The solvent was evaporated in vacuo, 213 ml of water and 36.5 ml of concentrated HCl were added to the residue, and the mixture was heated at 50°C for 30 min and cooled slowly. The precipitate was removed by filtration and washed on the filter with 2 M HCl (2 × 50 ml). The combined filtrates were evaporated to dryness, and the residue was dried in vacuo by heating on a boiling-water bath to give 17.0 g (98%) of XVII with mp 112°C (dec.). PMR spectrum (D_2O, δ): 4.15 [s, 2H, $C_{(2)}H_2$], 3.63 [t, 2H, J = 6.5 Hz, $C_{(4)}H_2$], 3.13 [broad t, 2H, J = 6.5 Hz, $C_{(6)}H_2$], 1.93 [quintet, 2H, J = 6.5 Hz, $C_{(5)}H_2$].

6-tert-Butyloxycarbonylamino-3-oxahexanoic Acid (XVIII). A solution of 14.0 g (98 mmole) of tert-butyloxycarbonyl azide in 120 ml of dioxane was added to a stirred solution of 12.5 g (73.7 mmole) of 6-amino-3-oxahexanoic acid hydrochloride and 9.0 g (0.225 mole) of magnesium oxide in 100 ml of water, and the mixture was maintained at 50°C for 10 h. The precipitate was removed by filtration and washed with water (50 ml), and the combined filtrates were saturated with sodium chloride and citric acid and extracted with ethyl acetate (3 × 100 ml). The extract was dried with sodium sulfate, and the solvent was removed by distillation in vacuo to give 14.6 g (85%) of XVIII in the form of a colorless oil. PMR spectrum (acetone-D_6, δ): 8.43 (broad s, 1H, COOH); 6.30 (m, 1H, NH); 4.05 [s, 2H, $C_{(2)}H_2$]; 3.63, 3.56 [dd, 2H, J = 6.5 Hz, $C_{(4)}H_2$]; 3.29, 3.11 [dd, 2H, J = 6.5 Hz, $C_{(6)}H_2$]; 1.36-2.00 [m, 2H, $C_{(5)}H_2$]; 1.45 (s, 9H, tert-Bu).

Methyl 6-Amino-3-oxahexanoate (XIX) Hydrochloride. A 3.0-ml sample of thionyl chloride was added dropwise with cooling to 0°C to a stirred suspension of 6.34 g (37.4 mmole) of XVII in 60 ml of dry methanol, after which the mixture was stirred at this temperature for another 15 min and then refluxed for 1.5 h. The solvent was evaporated in vacuo to give

*Obtained by the method in [5] from 46.8 g (0.335 mole) of glycine ethyl ester hydrochloride.

†Obtained by the method in [6]. The product had mp 75-76°C and was obtained in 72% yield.

6.86 g of XIX in the form of a hygroscopic colorless oil; the yield was virtually quantitative. PMR spectrum (D_2O, δ): 4.05 [s, 2H, $C_{(2)}H_2$], 3.57 (s, 3H, OCH_3), 3.50 [t, 2H, J = 6.5 Hz, $C_{(4)}H_2$], 3.30 [t, 2H, J = 6.5 Hz, $C_{(6)}H_2$], 1.77 [quintet, 2H, J = 6.5 Hz, $C_{(5)}H_2$].

Methyl 13-tert-Butyloxycarbonylamino-8-oxo-3,10-dioxa-7-azatridecanoate (XX). An 8.45-g (41 mmole) sample of DCC was added in portions at 0°C to a stirred solution of 8.86 g (38 mmole) of XVIII and 4.37 g (38 mmole) of N-hydroxysuccinimide in 80 ml of dry dimethoxyethane (DME), after which the mixture was stirred until the DCC had dissolved completely, and the solution was allowed to stand overnight at 0°C. The resulting precipitate was removed by filtration and washed on the filter with 20 ml of DME, and the combined filtrates were added at 20°C to a stirred suspension of 6.86 g (37.4 mmole) of XIX and 5.6 ml (40 mmole) of triethylamine in 80 ml of DME. The reaction mixture was stirred for 6 h at 20°C and then allowed to stand overnight. Water (100 ml) was added, and the reaction mixture was saturated with sodium chloride and extracted with ethyl acetate (4 × 80 ml). The extract was washed successively with 0.1 M HCl (2 × 200 ml), saturated sodium bicarbonate solution (2 × 200 ml), water (200 ml), and saturated sodium chloride solution (200 ml) and dried with sodium sulfate. The solvent was removed by distillation, and the residue was dried in vacuo at 50°C to give 10.83 g (80%) of XX in the form of a viscous colorless oil. PMR spectrum ($CDCl_3$, δ): 4.90 (m, 2H, NH), 4.08 [s, 2H, $C_{(9)}H_2$], 3.93 [s, 2H, $C_{(2)}H_2$], 3.75 (s, 3H, OCH_3), 3.10-3.80 [m, 8H, $C_{(4,6,11,13)}H_2$], 1.56-2.10 [m, 4H, $C_{(5,12)}H_2$], 1.47 (s, 9H, tert-Bu).

13-tert-Butyloxycarbonylamino-8-oxo-3,10-dioxa-7-azatridecanoic Acid Hydrazide (XXI). A 3.5-ml sample of 90% hydrazine hydrate was added to a solution of 5.68 g (15.7 mmole) of XX in 60 ml of ethanol, and the mixture was heated to 50°C and then allowed to stand overnight at 20°C. The solvent was removed by distillation, and the residue was dried in vacuo at 50°C to give 5.44 g (96%) of XXI with mp 117°C.

1,8-Dioxa-4,11-diazacyclotetradecane-3,10-dione (XXII). A stirred solution of 5.44 g (15 mmole) of XXI in 50 ml of trifluoroacetic acid was heated to 50°C, maintained at this temperature for 15 min, and evaporated in vacuo. The residue was dissolved in 50 ml of water, the solution was cooled to 0°C, and a solution of 1.1 g (16 mmole) of sodium nitrite in 8 ml of water was added. This solution was then added to a solution of 10.0 g of sodium bicarbonate in 900 ml of water at 20°C in the course of 4 h, after which the mixture was stirred at 20°C for another 4 h. The reaction mixture was evaporated to dryness in vacuo, and the residue was dried in vacuo and extracted with hot acetone (6 × 50 ml). The extract was evaporated to give 2.41 g (70%) of XXII with mp 200°C. IR spectrum (mineral oil, cm^{-1}): 3250, 3140 (NH); 1640 (C=O). PMR spectrum (acetone-D_6, δ): 4.18 [m, 4H, $C_{(7,14)}H_2$], 3.19 [s, 4H, $C_{(2,9)}H_2$], 3.20-3.83 [m, 4H, $C_{(5,12)}H_2$], 1.60-2.10 [m, 4H, $C_{(6,13)}H_2$].

1,8-Dioxa-4,11-diazacyclotetradecane (XXIII). This compound was obtained by the method described above for XIV from 1.2 g (5.22 mmole) of XXII, 2.38 g (62.6 mmole) of sodium borohydride, and 12.4 ml of boron trifluoride etherate in 100 ml of dry THF. This procedure was used to synthesize 0.7 g (66%) of XXIII with mp 135°C. IR spectrum ($CDCl_3$, cm^{-1}): 3040 (NH). PMR spectrum ($CDCl_3$, δ): 4.90 (broad s, 2H, NH), 3.53-3.90 (m, 8H, CH_2O), 2.70-3.30 (m, 8H, CH_2N), 1.70-2.20 [m, 4H, $C_{(6,13)}H_2$]. ^{13}C NMR spectrum ($CDCl_3$, δ relative to TMS): 72.5 [$C_{(2)}$], 66.3 [$C_{(7)}$], 57.3 [$C_{(3)}$], 53.3 [$C_{(5)}$], 24.0 [$C_{(6)}$]. M^+ 202. $C_{10}H_{22}N_2O_2$. M^+_{calc} 202.

LITERATURE CITED

1. A. A. Formanovskii and I. V. Mikhura, Summaries of Papers Presented at the 3rd All-Union Conference on the Chemistry and Biochemistry of Macrocyclic Compounds [in Russian], Part 1, Ivanovo (1988), p. 113.
2. Y. Okuno, K. Horita, O. Yonemitsu, K. Shibata, and R. H. Holm, *J. Chem. Soc., Perkin Trans.*, Part 1, No. 5, 1115 (1984).
3. L. A. Fedorov and A. N. Ermakov, *NMR Spectroscopy in Inorganic Analysis* [in Russian], Nauka, Moscow (1989), p. 123.
4. L. A. Carpino, *Accounts Chem. Res.*, **6**, 191 (1973).
5. K. Weygand and G. Hilgetag, *Experimental Methods in Organic Chemistry* [Russian translation], Khimiya, Moscow (1969), p. 549.
6. *Methods for Obtaining Chemical Reagents and Preparations* [in Russian], Vol. 26, All-Union Scientific-Research Institute of Chemical Reagents and Ultrapure Chemical Substances, Moscow (1974), p. 237.