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DEPENDENCE OF THE PHYSIOLOGICAL ACTIVITY OF THE SULFUR-CONTAINING ALKALOIDS OF *Dipthychocarpus strictus* ON THEIR CHEMICAL STRUCTURE

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A dependence of the physiological activity of the sulfur-containing alkaloids of Dipthychocarpus strictus *on their structure has been reveated.*

At the present time, there has been a rise in the interest of scientists in biologically active compounds of natural origin and in the elucidation of the dependence of physiological activity on chemical structure.

We have previously [1-3] reported the isolation from *Dipthychocarpus strictus* Trautv. (fam. Cruciferae) of a series of alkaloids that are sulfur-containing N-alkylurea derivatives. The attention devoted to the alkaloids from plants of the genus *Dipthychocarpus* is due to the presence of an atom of sulfur, as well as nitrogen, in the composition of many of them. Eleven sulfur-containing compounds have been isolated and their structures have been shown [4, 5].

Workers in the division of pharmacology and toxicology of the Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, have established the existence of local anesthetic, sedative, and hypotensive properties in the substances isolated. But their main property is an antihypoxic action detected by workers of the Scientific Research Institute of Cardiology, Ministry of Health of the Republic of Uzbekistan, under the direction of Prof. A. G. Kurmukov.

In consideration of the antihypoxic activity found, attempts have been made to synthesize compounds of this series for practical purposes, since the area of distribution and, consequently, supplies of *D. strictus* are small.

The investigations performed have shown the presence in the alkaloids of *D. strictus* of antihypoxic activity on various types of hypoxia [10, 11], the greatest activity being observed on hypoxic normobaric hypoxia. Thus, diptocarpaine (**1**) [12] in a dose of 100 mg/kg increases the survival time of mice by 52%, and diptocarpilidine (**2**) [13] and diptocarpidine (**3**) [14] in doses of 40 mg/kg by 62 and 87%, respectively. At the same time, gutimin (standard) in a dose of 100 mg/kg increased the survival time of mice by 105%, while the survival time of the majority of animals of this group agreed with the survival time of mice that had received the alkaloids. Consequently, the activity of the alkaloids on this form of hypoxia is equal to that of gutimin. In the case of hypoxic hypobaric hypoxia, the activity of the alkaloids studied was relatively low. The most active in this form of hypoxia was diptocarpidine, which increased the survival time of rats by 227%.

The spectrum of antihypoxic activity of the alkaloids studied is unique — in contrast to gutimin, kavergal, and a number of other antihypoxants, they exert a great effect on hypoxic normobaric hypoxia. Thus, the effect of the most active of these alkaloids — diptocarpidine — on hypoxic normobaric hypoxia was twice as great as that of gutimin. In the hermetic chamber, the other alkaloids exhibited an effect not inferior to that of gutimin.

We have attempted to establish a structure–activity relationship for these alkaloids. Analysis of the results obtained showed that the sulfoxide grouping was responsible for the action of the substances on hypoxic hypoxia, and the urea radical on cytotoxic hypoxia. Thus, having only a sulfoxide group, diptocarpaine [12] is ineffective against cytotoxic hypoxia but has an effect against hypoxic hypoxia. The most active substance against hypoxic hypoxia, diptocarpidine, contains two sulfoxide

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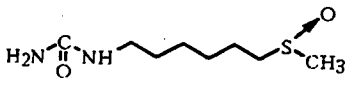
TABLE 1. Dependence of the Antihypoxic Action of Sulfur-Containing Compounds in Various Types of Hypoxia on Their Structure

Substance	Antihypoxic effect*			
	HhH	HnH	Ch	Total
Diptocarpilidine	161	62	5	228
Diptocarpaine	97	52	59	208
Diptocarpidine	227	87	78	392
Dimethyl sulfoxide	42	15	15	72

*HhH — hypoxic hypobaric hypoxia.
HnH — hypoxic normobaric hypoxia.
Ch — cytotoxic hypoxia.

groups. The sulfoxide group in relatively "pure" form — dimethyl sulfoxide — also exhibits a tendency towards an antihypoxic effect only in hypoxic hypoxia. The addition of a urea radical to a sulfoxide group (diptocarpidine) leads to the appearance of activity in cytotoxic hypoxia, as well.

Here we observe a tendency, found previously for many other compounds, towards an increase in activity when the molecule has a symmetrical nature, which finds its reflection in the most active compound in this respect, diptocarpidine.



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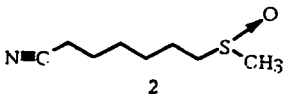

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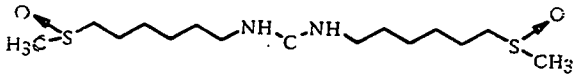

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Apparently, the decisive factor for the appearance of an antioxidant action in such structures is a symmetry of the terminal radicals. Synthetic analogs in which this rule is infringed are completely inactive [11]. The replacement of terminal methyl radicals by isopropyl radicals leads to a disappearance of the effect on hypoxic hypoxia. Conversely, the introduction of an acetyl group into the molecule and a shortening of the distance between the sulfoxide and the urea groupings makes the substance a specific hermetic chamber antihypoxant. In all cases, compounds with a sulfoxide group are more active than their deoxy derivatives.

Thus, the alkaloids investigated possess antihypoxic activity in hypoxic (hyponormobaric) and cytotoxic hypoxias. With respect to their antihypoxic action in hypoxic normobaric and cytotoxic hypoxias they are not inferior to gutimin, while some (diptocarpidine) are actually superior. The antihypoxic effect of the alkaloids is enhanced with an increase in the number of sulfoxide groups and with symmetry of the molecule (Table 1).

It is known that the action of biologically active compounds on a kinetic stage involving the transport of molecules of substances to a target cell and transfer through biological membranes is determined mainly by their hydrophobic properties [15]. Terminal atoms of nitrogen, oxygen (C=O), and sulfur, which possess unshared electron pairs, may act as active centers for the addition of molecules to transport proteins and receptors. It may be assumed that activity in this series of compounds will depend on the electronic structure and geometry of this fragment.

What has been said above can apparently be applied in full measure to the series of sulfur-containing analogs under study. The presence of antihypoxic activity exceeding that of known antihypoxic drugs in the alkaloids of *D. strictus* is of undoubted practical importance.

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