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PSYCHOTROPIC PREPARATIONS SYDNOPHEN AND SYDNOCARB AS DONORS OF NITROGEN MONOXIDE

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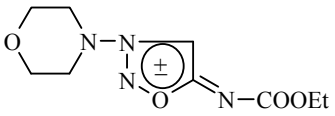
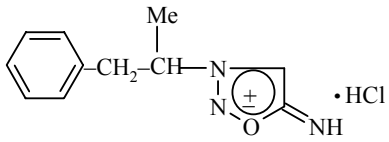
The metabolic chain of the antihypertensive drug Molsydomin, which belongs to the group of sydnonimine derivatives, was modelled in vitro with the psychotropic drugs Sydnophen and Sydnocarb, which are also derivatives of sydnonimine. Like Molsydomin, Sydnophen and Sydnocarb are hydrolyzed to N-nitroso compounds which liberate nitrogen monoxide, NO, on subsequent oxidation which may be related to the pharmacological effects of these drugs.

Keywords: nitroprusside anion, nitrogen monoxide NO, Sydnocarb, Sydnophen, hydrolysis, polarographic detection, oxidation.

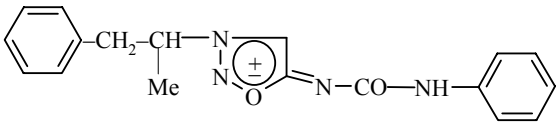
Among the derivatives of sydnonimine there are a large number of pharmacologically active substances, from which the drugs Molsydomin, Sydnophen, and Sydnocarb (Mesocarb) can be distinguished:



Molsydomin



Sydnophen



Sydnocarb

Molsydomin is an effective antihypertensive, the pharmacological activity of which has been connected recently [1] to its ability to release nitrogen monoxide in vivo. This ability to act as an NO donor arises from hydrolysis of the side chain of Molsydomin, accompanied by decarboxylation, and opening of the sydnonimine ring under these conditions to give N-nitroso derivative. It is known [2] that N-nitroso compounds are readily oxidized in the organism, the final result of which is the liberation of nitrogen monoxide. The suggested degradation of Molsydomin occurs as follows:

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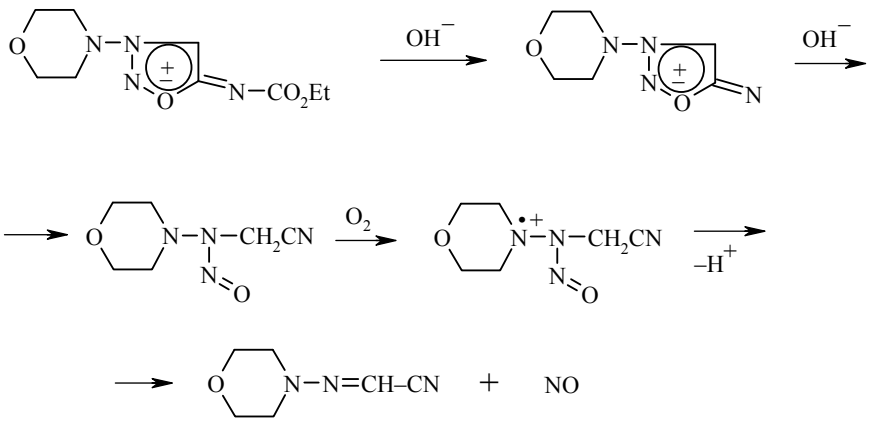

The vasodilatory ability of NO donors is well-known [2], and it is no wonder that drugs with these properties are antihypertensive drugs.

That Sydnophen and Sydnocarb, which have clearly expressed psychotropic activities [3], should also have similar properties is not directly based on the scheme shown above. On the other hand, the presence of sydnonimine unit in all three compounds, and the known properties of sydnonimines, related to their ability to be converted to N-nitroso compounds under appropriate conditions, provide a perfectly reasonable suggestion that preparations Sydnophen and Sydnocarb may act as NO donors. Despite their similar structures, Sydnophen and Sydnocarb belong to different pharmacological groups. The first is a sufficiently strong inhibitor of monoaminoxidase (MAO) which explains its antidepressive activity. Sydnocarb is an effective psychostimulator (considerably exceeding Sydnophen in this respect), showing an indirect sympathomimetic effect, probably based on the inhibition of the reverse capture of noradrenaline. On the other hand, the known neuromediating properties of NO in no way exclude that compounds capable of liberating it in the living organism should also possess psychotropic properties. The ability of these drugs to act as NO donors is studied using a method developed earlier, connected with the polarographic determination of the nitroprusside anion formed by the reaction of the liberated nitrogen monoxide with the ferrocyanide anion. It is known that sydnonimines are readily hydrolyzed in alkaline media into N-nitroso compounds [4,5]. The kinetic characteristics of the process differ considerably depending on the nature of the substituent on the endocyclic nitrogen atom of the sydnonimine nucleus.

We have studied the hydrolysis of Sydnophen (3-phenylisopropylsydnonimine) by polarography in deaerated solutions. The results obtained agree partially with published results [5] for 3-isopropylsydnonimine, however the hydrolysis of Sydnophen is easier than that of 3-isopropylsydnonimine. For example, 3-isopropylsydnonimine is absolutely stable at pH 1-7, while at pH 7.15-8.60 an equilibrium of 3-isopropylsydnonimine with N-nitroso-3-isopropylaminoacetonitrile was observed. We observed hydrolysis of Sydnophen in concentrated electrolyte solutions at low pH (to pH 5), but even at pH 8.2 Sydnophen was completely hydrolyzed in contrast to 3-isopropylsydnonimine. Under these conditions the half-wave potential $E_{1/2}$ for Sydnophen equals to -0.87 V (saturated calomel electrode) and for N-nitroso-N-phenylisopropylamino-acetonitrile $E_{1/2}$ = -1.32 V (saturated calomel electrode).

In 0.1 M phosphate buffer at pH 8.2 the half-wave potentials $E_{1/2}$ for Sydnophen and its hydrolysis product are -0.87 and -1.32 (saturated calomel electrode) respectively. The difference in the half-wave potentials for Sydnophen and its hydrolysis product is 0.45 V which is close to the generally observed difference for N-substituted sydnonimines and the corresponding N-nitrosoaminoacetonitriles [4, 5], so the product of the Sydnophen hydrolysis under deaeration conditions at physiological pH is identified as N-nitroso-N-phenylisopropylaminoacetonitrile, which corresponds to the scheme for the metabolism of Molsydomin. Further, when N-nitroso-N-phenylisopropylaminoacetonitrile was heated in anaerobic conditions with

potassium ferrocyanide to 80°C under either acidic or basic conditions evolution of NO from this compound did not occur in the absence of an oxidant. On additional heating in the presence of potassium ferricyanide and further treatment as described in [6, 7] practically quantitative formation of nitroprusside anion was observed, which also corresponds to the scheme for the metabolism of Molsydomin.

It has been established that the chemical degradation of Sydnocarb can also follow the same scheme if an initial stage of hydrolysis is carried out in 0.1 N sulfuric acid. In this way the phenylcarbamoyl group is removed, since in the polarogram both the initial Sydnocarb and Sydnophen are observed. In 0.1 N sulfuric acid with 20% of ethanol $E_{1/2}$ value for Sydnocarb is -0.58 V (saturated calomel electrode) and for Sydnophen $E_{1/2}$ = -0.90 V (saturated calomel electrode). Even in these vigorous conditions hydrolysis of Sydnocarb proceeds slowly: after 1.65 h the relative ratio of the concentrations of Sydnocarb and Sydnophen in solution was 1.85 and after 6 h it was 0.35.

Thus we have modelled *in vitro* the metabolization chain of Molsydomin for Sydnophen and Sydnocarb, although the conditions for carrying out the different stages, particularly the first, are different for these drugs. The vigorousness of the conditions necessary to carry out these conversions *in vitro* for Sydnophen and Sydnocarb do not rule out the possibility that they could occur *in vivo*, which follows from a comparison of the corresponding data for Molsydomin. It may be proposed that under the organism conditions Sydnophen and Sydnocarb are capable of liberating NO, which may contribute to the pharmacological effects of these drugs. This is not a basis for confirming that the pharmacological activity of these drugs is connected to a large degree with the liberation of NO, rather than to general scheme for the effect of indirect sympathomimetics [3]. To estimate the contribution of this or any mechanism of the psychotropic activity of Sydnophen and Sydnocarb special pharmacological and biochemical studies are required.

EXPERIMENTAL

Polarographic measurements at a dropping mercury electrode were carried out according to generally accepted methods [8]. Determination of NO at the oxidation of the compounds studied was carried out according to [6,7].

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