SYNTHESIS AND NEUROPHARMACOLOGICAL ACTIVITY OF DISULFIDE DERIVATIVES OF PYRIDOXINE

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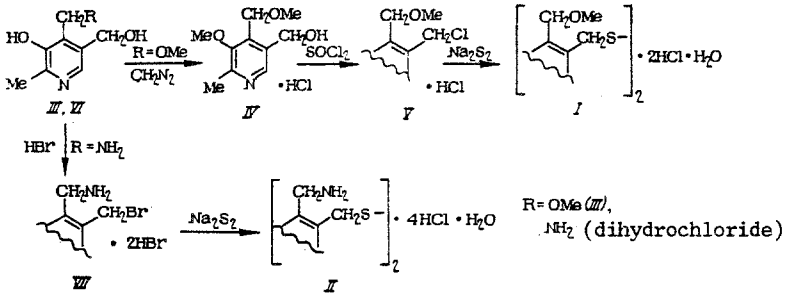
Special features of drug preparations based upon vitamins and enzymes are the presence of a wide activity spectrum, ease of penetration of the cell membrane, low toxicity, and almost complete absence of side effects [4].

The drug Piriditol [bis(2-methyl-3-hydroxy-4-hydroxymethyl-5-methyl) disulfide hydrochloride] belongs to this group of materials. This preparation is used in neuro-psychiatric practice for different forms of depression, disturbances of the cerebral blood circulation, mental insufficiencies in children, and other pathologies [1].

We earlier carried out an investigation in which the influence of substituents on the pyridine ring of the molecule on its psychopharmacological activity spectrum was studied. For this purpose we synthesized the 4'-methyl ether of Piriditol [bis(2-methyl-3-hydroxyl-4-methoxymethylpyridyl-5-methyl)disulfide] [2].

In continuation of these studies, we synthesized bis(2-methyl-3-methoxy-4-methoxymethylpyridyl-5-methyl)disulfide (I) and bis(2-methyl-3-hydroxy-4-aminomethylpyridyl-5-methyl)-disulfide (II) [5]. The starting material for the preparation of I was a byproduct of the preparation of vitamin B_6; 2-methyl-3-hydroxy-4-methyoxymethyl-5-hydroxymethylpyridine (III), methylated in ether with diazomethane to give 2-methyl-3-methoxy-4-methoxymethyl-5-hydroxymethylpyridine (IV). Treatment of IV with thionyl chloride gave 2-methyl-3-methoxy-4-methoxymethyl-5-chloromethylpyridine (V), and treatment of V with sodium sulfide gave I, isolated in the form of the dihydrochloride monohydrate.



Heating 2-methyl-3-hydroxy-4-aminomethyl-5-hydroxymethylpyridine (VI) with 48% HBr gave 2-methyl-3-hydroxy-4-aminomethyl-5-bromomethylpyridine hydrobromide (VII), which gave II with sodium sulfide.

EXPERIMENTAL (CHEMISTRY)

Melting points were obtained on a Koeffler hot stage, and are not corrected. The progress of the reactions and the purity of the compounds obtained were followed by TLC on Silufol UV-254 plates (ChSSR) in the systems: 1 = methyl ethyl ketone: 25% aqueous ammonia: water (17:1:2); 2 = dioxane:acetone:25% aqueous ammonia (9:9:2); and 3 = i-PrOH:25% aqueous ammonia (20:3).

Materials on the TLC plates were visualized with UV and with 2,6-dichloroquinone chloroimide (Gibbs reaction).

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2-Methyl-3-methoxy-4-methoxymethyl-5-hydroxymethylpyridine Hydrochloride (IV). To 100 ml of diethyl ether was added 30 ml of 40% KOH, the mixture was cooled to 0-5°C and 10 of nitrosomethylurea (obtained according to [3]) was introduced. The mixture was stirred for 1 h and the ether layer containing CH_2N_2 was separated from the aqueous layer. To 4 g of III in 20 ml of anhydrous alcohol was added the solution of diazomethane in ether at 5-10°C, and the solution was stirred and treated with carbon. The filtrate was concentrated to give a residue which was dried slightly with alcohol, crystallized from alcohol, saturated with HCl, and dried to give 3.43 g (67.65%) of IV, mp 140-142°C (negative Gibbs reaction), R_f 0.9 (system 2).

2-Methyl-3-methoxy-4-methoxymethyl-5-chloromethylpyridine Hydrochloride (V). To 6 g of IV was added 60 ml of dioxane and 6 ml of $SOCl_2$, and the mixture was stirred for 6 h. The solvent was removed under aspirator vacuum and the residue was washed with dioxane to give 6.24 g (96.44%) of V, mp 133-136°C, R_f 0.55 (system 3).

Bis(2-methyl-3-methoxy-4-methoxymethylpyridyl-5-methyl)disulfide Dihydrochloride Monohydrate (I). To a solution of sodium sulfide (4.3 g of $Na_2S \cdot 9H_2O$ and 0.55 g of S) cooled to 5°C was rapidly added a solution of 2.2 g of V. The mixture was stirred for 3 h, and the precipitate was separated, treated with 10 ml of 10% HCl, heated, filtered, and concentrated under vacuum. The precipitate was separated, washed with anhydrous alcohol and dried to give 1 g (44%) of I, mp 172-174°C, R_f 0.38 (system 3).

2-Methyl-3-hydroxy-4-aminomethyl-5-bromomethylpyridine Dihydrobromide (VII). A solution of 5 g of VI in 40 ml of 48% HBr was heated for 1 h at 126-130°C. The crystallized precipitate was separated, washed with acetone and dried to give 5.08 g (62%) of VII, mp >300°C.

Bis(2-methyl-3-hydroxy-4-aminomethylpyridyl-5-methyl)disulfide Tetrahydrochloride Monohydrate (II). To a solution of sodium disulfide (9 g of $Na_2S \cdot 9H_2O$ and 1.2 g of S) was added with cooling a solution of 5 g of VII in 50 ml of water. The mixture was heated at 40°C for 2 h and filtered. The precipitate was dissolved in 15 ml of 10% HCl, treated with carbon, and filtered. The filtrate was evaporated under aspirator vacuum to the beginning of crystallization and the precipitate was removed, washed with anhydrous alcohol, and dried to give 2.33 g (71.69%) of II, mp 223-224°C, R_f = 0.85 (system 1). $C_{16}H_{22}N_4O_2S_2 \cdot 4HCl \cdot H_2O$.

EXPERIMENTAL (PHARMACOLOGY)

The central neurotropic activity of the compounds was studied by generally accepted methods in experiments on white nonhybrid mice of both sexes weighing 20 ± 2 g. All materials were introduced intraperitoneally in aqueous solution 30-60 min before beginning the study. The control animals were treated with solvent of the corresponding volume. The activity of the synthesized compounds was compared with that of Piriditol in an equivalent dose. The acute toxicity was determined with mice by intraperitoneal injection, and the LD_{50} was calculated by the method of Kerber. Statistical workup of the experimental results was carried out by probit-analysis and by variant statistics using the Student test.

The results of these studies showed that I and II were significantly more toxic than Piriditol, and have a toxicity near to that of the 4'-methyl ether of Piriditol. The LD_{50}'s (in mg/kg by intraperitoneal injection) were Piriditol, 1039; 4'-methyl ether of Pyriditol, 434; I, 583.4; and II, 466.7.

Study of I and II in a series of neuropharmacological screening tests showed that both substances disrupted the behaviorial reactions of the animals, and depressed the orientational reaction (OR). ([ED_{50} (in mg/kg) in a test of the disruption of the OR of Piriditol = 86 (53.1-131.6); of the 4' methyl ether of Piriditol = 115 (96.6-136.8), of I = 14(8.7-22.4); of II = 140 (87.5-224)] and spontaneous motor activity (SM A) [I by 70-82% at doses of 56-168 mg/kg; II by 55-73% at doses of 86.9-217.4].) Piriditol shows similar activity at doses at 200-300 mg/kg, and the 4'-methyl ether of Piriditol at doses of 50-150 mg/kg. Compound II, in contrast to the other compounds, showed short-lived ataxia and myorelaxia at low doses (43.5-86.9 mg/kg) and weak muscular-weakening action of 3.5 h duration at high doses (217.4-260.9 mg/kg).

With respect to phenamine (amphetamine) hyperactivity (PHA), the subject materials showed activity in different directions: I strengthened the motor excitation of the animals stimulated by phenamine (by 40% at a dose of 11.2 mg/kg), and II, like the 4-methyl ether of Piriditol, depressed PHA (by 51% at doses of 43.5-86.9 mg/kg).

Piriditol showed practically no influence on the PHA.

Compound I was more active than Piriditol and its methyl ether in increasing the "group-type" toxicity of phenamine. The toxicity of phenamine in the presence of I for "grouped" animals increased 2.7 times, in the presence of Piriditol, 1.2 times, and in the presence of the methyl ether of Piriditol, 2.2 times. Compound II, however, did not influence the effects of phenamine in these tests. Compounds I and II increased the duration of the soporific action of hexobarbital-sodium by 2 and 3.2 times, respectively (the Piriditol increase was 1.7 times and the increase by Piriditol 4' methyl ether was 2.3 times). In this case, the increase in the duration of the marginal condition of the animals arises at the expense of the later reduction in their reflex disturbances. It is possible that the potentiating influence of I and II is connected not with their own depressive influence on the CNS, but with an inhibitory effect on the metabolism of barbiturates. Compound I, in comparison with other disulfide derivatives of pyridoxine, prevents the spread of the tonic components of the convulsion produced by subcutaneous injection of korazole.

Thus, in experiments on animals, compound I showed both a sedative (disruption of OR and SMA, elongation of hexylbarbital-sodium sedation), and a stimulative (strengthening of the effects of phenamine) action, and II produced only a sedative effect with signs of myorelaxation. These materials apparently require the presence of an amino group in position 4', in distinction to other compounds.

It was established earlier [2] that the substitution of hydroxyl in position 4' of the pyridine ring by a methoxy group leads to the formation of compounds acting on the CNS similarly to Piriditol, but possessing higher toxicity and a lower latitide in therapeutic action. Yet the substitution of hydroxyl in positions 3 and 4' by methoxy (compound II) brought about a strengthening of the stimulatory and antidepressant components in the spectrum of psychotropic activity of the materials of this series. And although I is more toxic than Piriditol, it possesses a sufficiently wide therapeutic activity.

The above results show that a further search for biologically active materials in the area of the sulfide derivatives of pyridoxine may bring about the creation of new, highly effective drugs.

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