SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF *MYO*-INOSITOL DERIVATIVES WITH NICOTINIC AND γ-AMINOBUTYRIC ACIDS

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One possible approach to the creation of potential drugs is the design and synthesis of new compounds by conjugating two or more substances with compatible pharmacological activities. This conjugation may result in decreasing the undesirable side effects and increasing the useful pharmacokinetic properties of the components. In particular, conjugates may exhibit prolonged activity, better permeability with respect to biological membranes, and directed transport to a damaged organ. A promising component for these conjugates is *myo*-inositol (MI) with a molecule containing six hydroxy groups, which provides the possibility for the regioselective attachment of pharmacologically active compounds to MI in various proportions. As is known, MI is the main component of phosphatidylinositols, which are characterized by a high rate of metabolism in some organs and tissues [1].

Nicotinic acid (NA) possesses hypolipidemic properties and is applied in the therapy of atherosclerosis [2]. However, the treatment implies administration of a large dose of this compound, which leads to certain side effects [3]. Attempts to reduce the side effects of NA led to the investigation of NA esters with polyatomic alcohols [4]. Among these, valuable therapeutic properties were reported for 1,2,3,4,5,6-hexa-O-nicotinoyl-MI (I) (hexopal, hexanicite) [5], whose mechanism of action *in vivo* involves a gradual hydrolysis to the corresponding penta-, tetra-, tri-, di-, and mononicotinates of MI, accompanied by sequential liberation of free NA [6]. The efficiency of drugs was related to the formation of more hydrophilic intermediate nicotinates of MI [5]. In this connection, it was of interest to synthesize and characterize these partly acylated MI derivatives having various structures. Earlier [7] we described the synthesis and some properties of compound I and 1,4,5,6-tetra-O-nicotinoyl-MI (IIa) [7]. Below we report on the synthesis of 1,4-di-(IIIa), and 1,3,5-tri-O-nicotinoyl-MI (IV) and present the results of studying the antisclerotic activity of these esters.

For the wide therapeutic use of γ-aminobutyric acid (GABA), which is a very important mediator of central nervous system inhibition [8], it is necessary to provide carriers that would help GABA to cross the blood-brain barrier. A large number of GABA derivatives have been synthesized for the purpose [9]. In this work we present data on the synthesis and pharmacological activity of 1,4-di-(IIIb), and 1,3,5,6-tetra-O-(γ-aminobutanoyl)-MI (IIb). Thus, the GABA carriers are represented by MI molecules capable of efficiently incorporating into various lipid structures *in vivo*.

The known methods of synthesis used in the chemistry of *myo*-inositol [1] allow us, in principle, to obtain MI derivatives with a desired structure, containing residues of two or more pharmacologically active substances. As is known, mechanical mixtures of MI derivatives (e.g., hexanicotinate I and MI hexasulfate) with a number of drug preparations either lead to synergism in the therapeutic action or eliminate side effects [10, 11]. It was therefore of interest to synthesize a MI derivative containing NA and GABA residues in the same molecule: 1,2-di-(γ-aminobutanoyl)-3,4,5,6-tetra-O-nicotinoyl-MI (V). This choice of components was inspired, in particular, by the successful clinical use of a cerebrovascular and nootropic drug Picamilon representing N-nicotinoyl-GABA [12].

The nicotinoyl derivatives IIIa and IV were obtained by exhaustive acylation of 1,2 : 4,5-di-O-isopropylidene-MI (VI) [13] and MI 1,3,5-orthoformate (VII) [14] with NA chloroanhydride in pyridine, as was described earlier for compounds I and IIa [7]. The removal of protective ketal groups in the final nicotinates VIIIa and IX was achieved by treatment with a solution of concentrated hydrochloric acid in dioxane. Compounds IIIa and IV were isolated in the form of hydrochlorides. Neutralization of these products with an aqueous ammonia yielded the corresponding free bases.

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Initial compounds for the synthesis of IIb and IIIb were represented by monoketal X [13] or diketal (VI) between MI and N-Boc-GABA, obtained with the aid of di-*tert*-butylpyrocarbonate [15]. The GABA residue can be introduced into ketal X by two methods. According to method A, the acylation is performed in the di-*tert*-butylpyrocarbonate – pyridine – dimethylaminopyridine system, which was successfully employed previously [16] for the acylation of alcohols with N-protected amino acids. In this case, however, the yield of product XI was insufficiently high. Note that N-Boc-aminopyrrolidone (XII) was isolated as a side product from the same reaction mixture [17]. Attempts to use different solvents (ethyl acetate, methylene chloride, tetrahydrofuran, chloroform) did not lead to higher yield of the target product XI.

A better result for the synthesis of γ-aminobutyroyl derivative XI was obtained by using the anhydride acylation technique (method B) [18]. According to this, N-Boc-GABA is treated with dicyclohexylcarbodiimide to form N-Boc-GABA anhydride. the latter anhydride reacts with ketal X in the presence of dimethylaminopyridine with the formation of compound XI, which was isolated by chromatography on a silica gel column. A similar acylation of diketal VI with N-Boc-GABA anhydride was used to synthesize diester VIIIb. The ketal and Boc-protective groups in compound XI were simultaneously removed by hydrolysis with hydrochloric acid, as described above for the case of nicotinoyl derivatives IIIa and IV. The resulting 1,4,5,6-tetra-γ-aminobutanoyl-MI was obtained in the form of tetrahydrochloride. Compound VIIIb was also used to obtain the dihydrochloride of IIIb ester.

In order to synthesize the MI derivative (V) containing both NA and GABA residues, the 1,4,5,6-tetra-O-nicotinoyl-MI (IIa) obtained as described earlier [7] was treated with N-Boc-GABA in the presence of di-*tert*-butylpyrocarbonate, pyridine, and dimethylaminopyridine in ethyl acetate. Acid hydrolysis of the resulting protected product (XIII) by concentrated hydrochloric acid in dioxane led to the formation of derivative V, which was isolated in the form of hexahydrochloride.

The structures of all MI derivatives was confirmed by the results of elemental analyses and the TLC, IR, and ^{1}H NMR spectroscopic measurements (Table 1). Data on the pharmacological activity of the synthesized MI derivatives are presented below.

EXPERIMENTAL CHEMICAL PART

The IR spectra were measured on a Unicam SP-1000 spectrophotomer using samples prepared by pelletizing with KCl. The ^{1}H NMR spectra were obtained on a Varian XL-100 A-12 spectrometer using duterochloroform as the solvent and TMS as the internal standard. Thin-layer chromatography was carried out on Silufol UV-254 plates eluted with chloroform – methanol mixtures (system A, 10 : 1; system B, 8 : 1). Column chromatography was performed using silica gel of the L40/100 grade. NA and GABA were purchased from Serva (Germany), 4-dimethylaminopyridine was obtained from Wako Pure (Japan), and the other reagents were represented by Russian commercial grades. The results of elemental analysis of all the synthesized compounds agreed with the analytically calculated values.

1,2 : 4,5-Di-O-isopropylidene-3,6-di-O-nicotinoyl-MI (VIIIa). To 7.5 g (0.056 mole) NA were added 4.4 g (0.02 mole) phosphorus pentachloride and 20 ml of dry pyri-

TABLE 1. Yields and Physicochemical characteristics of New *myo*-Inositol Derivatives

Compound	Yield, %	M.p., °C	Empirical formula	R_f (method)	IR spectrum (ν_{max}, cm^{-1})	^{1}H NMR spectrum (δ, ppm)
IIb	91.3	oil	$C_{22}H_{40}N_4O_{10} \cdot 4HCl$	–	3400 (OH) 1760 (C=O)	3.5 – 4.1 (m, 6H, 6CH), 1.5 – 2.3, 2.9 – 3.1 (m, 24H, $12CH_2$)
IIIa	95.2	268 – 272	$C_{18}H_{18}N_2O_8$	0.1 (A)	1770 (C=O)	7.5 – 7.6, 8.3 – 8.4, 8.8 – 9.2 (m, 8H, 8CH), 4.7 – 5.4 (m, 6H, 6CH)
IIIb	83.7	190 – 192	$C_{14}H_{26}N_2O_8 \cdot 2HCl$	–	3400 (OH) 1760 (C=O)	1.5 – 2.5 (m, 12H, $6CH_2$), 3.2 – 4.8 (m, 6H, 6CH)
IV	81.7	193 – 195	$C_{22}H_{21}N_3O_9$	0.2 (B)	1780 (C=O)	7.6 – 7.9, 8.3 – 8.4, 8.6 – 9.4 (m, 12H, 12CH), 4.0 – 4.4, 5.4 – 5.7, 6.4 – 6.5 (m, 6H, 6CH)
V	42	190 – 192	$C_{38}H_{38}N_6O_4 \cdot 6HCl$	–	1760 (C=O)	7.4 – 7.6, 8.0 – 8.4, 8.6 – 9.1 (m, 16H, 16CH), 1.1 – 1.7, 2.2 – 3.0 (m, 12H, $6CH_2$)
VIIIa	65.7	319 – 322	$C_{24}H_{26}N_2O_8$	0.57 (A)	1760 (C=O)	7.5 – 8.4, 8.9 – 9.3 (m, 8H, 8CH), 5.0 – 5.4 (m, 6H, 6CH)
VIIIb	53.9 (method A) 12.5 (method B)	144 – 146	$C_{30}H_{50}N_2O_2$	0.3 (B)	3470 (NH) 1760 (C=O) 1520 (NH)	5.1 – 5.4 (m, 6H, 6CH), 3.4 – 4.1 (d, 6H, 6CH), 1.8 – 2.1 (d, 12H, $6CH_2$), 2.4 – 2.5 (m, 12H, $6CH_2$), 3.0 – 3.2 (m, 12H, $6CH_2$), 1.1 – 1.6 (m, 30H, $10CH_3$)
IX	67.6	236 – 239	$C_{25}H_{19}N_3O_9$	0.5 (B)	1760 (C=O)	7.1 – 7.5, 8.0 – 8.4, 8.6 – 9.4 (m, 12H, 12CH), 5.6 – 6.4 (m, 6H, 6CH)
XI	53.1	116 – 120	$C_{45}H_{76}N_4O_{18}$	0.5 (B)	3470 (NH) 1760 (C=O)	4.2 – 5.5 (m, 6H, 6CH), 1.7 – 2.5, 3.1 – 3.8 (m, 24H, $12CH_2$), 1.2 – 1.6 (m, 42H, $14CH_3$)
XIII	33	120 – 122	$C_{58}H_{48}N_4O_{16}$	0.6 (B)	3470 (NH) 1760 (C=O)	7.3 – 7.5, 8.0 – 9.2 (m, 16H, 16CH), 5.5 – 6.2 (m, 6H, 6CH), 1.7 – 2.4, 2.6 – 3.4 (m, 12H, $6CH_2$), 1.1 – 1.5 (m, 18H, $6CH_3$)

dine, and the mixture was boiled for 1 h and cooled. Then 4 g (0.015 mole) of 1,2 : 4,5-di-O-isopropylidene-MI (VI) was added and the mixture was boiled for another 1.5 h, poured into a saturated NaCl solution, and extracted with chloroform. The organic layer was separated, dried over Na_2SO_4, and evaporated to obtain 4.74 g of derivative VIIIa.

1,4-Di-O-nicotinoyl-MI (IIIa). A mixture of 4.75 g of derivative VIIIa with a solution of 30 ml of concentrated HCl in 200 ml dioxane and 100 ml of methanol was boiled for 25 min, cooled, and neutralized with $NaHCO_3$. The residue was filtered, the mother liquor was evaporated, and the total residue was dried over P_2O_5 in vacuum to obtain 2 g of dihydrochloride IIIa. To obtain the free base, the dihydrochloride was dissolved in water and neutralized with ammonia solution with intense stirring, and the precipitate was isolated. Yield of IIIa diester, 1.5 g.

1,3,5-Orthoformyl-2,4,6-tri-O-nicotinoyl-MI (IX). Compound IX was obtained by a method similar to that used for the synthesis of VIIIa, proceeding from 3.5 g (0.026 mole) NA and 1 g (5.2 mole) of orthoformate VII. Yield of derivative IX, 1.79 g.

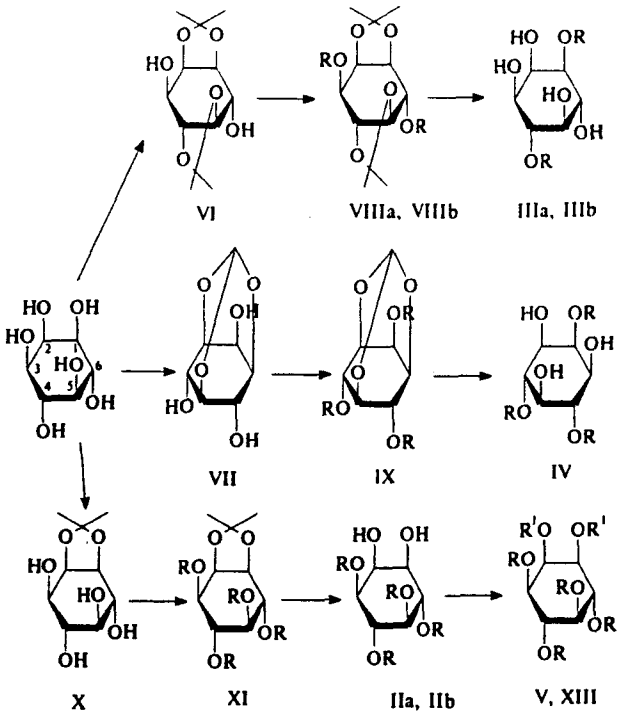
1,3,5-Tri-O-nicotinoyl-MI (IV). Triester IV was obtained by the hydrolysis of 0.03 mole of derivative IX as described for the synthesis of diester IIIa. Yield of triester trihydrochloride IV, 1.74 g.

1,2-O-Isopropylidene-3,4,5,6-tetra-O-[4-(N-Boc)-aminobutanoyl]-MI (XI) and N-Boc-aminopyrrolidone (XII).

Method A. A mixture of 220 mg (1 mmole) of isopropylidene derivative X, 1.25 g (5.5 mmole) di-*tert*-butylpyrocarbonate, 935 mg (5.5 mmole) N-Boc-GABA, 0.25 ml pyridine, and 20 mg dimethylaminopyridine in 50 ml ethyl acetate was stirred at 20°C until the CO_2 evolution ceased. Then the mixture was washed with a saturated $NaHCO_3$ solution and water, dried over Na_2SO_4, and reduced in volume by evaporation. The residue was chromatographed on a silica gel column using a mixture of benzene with increasing gradient of ethyl ether as the eluent. This yielded 150 mg of derivative XI and 350 mg of compound XII; R_f, 0.8 (A); IR spectrum (ν_{max}, cm^{-1}): 1715 (OC=O); ^1H NMR spectrum (δ, ppm): 3.0 (q, 2H, CH_2), 2.3 (q, 2H, CH_2), 1.8 (q, 2H, CH_2), 1.4 – 1.5 (9H, $3CH_3$); $C_9H_{15}NO_3$.

Method B. A mixture of 1.9 g (5 mmole) of freshly prepared N-Boc-GABA anhydride [18], 220 mg (1 mmole) of isopropylidene derivative X, and 40 mg (5 mmole) of dimethylaminopyridine in 20 ml of dry pyridine was heated for 6 h at 80°C. Then the solution was evaporated to dryness, the residue was dissolved in chloroform, washed with a saturated $NaHCO_3$ solution and water, dried over Na_2SO_4, and reduced in volume by evaporation. The residue was chromatographed as described in method A to yield 510 mg of derivative XI and 210 mg of compound XII.

1,2 : 4,5-Di-O-isopropylidene-3,6-di-O-[4-(N-Boc)-aminobutanoyl]-MI (VIIIb). Compound VIIIb was obtained by method B similarly to derivative XI, proceeding from 260 mg (1 mmole) of diketal VI. Chromatographic separation of the reaction mixture on a silica gel column with a benzene – ethyl ether mixture yields 340 mg diester VIIIb and about 20% of compound XII.



R = nicotinoyl (IIa, IIIa, IV, V, VIIIa, IX, XIII),
γ-aminobutanoyl (IIb, IIIb),
γ-(N-Boc)-aminobutanoyl (VIIIb, XI),
R′ = γ-aminobutanoyl (V),
γ-(N-Boc)-aminobutanoyl (XIII).

1,4,5,6-Tetra-O-(4-aminobutanoyl)-MI (IIb) and di-O-(4-aminobutanoyl)-MI (IIIb). The tetrahydrochloride of tetraester IIb and the dihydrochloride of diester IIIb were obtained by acid hydrolysis of protected derivatives XI and VIIIb using the procedure described for compound IIIa (see Table 1).

1,4,5,6-Tetra-O-nicotinoyl-2,3-di-O-[4-(N-Boc)-aminobutanoyl]-MI (XIII). A mixture of 100 mg (0.017 mmole) of tetranicotinate IIa, 0.12 g (0.53 mmole) di-*tert*-butylpyro-

TABLE 2. Antisclerotic Activity of *myo*-Inositol Derivatives with Nicotinic Acid

Compound, test	Cholesterol, mM	Triglycerides, mM	Lipoproteins, arb.u.
Intact	1.7 ± 0.05	0.65 ± 0.08	104 ± 18.2
Control	2.32 ± 0.07	1.04 ± 0.11	150 ± 12.4
I	2.05 ± 0.08	0.44 ± 0.7	104 ± 6.0
IIa	1.66 ± 0.13	0.58 ± 0.08	127 ± 8.7
IIIa	1.89 ± 0.04	1.01 ± 0.14	108 ± 11.7
IV	1.77 ± 0.12	0.49 ± 0.05	98 ± 4.9
NA	1.95 ± 0.10	0.54 ± 0.09	118 ± 9.4

carbonate, 90 mg (0.53 mmole) N-Boc-GABA, 0.05 ml pyridine, and 10 mg dimethylaminopyridine in 50 ml ethyl acetate was stirred at 20°C until the CO_2 evolution ceased. Then the mixture was washed with a saturated $NaHCO_3$ solution and water, dried over Na_2SO_4, reduced in volume by evaporation, and separated on on a silica gel chromatographic column to yield 59.62 mg of derivative XIII.

1,4,5,6-Tetra-O-nicotinoyl-2,3-di-O-(4-aminobutanoyl)-MI (V). Treatment of 500 mg (0.5 mmole) of derivative XIII with a solution of 6 ml concentrated HCl in 40 ml dioxane at 20°C as described above for IIIa yields 200 mg of haxahydrochloride V.

EXPERIMENTAL PHARMACOLOGICAL PART

Study of the Antisclerotic Properties of Di-, Tri-, Tetra-, and Hexa-O-Nicotinoyl-MI (IIIa, IV, IIa, and I)

The pharmacological tests were performed on Wistar male rats weighing 270 – 300 g. The experimental atherosclerosis was modeled by a 5-day introduction of cholesterol (40 mg/kg) and ergocalciferol (350,000 USP units/kg) via gastric tubes. All preparations and NA (reference compound) were introduced into the animals via gastric tubes as aqueous solutions or suspensions at a dose of 10 and 50 mg/kg, respectively (each compound was tested on a group of 4 animals), simultaneously with the development of model pathology.

The antisclerotic activity of the synthesized compounds was objectively judged by the degree of reduction in the total cholesterol, triglycerides, and lipoproteins in the blood serum of animals killed on the 5th day of experiment.

Study of the Hypotensive Activity of Di- and Tetra-γ-aminobutanoyl-MI (IIIb and IIb)

GABA and its derivatives produce inhibiting effect on various pathogenic mechanisms involved in the development of hypertensive disease [19]. Therefore, the aminobutyryl derivatives were expected to exhibit hypotensive activity. The hypotensive action of these derivatives was studied on white mongrel mice narcotized with pentobarbital (40 mg/kg, i.p.). The samples were dissolved in 10% aqueous ethanol and injected into external jugular veins (each compound was tested in 4 experiments). The systemic arterial pressure was measured in the carotid artery 1, 5, 15, 30, 45, and 60 min after the drug injection. The experimental data were processed by methods of variation statistics using the Student's t-criterion.

Study of the Antiarrhythmic Activity of Tetra-γ-aminobutanoyl-MI (IIb)

The experiments were performed on white male mongrel mice narcotized with pentobarbital (50 mg/kg, i.p.). The arrhythmia was induced by calcium chloride injected at a dose of 250 mg/kg. Compound IIb was introduced intravenously 10 min before the calcium chloride injections. The control group of animals was injected with the same volume of 10% aqueous ethanol.[3] The character of heart rhythm violations was determined from ECG. The antiarrhythmic effect was assessed against that of sodium valproate, a well-known antiarrhythmic and anticonvulsive drug [20]. The antiarrhythmic activity of the synthesized compounds was evaluated as the effective dose (ED_{50}) preventing heart arrhythmia in 50% experiments on rats intoxicated with calcium chloride. The ED_{50} values were determined by a graphical method.

Results. As is seen from the data summarized in Table 2, all the studied compounds reduce to a higher or lower degree the parameters of lipid exchange as compared to the level determined for the control group, thus showing antisclerotic properties with respect to the particular experimental model. As for the degree of hypocholesteremic effect, the compounds can be arranged in the following order of decreasing activity: IIa > IV > IIIa > NA > I. Therefore, the hypocholesteremic activity increases with increasing NA residue in the MI derivative. The most pronounced hypotriglyceridemic effect was produced by hexanicotinate I, while the maximum hypolipoproteinemic effect was observed for trinicotinate IV. With respect to the main characteristics of antisclerotic activity, most compounds proved to be more efficient than NA, despite the fact that latter compound was injected at a higher dose.

It was found that diester IIIb produced pronounced hypotensive effect at a dose of 20 or 100 mg/kg (Table 3), with an ED_{20} value of 20 mg/kg. Note that GABA produces a similar effect at a dose as large as 200 mg/kg. Thus, the hypotensive activity of compound IIIb is 10 times that of GABA. At the same time, tetraester IIb, introduced at a dose of 5 or

[3] 10% ethanol solutions have virtually no effect on the arrhythmia development.

TABLE 3. Effect of Di- and Tetra-(4-aminobutanoyl)-MI on the Systemic Arterial Pressure in Narcotized Rats

Compound	Dose, mg/kg	Initial systolic pressure, Torr	Variation of systolic pressure, Torr					
			1 min	5 min	15 min	30 min	45 min	60 min
IIb	5	110.69 ± 8.67	106.38 ± 7.54	108.69 ± 6.96	107.33 ± 9.33	98.0 ± 10.0	96.0 ± 10.0	95.0 ± 9.0
	10	118.58 ± 1.5	114 ± 4.0	118.58 ± 1.5	111 ± 5.0	108	104	–
IIIb	5	120	106 (– 11.67)	102 (– 15.0)	105 (– 12.5)	–	–	–
	20	108 ± 4.56	85.6 ± 4.01*	91.0 ± 3.0*	90.4 ± 6.11	93.0 ± 3.1*	86 ± 5.09*	95 ± 3.41
	100	122	96	84	90	82	80	76

* Difference vs. the initial level reliable for $p < 0.05$.

10 mg/kg, produced virtually no effect on the arterial pressure (Table 3).

For the antiarrhythmic effect, compound IIb had ED_{50} = 16.6 mg/kg, while sodium valproate exhibited pharmacological activity only at a dose of 150 mg/kg. Thus, the antiarrhythmic activity of tetra(4-aminobutanoyl)-MI IIb exceeded that of sodium valproate by 9 times.

Thus, the antisclerotic, hypotensive, and antiarrhythmic activity observed in MI derivatives containing NA and GABA residues imply that these compounds are worthy of study with respect to a broad spectrum of therapeutic action.

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