Russian Journal of Bioorganic Chemistry, Vol. 31, No. 2, 2005, pp. 189–195. Translated from Bioorganicheskaya Khimiya, Vol. 31, No. 2, 2005, pp. 206–212.

New Oxaanalogues of Spermine

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Received May 25, 2004; in final form, September 28, 2004

Abstract—A new isosteric charge-deficient spermine analogue, 1,12-diamino-4,9-diaza-5-oxadodecan, and *O*-(7-amino-4-azaheptyl)oxime of 3-aminopropanal, a stable analogue of the Schiff base intermediate in the enzymatic oxidation of spermine, were synthesized. The possible use of these compounds for the inhibition of spermine oxidase is discussed.

Key words: oxaspermine, polyamine analogues, polyamines, spermine oxidase

INTRODUCTION

A selective control of activity of the enzymes involved in the metabolism of polyamines is widely used at studying the role of spermine and spermidine in the processes of growth and differentiation of cells.[2] These investigations are of a certain scientific and applied importance due to significance and a variety of cellular functions of polyamines and their increased content in tumor cells in comparison with that on normal cells [1, 2].

The activation of the enzymes of polyamine catabolism is the most effective way of the exhaustion of the intracellular pool of spermine and spermidine [3]. Therefore, in recent years, the study of these enzymes is one of important directions in the polyamine biochemistry.

The classical pathway of spermine degradation consists in its N^1-acetylation catalyzed by SSAT and the subsequent oxidation of the product by PAO (Scheme 1) [4]. A selective effectively acting nonreversible inhibitor N^1,N^4-bis(2,3-butadienyl)-1,4-diaminobutane (MDL-72.527, see the figure) is known for the well-known flavin-dependent PAO; it exhibits K_i 0.09 μM and $\tau_{1/2}$ 2.2 min toward to the isolated enzyme [5].

Recently, SMO has been found in animal cells; this is a new flavin-dependent enzyme that oxidizes Spm into Spd without the preliminary N^1-acetylation [6–11]. Therefore, the Spm degradation can proceed by two independent pathways (Scheme 1). Several SMO inhibitors are known; the best of them, *cis*-3,8,13,18,23,28,33,38,43,48-decaazapentacontene-25 (SL-11150, figure), has IC_{50} 10^{-7} M [8]. A similar flavin-dependent Spm oxidase also exists in plants, whereas 1,17-bis(guanidyl)-9-azaheptadecane (guazatine, figure) inhibits the enzyme from maize with K_i 7.5×10^{-9} M [12]. The X-ray study of the enzyme–inhibitor complex (E–I) showed that the inhibition efficiency is due to a firm noncovalent binding of this compound in the active site of enzyme [13].

The syntheses of two new compounds, 1,12-diamino-4,9-diaza-5-oxadodecane (**I**) (Scheme 2) and *O*-(7-amino-4-azaheptyl)oxime of 3-aminopropanal (**II**) (Scheme 3), are described in this communication; we suggest the use of these compounds for the SMO inhibition and the study of the mechanism of action of this enzyme.

RESULTS AND DISCUSSION

The enzymatic oxidation of Spm was shown to proceed through the intermediate formation of a Schiff base, hydrolyzed to 3-aminopropanal and Spd (Scheme 4) [10].

Here we describe the substitution of oxygen atom for the methylene group of Spm in position 5, which resulted in *N*,*O*-dialkylhydroxylamine (**I**), in order to obtain new potential inhibitors of SMO. Since oxa-Spm (**I**) is an isostere of Spm, one can expect that this compound will be a good competitive inhibitor of SMO. Oxygen atom in the fifth position of (**I**) decreases the basicity of the adjacent NH group (pK_a ~ 5.5) in comparison with Spm (pK_a of the NH group of 7.97 [14]), and, therefore, (**I**) exists in the form of trication at the

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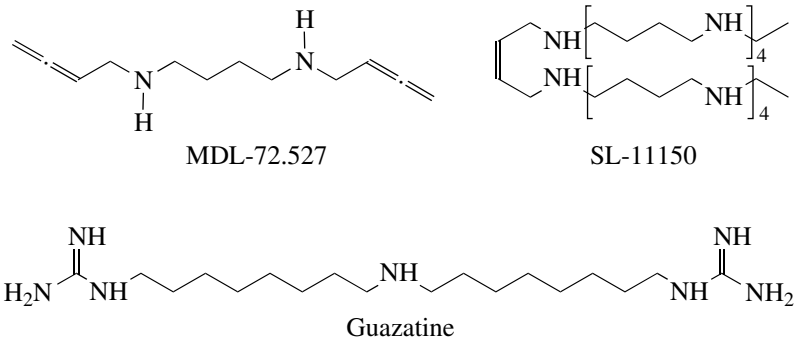
[2] Abbreviations: Bpoc, 2-(4-biphenyl)prop-2-yloxycarbonyl; Mts, mesitylenesulfonyl; Ns, 2-nitrobenzenesulfonyl; PAO, polyamine oxidase (EC 1.5.3.11); Pmc, 2,2,5,7,8-pentamethyl-6-chromanesulfonyl; Spd, spermidine (1,8-diamino-4-azaoctane); Spm, spermine (1,12-diamino-4,9-diazadodecane); SMO, spermine oxidase; and SSAT, spermine/spermidine N^1-acetyltransferase (EC 2.3.1.57).



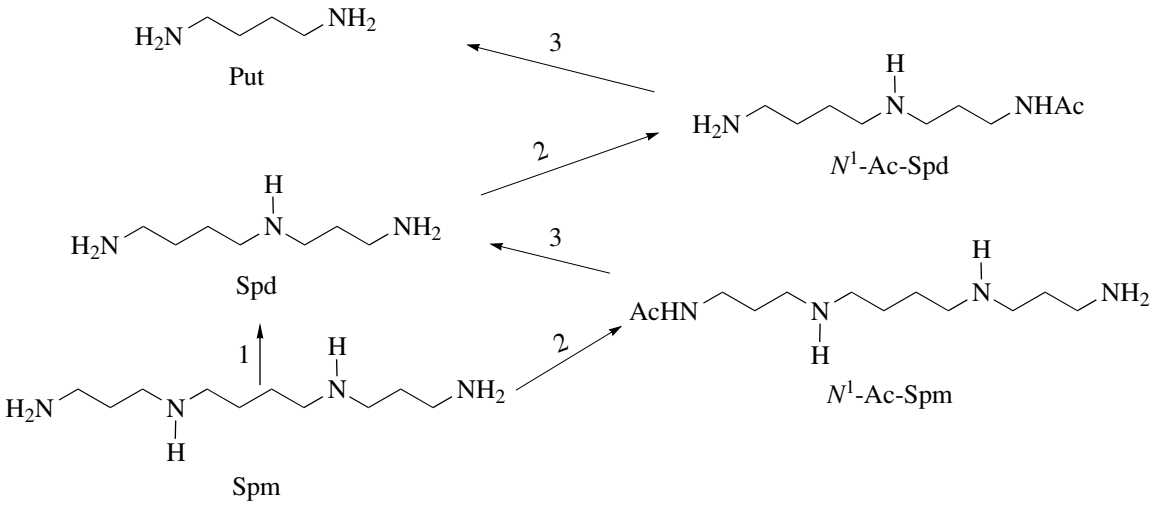
The SMO and PAO inhibitors

physiological pH value. Deprotonation of the secondary amino group of Spm that proceeds in the active site of SMO precedes its oxidation, and oxa-Spm (**I**) could hence be considered as a peculiar analogue of the tricharged form of Spm intermediately arising in the active site of SMO. The formation of covalent adduct with coenzyme, similar to that described for the oxidation of 1-cycloheptylmethyl-12-ethylnorspermine (CHENSpm) by the enzyme from maize [13], cannot be excluded at the enzymatic oxidation of (**I**). If (**I**) would be oxidized like Spm, oxime (**II**), a stable analogue of the Schiff base, should be formed in the active site of SMO *in situ* (Scheme 4). The obtaining of stable analogues of intermediates in enzymatic reactions is known to be the rather universal algorithm of the design of effective inhibitors of various enzymes (cf. the review [15]). Therefore, in this work, we describe also the preparation of oxime (**II**) along with the synthesis of (**I**). A comparative study of the interaction of these compounds with SMO would allow the obtaining of a new information on the mechanism of the SMO action and the methods of regulation of its activity.

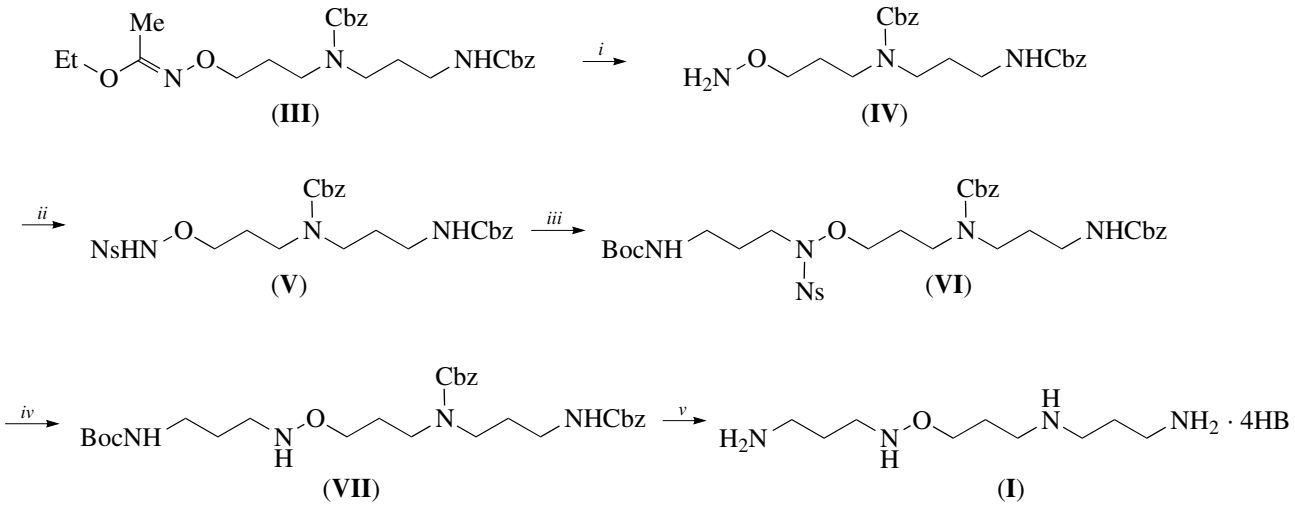
The general method of the synthesis of *O*,*N*-disubstituted hydroxylamines is the reduction of *O*-substituted oximes with complex borohydrides in a moderately acidic medium (pH ~3). The 1,8-diamino-4-aza-5-oxaoctane analogue of Spd was obtained by this method starting from 3-azidopropanal and 3-aminooxy-1-(*N*-benzyloxycarbonyl)aminopropane [16].

An alternative scheme of synthesis of 1,8-diamino-4-aza-5-oxaoctane consists in the condensation of Pmc derivative of *N*-(3-aminooxypropyl)phthalimide with 3-*N*-Bpoc-aminopropanol under the conditions of Mitsunobu reaction, followed by the removal of protective groups [17]. The preparation of the bisoxaanalogue of Spm, 1,12-diamino-4,9-diaza-5,8-dioxadodecane, is based on the interaction of 3-*N*-Bpoc-aminopropanol with bis-Pmc-derivative of 1,2-diaminooxyethane [17].

The pathway whose key stage was the alkylation of 2-nitrobenzenesulfonyl derivative of 1,4-bis(benzyloxycarbonyl)-7-aminooxy-4-aza-1-aminoheptane (**V**)

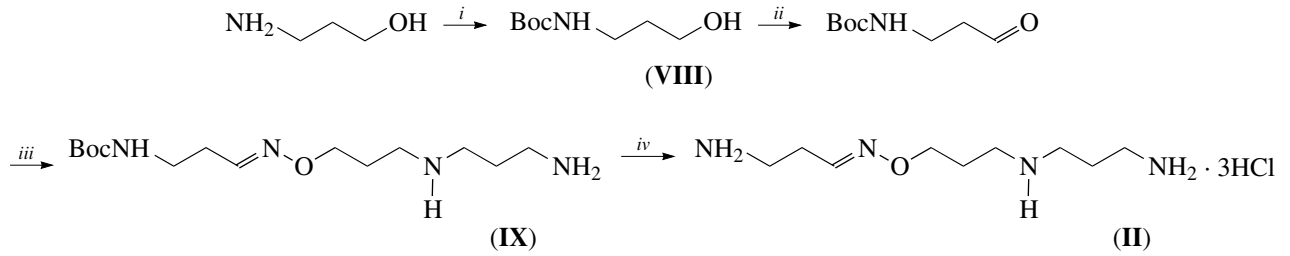


Scheme 1. Catabolism of polyamines [4]. *1*, SMO (spermine oxidase); *2*, SSAT (spermine/spermidine N^1-acetyltransferase); *3*, PAO (polyamine oxidase); and Put, putrescine.



i, HCl/*i*-PrOH/H_2O, *ii*, Ns-Cl/CH_2Cl_2, *iii*, $BocNH(CH_2)_3I/K_2CO_3$/DMF, *iv*, $PhSH/K_2CO_3$/DMF, *v*, HBr/AcOH.

Scheme 2. The scheme of synthesis of 1,12-diamino-4,9-diaza-5-oxadodecane (**I**).



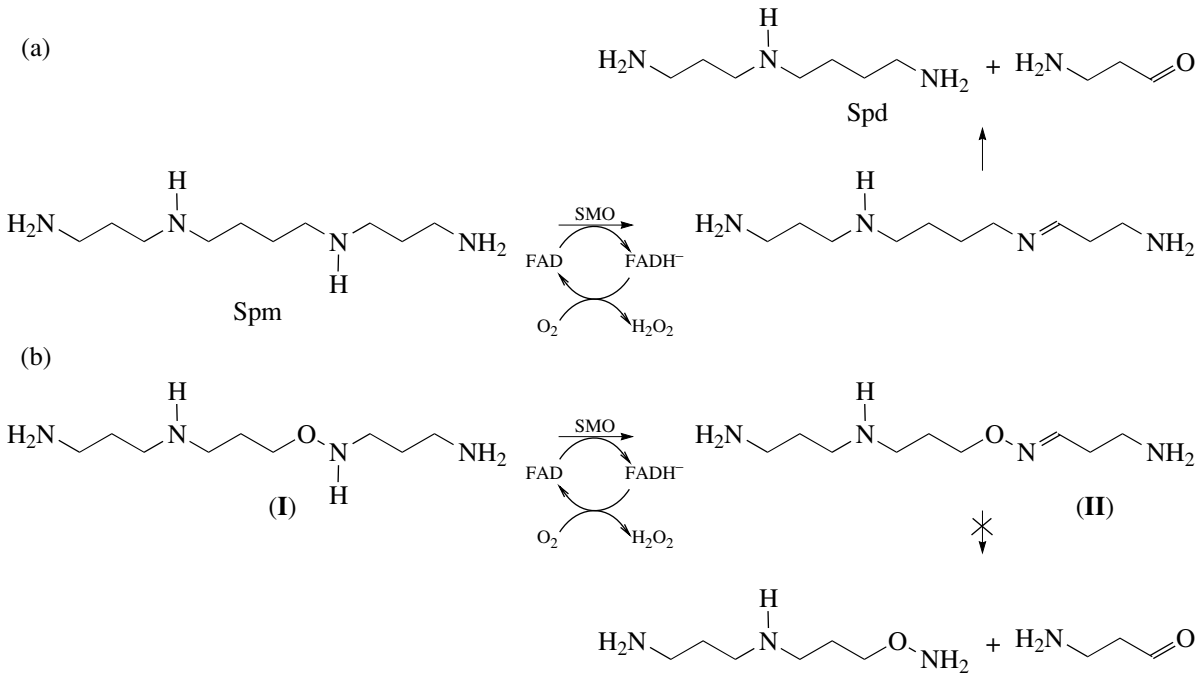
i, Boc_2O/THF, *ii*, $CrO_3 \cdot Py \cdot HCl/Al_2O_3/CH_2Cl_2$, *iii*, $H_2NO(CH_2)_3NH(CH_2)_3NH_2$/MeOH/$H_2O$, *iv*, HCl/MeOH.

Scheme 3. The scheme of synthesis of *O*-(7-amino-4-azaheptyl)oxime of 3-aminopropanal (**II**).

with 3-*N*-Boc-aminopropyl iodide was chosen for the obtaining of 1,12-diamino-4,9-diaza-5-oxadodecane (**I**) (Scheme 2).

The *gem*-bis-Mts-derivative of *O*-substituted hydroxylamine is known to be formed under the standard conditions of the synthesis of arenesulfonylamides with the use of triethylamine as a base and only at an excess mesitylenesulfonyl chloride (Mst-Cl) [18]. The interaction of 2-nitrobenzenesulfonyl chloride (Ns-Cl) with hydroxylamine (**IV**) proceeds ambiguously even at the equimolar ratio Ns-Cl : $RONH_2$: Et_3N. However, the reaction with 2.5–3.0-fold excess of *O*-substituted hydroxylamine in the absence of other bases leads to mono-NS-derivative (**V**) in yield of approximately 70%. The further conversions consisted in the alkylation of (**V**) with 3-*N*-Boc-aminopropyl iodide, selective denosylation of (**VI**) with thiophenol (like that described for amines [19, 20], and the removal of Cbz groups by HBr/AcOH, which resulted in the target tetrahydrobromide of 1,12-diamino-4,9-diaza-5-oxadodecane (**I**).

The synthesis of oxime (**II**) was achieved starting from 3-*N*-Boc-aminopropanol (**VIII**) (Scheme 3), which was oxidized at the first stage by pyridinium chlorochromate on neutral alumina to the corresponding aldehyde (Scheme 3). 3-(*N*-*tert*-Butyloxycarbonyl)aminopropanal was not isolated in pure state, but was directly subjected to the reaction with 1-amino-4-aza-7-aminooxyheptane. The resulting oxime (**IX**) was isolated by column chromatography on silica gel as a mixture of *syn*- and *anti*-isomers at the ratio of 40 : 60



Scheme 4. (a) Oxidative cleavage of spermine in animals [10], and (b) the presumed enzymatic oxidation of (**I**) to oxime (**II**).

(^{1}H NMR data). The subsequent removal of Boc-protective group by the treatment with HCl/MeOH at 0°C and recrystallization led to the desired (**II**) trihydrochloride; in this case, the ratio of *syn*- and *anti*-isomers remained almost unchanged (35 : 65).

Note that the reduction of (**II**) with $NaCNBH_3$ should lead to oxa-Spm (**I**), because the reduction of oximes is the general method of synthesis of *O*,*N*-dialkylhydroxylamine (see above).

EXPERIMENTAL

The reagents Cbz-Cl, Boc_2O, PhSH, absolute EtOH, and 1-amino-3-bromopropane were from Fluka; 2-nitrobenzenesulfonyl chloride and 3-aminopropanol, from Aldrich. 7-Aminooxy-4-aza-1-aminoheptane and 7-(1'-ethoxyethylidene)aminooxy-4-(*N*-benzyloxycarbonyl)aza-1-(*N*-benzyloxycarbonyl)aminoheptane were synthesized as described in [21], and pyridinium chlorochromate adsorbed on Al_2O_3 was synthesized as described in [22].

TLC was carried out on precoated Kieselgel 60 F_{254} plates (Merck) in the following systems: (A) 95 : 5 chloroform–methanol, (B) chloroform, (C) 4 : 2 : 1 : 2 *n*-butanol–acetic acid–pyridine–water, (D) 9 : 1 chloroform–methanol, and (E) 8 : 2 dioxane–25% ammonia. Substances were detected on the chromatograms by their absorption of UV light and by the color reaction with ninhydrin; the aminooxy compounds, in the form of fluorescent oximes of pyridoxal-5'-phosphate. Column chromatography was carried out on Kieselgel (40–63 μm, Merck), elution systems being specified in text.

NMR spectra were registered on a Bruker Avance 500 DRX instrument (Germany) with the working frequency of 500.1 MHz for ^{1}H and 125.8 MHz for ^{13}C nuclei. Tetramethylsilane was used as an internal standard in $CDCl_3$ and CD_3OD solutions and sodium salt of 3-trimethylsilyl-1-propanesulfonic acid in D_2O. Chemical shifts are given in ppm, and spin–spin coupling constants in Hz.

7-Aminooxy-4-(*N*-benzyloxycarbonyl)aza-1-(*N*-benzyloxycarbonyl)aminoheptane (IV). Concentrate HCl (1.5 ml) was added to a solution of (**III**) (4.7 g, 9.73 mmol) in isopropanol (10 ml), the solution was kept for 10 min at room temperature and evaporated in a vacuum to dryness. The residue was dissolved in water (5 ml), 10 M NaOH (1.5 ml) was added, and extracted with chloroform (3 × 5 ml). The extract was washed with a saturated solution of NaCl (2 × 2 ml), dried with $MgSO_4$, and evaporated in a vacuum to dryness. The residue was dissolved in chloroform (6 ml) and purified by column chromatography on silica gel (60 g), successively eluting with chloroform and 97 : 3 chloroform–methanol. The target (**IV**) was dried in a vacuum over P_2O_5; viscous oil; yield 2.71 g (73%); R_f 0.37 (A); ^{1}H NMR ($CDCl_3$): 7.4–7.2 (10 H, m, Ph); 5.12 (2 H, s, CH_2Ph), 5.08 (2 H, s, CH_2Ph), 3.77 (2 H, m, $H_2NOC\underline{H}_2$), 3.46 (2 H, m, $H_2NOCH_2CH_2C\underline{H}_2N$), 3.35–3.08 [4 H, m, $NC\underline{H}_2(CH_2)_2NHCbz$ +

$N(CH_2)_2C\underline{H}_2NHCbz]$, and 1.65–1.38 (4 H, m, $H_2NOCH_2C\underline{H}_2CH_2N + NCH_2C\underline{H}_2CH_2NHCbz$).

7-(*N*-2-Nitrobenzenesulfonyl)aminooxy-4-(*N*-benzyloxycarbonyl)aza-1-(*N*-benzyloxycarbonyl)aminoheptane (V). A solution of Ns-Cl (0.48 g, 2.2 mmol) in dichloromethane (6.5 ml) was added to a solution of (**IV**) (2.71 g, 6.5 mmol) in dichloromethane (8 ml). The reaction mixture was kept for 24 h at room temperature and evaporated in a vacuum to dryness. The residue was dissolved in 99 : 1 chloroform–methanol mixture (6 ml) and purified on a silica gel column (60 g) eluted with 99 : 1 chloroform–methanol. The target (**V**) was dried in a vacuum over P_2O_5 to give a viscous oil; yield 1.3 g (65% from Ns-Cl); R_f 0.57 (A); ^{1}H NMR ($CDCl_3$): 8.18 (1 H, m, Ns), 7.99 (1 H, m, Ns), 7.85 (1 H, m, Ns), 7.74 (1 H, m, Ns), 7.36–7.26 (10 H, m, Ph), 5.60 (1 H, s, HNO), 5.12 (2 H, s, CH_2Ph), 5.08 (2 H, s, CH_2Ph), 4.04 (2 H, m, $NsHNOC\underline{H}_2$), 3.30–3.28 (4 H, m, $H_2NOCH_2CH_2C\underline{H}_2N + NC\underline{H}_2(CH_2)_2NHCbz$), 3.13 (2 H, m, $N(CH_2)_2C\underline{H}_2NHCbz$), and 1.88–1.67 (4 H, m, $NsHNOCH_2C\underline{H}_2CH_2N + NCH_2C\underline{H}_2CH_2NHCbz$).

1-(*N*-*tert*-Butyloxycarbonyl)amino-4-aza-5-oxa-9-(*N*-benzyloxycarbonyl)aza-12-(*N*-benzyloxycarbonyl)aminododecane (VII). A cooled to +4°C solution of 3-bromo-1-aminopropane hydrobromide (5.5 g, 25 mmol) in water (7 ml) was mixed with 10 M NaOH (2.5 ml), dioxane (20 ml) and a solution of Boc_2O (6 g, 28 mmol) in dioxane (10 ml). The reaction mixture was stirred for 16 h at room temperature, evaporated to dryness in a vacuum, and the residue was dissolved in chloroform. The solution was successively washed with water (2 × 10 ml), 10% citric acid (2 × 10 ml), and water (3 × 10 ml), dried with $MgSO_4$, and evaporated to dryness in a vacuum. The residue was dissolved in acetone (20 ml), NaI (4.1 g, 27.2 mmol) was added, and the mixture was stirred for 18 h at room temperature. The precipitate was separated, the filtrate was evaporated to dryness in a vacuum, and the residue was dissolved in chloroform. The solution was washed with water (2 × 2 ml), dried with $MgSO_4$, and evaporated, and the residue was dried in a vacuum at +4°C over P_2O_5 to give 1-(*N*-*tert*-butyloxycarbonyl)amino-3-iodopropane in the form of a viscous slowly solidifying yellowish oil; yield 5.35 g (83%). A part of the semicrystalline product was triturated with a small quantity of hexane and kept overnight at +4°C; the solid was separated, washed with cold hexane, dried in a vacuum over paraffin and P_2O_5, and obtained colorless crystals of $BocNH(CH_2)_3I$; R_f 0.36 (B); mp 41–42°C; ^{1}H NMR (CD_3OD): 4.58 (1 H, br. s, NH), 3.26 (2 H, m, $NHC\underline{H}_2$), 3.16 (2 H, t, *J* 6.5, CH_2I), 2.06–1.98 (2 H, m, $CH_2C\underline{H}_2CH_2$), and 1.48 [9 H, s, $C(CH_3)_3$].

A mixture of (**V**) (1.3 g, 2.2 mmol), K_2CO_3 (1.19 g, 8.64 mmol), and **$BocNH(CH_2)_3I$** (0.8 g, 2.8 mmol) was stirred in DMF (10 ml) for 24 h at room temperature; the residue was separated; and the filtrate was evaporated in a vacuum to dryness. The residue was dissolved in chloroform, successively washed with water (2 × 5 ml) and a saturated solution of NaCl (2 × 5 ml), and dried with $MgSO_4$. The solution was evaporated in a vacuum to dryness, and the raw 1-(*N*-*tert*-butyloxycarbonyl)amino-4-(*N*-2-nitrobenzenesulfonyl)aza-5-oxa-9-(*N*-benzyloxycarbonyl)aza-12-(*N*-benzyloxycarbonyl)aminododecane (**VI**) was dissolved in DMF (30 ml). The solution was mixed with K_2CO_3 (1.2 g, 8.72 mmol) and PhSH (0.27 ml, 2.6 mmol) and stirred for 4 h at room temperature. The reaction mixture was evaporated to dryness in a vacuum, the residue was suspended in chloroform, and the precipitate was separated by centrifugation and washed with a small quantity of chloroform. The combined organic solutions were successively washed with water (5 ml), 10% citric acid (2 × 10 ml), 1 M $NaHCO_3$ (2 × 10 ml), and water (10 ml) and evaporated in a vacuum. The residue was dissolved in 100 : 1 chloroform–methanol mixture (6 ml) and purified by a chromatography on a silica gel column (60 g), eluted with 100 : 1 chloroform–methanol mixture to get (**VII**) as a viscous oil dried in a vacuum over P_2O_5; yield 0.58 g (46%); R_f 0.37 (A); ^{1}H NMR ($CDCl_3$): 7.36–7.26 (10 H, m, Ph), 5.12 (2 H, s, CH_2Ph), 5.09 (2 H, s, CH_2Ph), 3.62 (2 H, m, $HNOC\underline{H}_2(CH_2)_2NCbz$), 3.34–3.28 $C\underline{H}_2N(Cbz)C\underline{H}_2$); 3.23–3.11 (4 H, m, $BocNHC\underline{H}_2 + C\underline{H}_2NHCbz$), 2.86 $BocNH(CH_2)_2C\underline{H}_2NHO$); 1.78–1.60 (6 H, m, $BocNHCH_2C\underline{H}_2CH_2NHO + HNOCH_2C\underline{H}_2CH_2N + NCH_2C\underline{H}_2CH_2NHCbz$), and 1.41 [9 H, s, $C(CH_3)_3$).

1,12-Diamino-4,9-diaza-5-oxadodecane tetrahydrobromide (I). A 32.3% solution of HBr in AcOH (3 ml) was added to a solution of (**VII**) (0.58 g, 1.01 mmol) in AcOH (5 ml). The mixture was kept at room temperature until the evolution of CO_2 ceased. The precipitated solid was separated, washed with diethyl ether, and dried in a vacuum over P_2O_5/KOH to give (**I**); yield 0.36 g (69%); R_f 0.27 (B); mp 169–171°C (decomp.); ^{1}H NMR (D_2O): 4.11 (2 H, t, *J* 6.0, $HNOC\underline{H}_2$), 3.31 (2 H, t, *J* 7.6, $OHNC\underline{H}_2CH_2CH_2NH_2$), 3.17 *J* 7.9, $HNO(CH_2)_2C\underline{H}_2NH_2$); 3.14 *J* 8.0, $CH_2HN(CH_2)_2C\underline{H}_2NH_2$); 3.08 (2 H, t, *J* 7.4, $HNOCH_2CH_2C\underline{H}_2$), 3.07 [2 H, t, *J* 7.4, $CH_2HNC\underline{H}_2(CH_2)_2NH_2$); and 2.10–2.01 (6 H, m, $OHNCH_2C\underline{H}_2CH_2NH_2 + HNOCH_2C\underline{H}_2 + CH_2HNCH_2C\underline{H}_2CH_2NH_2$); ^{13}C NMR ($D_2O$): 73.83 (t, HNOCH2), 49.84 (t, $OHN\underline{C}H_2CH_2CH_2NH_2$), 47.79 (t, $HNOCH_2CH_2\underline{C}H_2$), 47.62 [t, $CH_2HN\underline{C}H_2(CH_2)_2NH_2$], 40.09 [t, $HNO(CH_2)_2\underline{C}H_2NH_2$], 39.52 [t, $CH_2HN(CH_2)_2\underline{C}H_2NH_2$], 27.48 (t, $HNOCH_2\underline{C}H_2$), 26.73 (t, $CH_2HNCH_2\underline{C}H_2CH_2NH_2$), and 25.56 (t, $OHNCH_2\underline{C}H_2CH_2NH_2$).

Found, %: C 20.51, H 5.28, N 10.50. $C_9H_{28}Br_4N_4O$. Calc., %: C 20.47, H 5.35, N 10.61.

3-(*N*-*tert*-Butyloxycarbonyl)aminopropanol (VIII). A solution of Boc_2O (1.5 g, 7 mmol) in THF (7 ml) was added to a solution of 3-aminopropanol (0.5 g, 7 mmol)

in THF (7 ml). The mixture was kept for 12 h at room temperature and evaporated in a vacuum to dryness. The residue was dissolved in chloroform; the solution was successively washed with 10% citric acid (2 × 5 ml), 1 M $NaHCO_3$ (2 × 5 ml), and water (5 ml); and was evaporated in a vacuum to dryness. The residue was dried in a vacuum over P_2O_5, to get (**VIII**) as a viscous oil; yield 1 g (82%); R_f 0.5 (D); ^{1}H NMR ($CDCl_3$): 4.82 (1 H, s, NH), 3.65 (2 H, m, $C\underline{H}_2OH$), 3.27 (2 H, m, $NHC\underline{H}_2$), 3.08 (1 H, s, OH), 1.65 (2 H, m, $C\underline{H}_2CH_2OH$), and 1.43 [9 H, s, $C(CH_3)_3$].

***O*-(7-Amino-4-aza)heptyloxime of 3-(*N-tert*-butyloxycarbonyl)aminopropanal (IX).** Pyridinium chlorochromate on neutral Al_2O_3 (7 g) was added to a solution of (**VIII**) (0.7 g, 4 mmol) in anhydrous benzene (40 ml). The mixture was stirred for 4 h at 20°C, the precipitate was separated, and the filtrate was evaporated in a vacuum to dryness. The residue was dissolved in methanol (5 ml) and treated with a neutral solution of 7-aminooxy-4-aza-1-aminoheptane trihydrochloride (0.256 g, 1 mmol) in 50% methanol (10 ml). The reaction mixture was stirred for 2 h at room temperature, evaporated to dryness in a vacuum, and the residue was dissolved in 95 : 5 dioxane–25% ammonia (6 ml). The purification on a silica gel column (60 g) successively eluted with 95 : 5 dioxane–25% ammonia and 8 : 2 dioxane–25% ammonia gave, after drying the target fraction in a vacuum over P_2O_5, 0.2 g (66% from 7-aminooxy-4-aza-1-aminoheptane trihydrochloride) of (**IX**) as a viscous oil; R_f 0.5 (E). ^{1}H NMR of isomer I ($CDCl_3$): 7.38 (1 H, t, *J* 5.4, $NHCH_2CH_2C\underline{H}$=NO), 4.09 (2 H, t, *J* 6.2, $NOC\underline{H}_2CH_2CH_2NH$), 3.32 (2 H, br. m, $NHC\underline{H}_2CH_2CH$=NO), 2.79 (2 H, t, *J* 6.3, $NHCH_2CH_2C\underline{H}_2NH_2$), 2.70 [4 H, m, $NHC\underline{H}_2(CH_2)_2NH_2$ + $NO(CH_2)_2C\underline{H}_2NH$], 2.37 (2 H, dt, *J* 5.9, $NHCH_2C\underline{H}_2CH$=NO), 1.83 (2 H, m, $NOCH_2C\underline{H}_2CH_2NH$), 1.66 (2 H, m, $NHCH_2C\underline{H}_2CH_2NH_2$), and 1.44 [9 H, s, $C(CH_3)_3$]; isomer II: ^{1}H NMR ($CDCl_3$): 6.69 (1 H, t, *J* 5.5, $NHCH_2CH_2C\underline{H}$=NO), 4.14 (2 H, t, *J* 6.1, $NOC\underline{H}_2CH_2CH_2NH$), 3.28 (2 H, br. m, $NHC\underline{H}_2CH_2CH$=NO), 2.51 (2 H, dt, *J* 5.9, $NHCH_2C\underline{H}_2CH$=NO), and 1.86 (2 H, m, $NOCH_2C\underline{H}_2CH_2NH$); chemical shifts of other protons coincide with those of isomer I. The isomer I/isomer II ratio was 60 : 40.

***O*-(7-Amino-4-azaheptyl)oxime of 3-aminopropanal trihydrochloride (II).** A solution of (**IX**) (0.15 g, 0.5 mmol) in absolute methanol (5 ml) cooled to 0°C was treated with 4 M HCl/MeOH (5 ml) and kept overnight at 4°C. The reaction mixture was evaporated to dryness in a vacuum, and the residue was coevaporated with MeOH, recrystallized from MeOH–EtOH, and dried in a vacuum over P_2O_5/KOH. Crystalline (**II**) was obtained; yield 0.106 g (68%); R_f 0.1 (E); mp 193–194°C (decomp.); isomer I: ^{1}H NMR (D_2O): 7.59 (1 H, t, *J* 5.3, CH=NO), 4.18 (2 H, t, *J* 6.0, $NOCH_2$), 3.26 (2 H, t, *J* 7.0, $NH_2C\underline{H}_2CH_2CH$=NO), 3.22–3.16 [4 H, m, $NHC\underline{H}_2(CH_2)_2NH_2$ + $NO(CH_2)_2C\underline{H}_2NH$], 3.12 (2 H, t, *J* 5.7, $NHCH_2CH_2C\underline{H}_2NH_2$), 2.65 (2 H, dt, *J* 7.0, $NH_2CH_2C\underline{H}_2CH$=NO), and 2.15–2.04 (4 H, m, $NHCH_2C\underline{H}_2CH_2NH_2$ + $NOCH_2C\underline{H}_2CH_2NH$); ^{13}C NMR ($D_2O$): 152.58 (d, N=CH), 73.24 (t, CH_2O), 48.10 [t, $\underline{C}H_2(CH_2)_2O$], 47.48 [t, $NH_2(CH_2)_2\underline{C}H_2$], 39.43 [t, $NH_2\underline{C}H_2(CH_2)_2$], 39.10 (t, $NH_2\underline{C}H_2CH_2CH$=N), 29.86 (t, $\underline{C}H_2CH$=N), 28.04 (t, $\underline{C}H_2CH_2O$), and 26.57 (t, $NH_2CH_2\underline{C}H_2CH_2$); isomer II: ^{1}H NMR (D_2O): 6.96 (1 H, t, *J* 5.5, CH=NO), 4.23 (2 H, t, *J* 6.0, $NOCH_2$), 3.24 (2 H, t, *J* 7.3, $NH_2C\underline{H}_2CH_2CH$=NO), and 2.77 (2 H, dt, *J* 7.3, $NH_2CH_2C\underline{H}_2CH$=NO); ^{13}C NMR ($D_2O$): 151.95 (d, N=CH), 73.34 (t, CH_2O)), 47.96 [t, $\underline{C}H_2(CH_2)_2O$], 47.45 [t, $NH_2(CH_2)_2\underline{C}H_2$]; 39.14 (o, $NH_2\underline{C}H_2CH_2CH$=N); 28.26 (t, $\underline{C}H_2CH_2O$), 26.68 (t, $\underline{C}H_2CH$=N), and 26.60 (t, $NH_2CH_2\underline{C}H_2CH_2$); chemical shifts of other nuclei coincide with those of isomer I. The isomer I/isomer II ratio was 65 : 35.

Found, %: C 34.84, H 8.11, N 17.54. $C_9H_{25}Cl_3N_4O$. Calc., %: C 34.68, H 8.08, N 17.98.

ACKNOWLEDGMENTS

This work was supported by the Russian Foundation of basic Research (project no. 03-04-49080) and by the Academy of Sciences of Finland.

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