SYDNOPHENE – A NEW PSYCHOSTIMULATOR

R. A. Al'tshuler, O. N. Volzhina,
F. Ya. Leibel'man, M. D. Mashkovskii,
I. S. Slyusarenko, and V. G. Yashunskii

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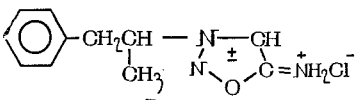
As a result of investigations carried out in the S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical Chemistry Institute (VNIKhFI) in the field of the chemistry of sydnones and sydnonimines (representatives of the class of so-called meso heterocycles), routes and methods for the synthesis of these compounds were developed, and their structures, reactivities, and physical and chemical properties were studied in detail [1].

Among the large number of sydnones and sydnonimines synthesized in the biological departments of VNIKhFI, substances with antibacterial [2], antiblastic [3], and neurotropic [4] activity were observed. Several sydnonimine salts were effective inhibitors of monoaminoxidase [5].

Investigation of the pharmacological properties of 3-phenylalkyl derivatives of sydnones and sydnonimines made it possible to establish that they have a stimulating effect on the CNS [6].

After pharmacological study, one of the compounds of this series – sydnophene – was subjected to clinical tests in the Institute of Psychiatry of the Academy of Medical Sciences of the USSR, in the Department of Nerve Diseases of the First Moscow Medical Institute, and in other medical institutions, and was recommended by the Pharmacological Committee of the Ministry of Public Health of the USSR for use in medical practice as a CNS stimulator.

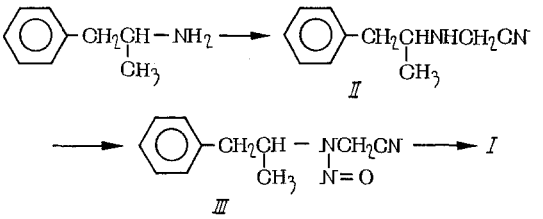
Sydnophene is the hydrochloride of 3-(β-phenylisopropyl)sydnonimine (I).



I

It is a white, crystalline powder, readily soluble in water, insoluble in the usual organic solvents, with mp 156-159°C. It decomposes under the influence of alkali and on standing in light. It is produced in the form of 0.005-g tablets for medical application.

This compound was previously obtained via the well-known scheme for the synthesis of sydnonimine salts. β-Phenylisopropylamine was condensed with formalin and potassium cyanide; the β-phenylisopropylaminoacetonitrile (II) obtained was converted, without isolation, to the corresponding N-nitroso derivative (III) which, also without isolation, was cyclized in hydrochloric acid to (I).



II

III

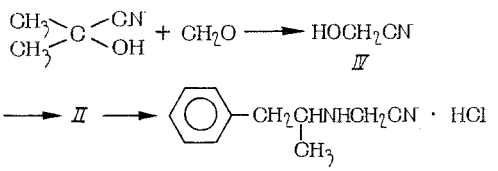
S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical Chemistry Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 5, pp. 59-62, April, 1971. Original article submitted April 30, 1970.

However, this method is of limited suitability for preparing sydnophene in large quantities because of the necessity for using the highly toxic potassium cyanide as well as because of the nontechnological character of the individual steps of the process.

Investigations were therefore undertaken to develop a technologically acceptable method for preparing sydnophene. The use of acetone cyanohydrin, which is not poisonous and is extremely accessible, as the cyanating agent made it possible to exclude potassium cyanide from the synthesis [9].

Glycolonitrile (IV) was obtained by condensation of acetone cyanohydrin with formalin under mild conditions in the presence of an alkaline catalyst and was introduced directly without isolation into reaction with β-phenylisopropylamine. The reaction proceeded smoothly and (II) was obtained in high yield as a viscous oil.

One of the drawbacks in this synthesis of sydnophene is the fact that the process, from beginning to end, was carried out without isolation of the intermediate products. Attempts were therefore made to isolate and purify aminonitrile (II) since purification of the product obtained in the subsequent step—nitroso derivative (III)—is extremely difficult since it is a viscous syrup which cannot be distilled in vacuo without decomposition. It turned out that aminonitrile (II) also underwent decomposition during fractional distillation even under rather high vacuum. It could be isolated as the hydrochloride by treatment of the technical base (II) with a hydrogen chloride solution in isopropyl alcohol



The hydrochloride of aminonitrile (II) was nitrosated in an ethyl acetate-water mixture. The ethyl acetate solution of nitroso derivative (III) was removed, thoroughly dried, and treated with a solution of hydrogen chloride in absolute isopropyl alcohol. The technical sydnophene which precipitated on standing was recrystallized from absolute isopropyl alcohol. The overall yield of sydnophene by this method was 50.3% based on the starting β-phenylisopropylamine.

Pharmacological investigations indicated that sydnophene has a number of properties characteristic for psychostimulating and antidepressive preparations.

The ability of sydnophene (40-60 mg/kg subcutaneously) to raise the reflector excitability and to induce an aggressive state was observed in experiments with mice and rats. In animals under the influence of the preparation the respiration was increased and exophthalmia and piloerection were noted. In cats, alertness and fearfulness appeared 15-20 min after introduction of sydnophene (10-20 mg/kg subcutaneously) followed by tremor of the forelegs and stereotypic movements of the head after 1 to 1.5 h. The reflector excitability in cats under the influence of sydnophene was intensified so markedly that paroxysms of clonic-tonic spasms developed in response to a sound stimulus in several animals. In electroencephalographic investigations, the stimulating action of sydnophene in cats was manifested by activation in the sensomotor and visual regions and improvement in the reaction of the cortex of the cerebrum to the application of functional charges.

It was also observed that sydnophene displays antagonism with respect to the depressive effects of reserpine. In experiments with mice, introduction of sydnophene (25 mg/kg subcutaneously) simultaneously with reserpine (2 mg/kg intraperitoneally) prevented the development of the blepharoptosis, adynamia, and hypothermia characteristic for reserpine. Introduction of sydnophene 2 h after reserpine induced a decrease in ptosis and motor hindrance as well as normalization of the body temperature in some of the animals.

A peculiarity of the action of sydnophene on the CNS is also its capacity to intensify the stimulating effects of β-phenylethylamine, tryptamine, and 5-hydroxytryptophan. The intensification of the central effects of these biogenic substances under the influence of sydnophene is probably associated with its capacity to retard monoaminoxidase activity. In in vitro experiments it was shown [5] that the preparation inhibits the activity of this enzyme, during which the depressive effect of sydnophene on the oxidative deamination of tyramine and serotonin is expressed approximately to the same degree as in iproniazide (iprazide). In contrast to the latter, the effect of sydnophene is reversible and competitive.

Sydnophene also affects the peripheral adrenal reactive systems: in experiments on narcotized cats the preparation (2-3 mg/kg intravenously) induces a short-lived moderate increase in the arterial pressure and reinforces the pressor activity of adrenalin and noradrenalin by factors of two to three.

Sydnophene is relatively slightly toxic. LD_{50} for white mice is 51 mg/kg (intravenously), 123 mg/kg (subcutaneously), and 225 mg/kg (internally). No cumulative effects were observed during repeated introduction of the preparation in animals. No changes in the internal organs were detected in pathomorphological investigations.

In clinical investigations, sydnophene was effective for various neurological and psychic ailments which are accompanied by asthenic symptom complex in the presence of narcolepsy and a symptom of pathological fatigability, as well as for simple depressions and depressions of retarded character.

The preparation was administered internally (5-mg tablets). Single doses ranged from 5 to 20 mg, average doses from 20 to 60 mg, and maximum doses are 100 mg per day. The preparation is alloted to the patient in two to three doses, and the last time, to avoid interference with sleep, no later than 5 p.m. (except for those ill with narcolepsy). The course of treatment and the doses are selected strictly individually.

The therapeutic effect of sydnophene is usually manifested four to seven days after the start of treatment. Stimulating and moderate thymoanaleptic action was observed. The stimulating action of the preparation was primarily manifested in asthenic nervous individuals and asthenia due to chronic nerve infections, somatogenic and postinfection disturbances: the patients became active, their work capacity increased, and confidence in their strength and cheerfulness was manifested. In addition, the patients' frame of mind improved, and the preparation removed the depressive coloration of psychasthenic experiences. The patients noted that, in comparison with phenamine, the stimulating effect of sydnophene is manifested less sharply: there is no sensation of increased excitability. Sydnophene is usually satisfactorily transported and therefore can be used not only in stationary practice but also in ambulatory practice; however, considering that the healing action of the preparation is associated with stimulation of the CNS, it should be used only by prescription and under the supervision of a doctor. The preparation should be dispensed only by prescription (List A).

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