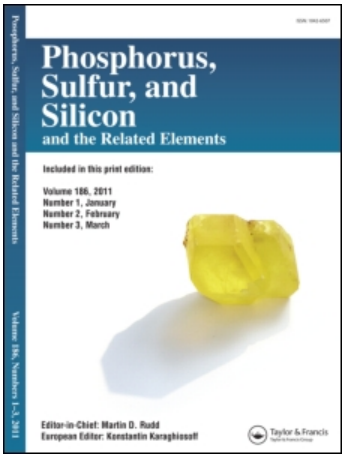

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The First Nootrops Among Non-Anticholinesterase Organophosphorus Compounds. Study of Structure-Neurotropic Activity Relationships of Nitrogen-Containing Phosphorylacetic Acid Derivatives.

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THE FIRST NOOTROPS AMONG NON-ANTICHOLINESTERASE ORGANOPHOSPHORUS COMPOUNDS. STUDY OF STRUCTURE-NEUROTROPIC ACTIVITY RELATIONSHIPS OF NITROGEN-CONTAINING PHOSPHORYLACETIC ACID DERIVATIVES.

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ABSTRACT. New series of nitrogen-containing phosphorylacetic acid derivatives (I-V) were synthesized. The antidepressant,neuroleptic,sedative,anxiolytic,antialcoholic and nootropic effects of new compounds(I-V) were studied. Efficiency of neurotropic action depends on the presence both phosphoryl and acyl fragments of molecule. A novel preparation(I-B) has been discovered as having high potential of nootropic activity.The receptor binding studies and investigation of nootropic and antidepressant actions mechanism of hydrazids(I) were conducted.

INTRODUCTION.

A new series of active neurotropic and non-anticholinesterase compounds studied by us belong to phosphorylacetic acid derivatives. The first representative of these series is diphenylphosphinylacetic acid hydrazid, named PHOSENAZID [1]. Initially PHOSENAZID was proposed for medical application as a "day-time" tranquillizer with marked vegetotropic activity and antiepileptic action. When examined more closely it displayed a specific antialcoholic action and properties of nootrope and adaptogene. That makes possible to apply PHOSENAZID for correcting the disturbances of mental function resulting from hypoxia,intoxication,acute and chronic alcoholism,and for reducing the delay in children's mental development [2].

SYNTHESIS.

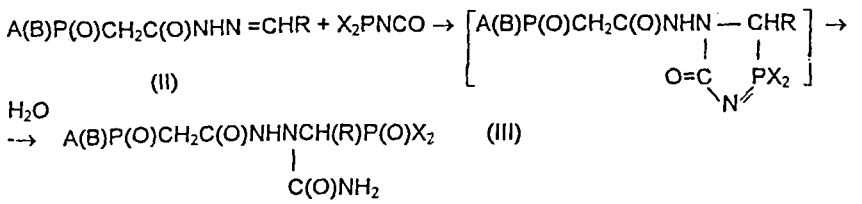
To screen the neurotropic activity and to develop general strategy for phosphorus-containing drug design we have synthesized numerous phosphorylacetic acid and aldehyde derivatives(I-V) combined by common formulas $ABP(O)CH_2C(=X)Y$.

	I	II	III	IV	V
X	O	O	O	O	NN^+HR_2
Y	NHNHR	NHN=CHR	NHN(R)C(O)R'	$O^-[N^+H_3R]$	H

Unsubstituted phosphorylacetic acid hydrazids formed the main part of the compounds(I). They were obtained by an interaction of phosphorylacetic acid esters and hydrazine [3]. In hydrazid group the substituent R was introduced via the reaction between unsubstituted hydrazids(I) and chloral or phosphonchloral [4].

Hydrazons(II) were easily formed by interaction of phosphorylated hydrazids (I) and aldehydes [5].

To obtain the compounds(III) we used both well-known acylation of hydrazids(I) and original reaction of [2+3]-cycloaddition with participation of isocyanatophosphine [6].



The salts(IV) were obtained on the basis of mono- or dibasic phosphorylacetic acids prepared by alkaline or acid hydrolysis of their esters. In cation moiety these salts contained ethyl esters of neuroactive amino acids such as glycine, alanine, etc. Phosphorylethylidene hydrazins' salts(V) were produced by the reaction of phosphorylacetic acid aldehydes and hydrazine salt [7].

TOXICITY AND NEUROTROPIC EFFECTS.

The acute toxicity data showed that in studied series(I-V) effect manifestation depended on electron influence of the substituents at both phosphorus and acetic acid fragment. The highest toxicity was observed in unsubstituted hydrazids(I). In these series the values of lethal doses (DL_{50}) increased as the number of alkoxylic groups at phosphorus grew.

TABLE 1. Acute toxicity of hydrazids(I).

	A=B=	A=B=	A=B=	A=Me_2NPh	A=B=
DL_{50}	4-ClPh	Ph	4-FPh	B=OC_2H_4Cl	OC_2H_4Cl
mg/Kg	300±25.7	315±24.8	810±41.6	960±35.0	2500±86.2

Any changes at hydrazid fragment of compounds (I-III) led to decrease of their toxicity. As it can be seen from table 2 the major part of hydrazons(II),some phosphorylated semicarbazides (III) and salts(IV) were practically non-toxic. A passage from the structure of phosphorylacetic acid derivatives(I-IV) to one of phosphorylethylidene hydrazins' salts(V) considerably increased toxicity of the latter.

TABLE 2. Acute toxicity interval of compounds(I-V)

	I	II	III	IV	V
DL_{50} mg/Kg	300÷2500	970÷5000 and more	850÷5000 and more	1500÷4500	400

The neuropharmacological action estimation of each series was made on models characterising a wide variety of their neurotropic effects. The antidepressant, neuroleptic, sedative, anxiolytic, antialcoholic and nootropic properties of new compounds (I-V) were investigated.

Analysis of the obtained data showed versatility and high neurotropic activity of compounds(I-III),which molecule contained a chain of $>P(O)CH_2C(O)NHN<$, atoms.

The great number of active substances was observed in the unsubstituted hydrazids(I). At that, the phosphinate (I-B) with arylic and β-chlorine ethoxylic group at phosphorus had optimum activity. The phosphine oxides with two arylic groups possessed also a wide spectrum of action. The neurotropic effects of hydrazons(II) were present too but in a less marked form, and some representatives of semicarbazides(III) were as active as hydrazids(I).

Thus, in studied series(I-III), the neurotropic action efficiency depended on the presence of both phosphoryl and hydrazid fragments in molecule. The lack of hydrazid moiety in the salts(IV) as well as passage to the structure of phosphorylethylidene hydrazins' salts (V) led to reduced activity In the series(IV) the structural change caused appearance of neuroleptic effect, when the hydrazid derivatives(I-III) didn't have them.

PHOSENAZID(I-A), hydrazid(I-B) and their analogues was shown to display nootropic effects [8]. In our experiments, hydrazid (I-B) was the most active compound among studied. Their antihypoxic and antiamnesic effects exceeded those of classical nootrope PYRACETAM. In distinction from PYRACETAM hydrazid(I-B) prevented hyperfermentemia and normalized metabolic changes in blood of animals under hypoxia.

STUDY OF MECHANISM.

Potent active hydrazids(I-A) and (I-B) possessed variety of effects specifying their nootropic action. In experiments in vivo and in vitro these compounds displayed membrane-stabilising activity and antioxidant property. The studied hydrazids(I) were found to increase the level of nuclear acids in cerebral cortex of rats.

One of the original characteristics of the investigated mechanism was choline-sensibilising action of hydrazids(I) discovered by the synaptic effects studies. This action and the ability of hydrazids(I) to ease up the process of signal transmission in cholinergic synapses evidenced their properties to restore the disturbed memory

and to improve training. It makes also possible to forecast positive results when treating Alzheimer's disease.

It's important that hydrazids(I-A) and (I-B) do not influence the state of synaptic acethylcholynesterase, which proves the absence of their anticholinesterase action.

There is another peculiar feature of the studied hydrazids, namely, a dose-dependent character of their effects manifestation. Thus,the membrane-stabilising action was getting greater when the preparation dose was diminished to 1/1000 DL_{50}. The mechanism of hydrazids (I-A) and (I-B) antidepressant activity changes also depending on the doses. At relatively large dose (1/10 DL_{50}) the antidepressant effect is apparently connected with the ability of the compounds to inhibit the monoaminooxidase ferment. However, at small doses (1/100-1/1000 DL_{50}), this activity was perhaps the consequence of their nootropic action. Moreover, the hydrazid(I-B) antidepressant effect is displayed in a wide range of doses and developed much earlier than with the tricyclic antidepressants.

The receptor binding studies showed that at doses of 1-100 micromolar, there was no marked affinity of hydrazids(I) at wide variety of receptors (sigma, adenosine, GABA, 5-HT, muscarinic, nicotinic, CCK, opiod, neurokinin NK1) or at Ca, K or Na channels. From the receptorscan, the main lead is an apparent action of the compounds(I) at the glycine site of the NMDA complex. Such an action could result in both neuroprotection and memory enhancement.

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