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SYNTHESIS AND ACUTE TOXICITY OF SOME PHOSPHORYLATED DERIVATIVES OF EPHEDRINE ALKALOIDS

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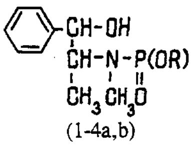
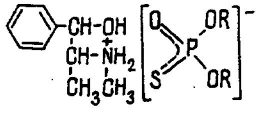
The results are given of the synthesis and a comparative study of the toxicities of some phosphorylated derivatives of the alkaloids l-ephedrine and d-pseudoephedrine. It has been shown that the introduction of phosphorus- and sulfur-containing fragments considerably lowers the toxicity of the alkaloids.

One of the promising directions of the creation of new biologically active compounds is the structural modification of known drugs. Practice shows that sometimes only slight changes in their structure can substantially change the pharmaceutical properties of the derivatives [1, 2]. It must also be mentioned that the structures of a considerable proportion of the drugs used in medicine contain various phosphorus-containing fragments [3].

In this connection, we have continued a search for biologically active substances among new phosphorylated derivatives of ephedrine alkaloids. We have previously obtained phosphoramidate (**1-4a, b**) and phosphorothiate (**5-8a, b**) [4] derivatives of *l*-ephedrine (a) and *d*-pseudoephedrine (b). In the present paper we give the results of an investigation of of the interaction of *l*-ephedrine with dialkyl phosphorodithioates and of a comparative analysis of acute toxicity among phosphorylated alkaloid derivatives.



(1-4a,b)



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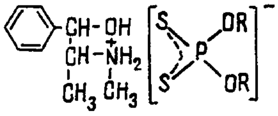

(9-12a,b)

R = CH_3, C_2H_5, i-C_3H_7, C_4H_9

The formation of phosphorodithioates of *l*-ephedrine (**9-12a**) was likewise readily achieved by scheme [4] in benzene, with quantitative yields of products. The salts obtained consisted of white crystalline substances readily soluble in water, alcohol, and acetone, which confirmed the formation of quaternary ammonium compounds.

Yields and physicochemical constants of the *l*-ephedrine dialkyl phosphorodithioates (**9-12a**) are given in Table 1.

The IR spectra of compounds (**9-12a**) showed absorption bands in the 2400-2700 cm^{-1} region due to the vibrations of the N–H bond of a group of the NH_2^+ type in a secondary ammonium salt. Absorption bands were also revealed in the regions of (cm^{-1}) 3200-3380 (OH), 2820-2940 (CH_{ar}) and 950-1040 (P–O–C).

Acute toxicity was studied on random-bred white mice of both sexes with body weights of 15-25 g, using intraperitoneal injection. On a single injection of the listed preparations in toxic doses, they all, after 1-2 min, like *l*-ephedrine caused an increase in respiratory activity, exophthalmos, tremor, and clonicotonic spasms with the death of the animals at the height of a convulsive seizure or immediately after it from a depression of respiration. With respect to acute toxicity, substances (**3**) and (**4b**) were equal to *l*-ephedrine, while the other substances were considerably less toxic (Table 2). The replacement of the oxygen atom in the structure of a thio salt of *l*-ephedrine (**7a**) by a second sulfur atom (**11a**) led to a slight rise in toxicity (600 and 465 mg/kg for (**7a**) and (**11a**), respectively).

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TABLE 1. Physicochemical Constants of *l*-Ephedrine O,O-Dialkyl Phosphorodithioates

Compound	Empirical formula	Yield, %	T. mp, °C	Chemical shifts, δ, ppm				
				C—CH3	—CH3	P—O—R*	Ph	δ_P
9a	C12H22O3NPS2	89	53—54	1.07 d	2.78 s	2.96 m	7.30 m	110.2
10a	C14H26O3NPS2	94	92—93	1.08 d	2.80 s	3.83 m	7.41 m	104.5
11a	C16H30O3NPS2	95	107	1.25 d	2.79 s	3.52 m	7.45 m	109.3
12a	C18H34O3NPS2	92	64—65	1.07 d	2.79 s	3.83 m	7.36 m	106.4

*R = CH_3 (**9**), CH_3-CH_2 (**10**), $(CH_3)_2-CH$ (**11**), $CH_3-(CH_2)_2-CH_2$ (**12**). The elemental analyses of all the compounds corresponded to the calculated figures.

TABLE 2. Acute Toxicities of Some Phosphorylated Derivatives of *l*-Ephedrine (*a*) and of d-Pseudoephedrine (b)

Compound	LD_{50}, mg/kg (intraperitoneally)
l-Ephedrine	170±25
3a	188±20
3b	674±25
4a	340±60
4b	180±45
6b	2577±22
7a	600±12
7b	450±80
11a	465±20

EXPERIMENTAL

IR spectra of the compounds were taken on a UR-20 instrument in tablets with KBr, and PMR spectra on a Tesla BS-467 instrument at a frequency of 100 MHz with HMDS as internal standard. ^{31}P NMR spectra were taken on an instrument constructed in Kazan' State University at a working frequency of 8 MHz relative to 85% H_3PO_4.

The acute toxicities of the preparations were studied in the Institute of Physiology and Labor Hygiene, National Academy of Sciences, Republic of Kazakhstan.

Synthesis of *l*-Ephedrine Dialkyl Phosphorothioates. With stirring a dialkyl phosphorodithioate was added dropwise to a solution of the alkaloid in absolute benzene After the end of the reaction, the crystals that had deposited were filtered off and were recrystallized from acetone–hexane.

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