# SYNTHESIS OF ANALOGS OF 5(4)-AMINOIMIDAZOLE-4(5)-CARBOXAMIDE AND PURINES.

## X. SYNTHESIS AND STUDY OF PROPERTIES OF NEW ANALOGS OF BREDININ AGLYCONE

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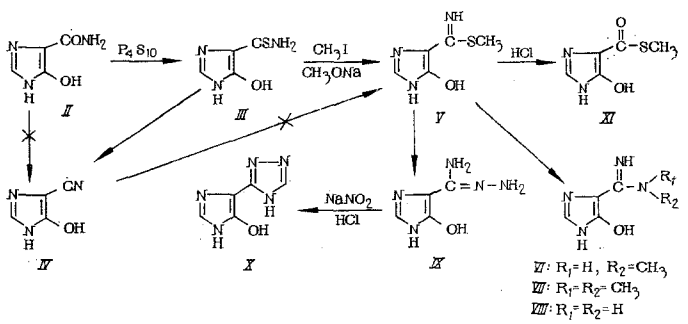
UDC 615.332(Bredininum)]012.1

We have already described the synthesis of certain analogs of 5(4)-aminoimidazole-4(5)-carboxamide and purines [1]. The antibiotic bredinin (I), 1-β-D-ribofuranosyl-5-hydroxyimidazole-4-carboxamide, and also its aglycone, 5(4)-hydroxyimidazole-4(5)carboxamide (II) have antibacterial, immunodepressive and antitumorigenic activity [2, 3].

We modified the carboxamide group of bredinin aglycone, and studied the biological activity of the compounds synthesized. In the reaction of (II), obtained as in [4], with $P_4S_{10}$ in dioxane, only the carboxamide group is thionated, and 5(4)-hydroxyimidazole-4(5)-carbothioamide (III) is formed. In attempts to synthesize 5(4)-hydroxyimidazole-4(5)-carbonitrile (IV) by reacting (II) with dehydrating agents, compound (IV) could not be isolated from the reaction mixture. Compound (IV) could only be obtained in a good yield when an ammoniacal solution of (III) was treated with $HgCl_2$. However, under all the conditions studied, attempts to convert the nitrile group in compound (IV) into an iminoether group were unsuccessful. As the result of the reaction, a complex mixture of products is obtained, which could not be separated by known methods. Therefore to obtain 5(4)-hydroxyimidazole with a thioiminoether group in the 4(5)-position of the ring, we studied the methylation of III with methyl iodide. Despite the presence of four nucleophilic centers in the molecule of 5(4)-hydroxyamidazole-4(5)-thioamide, 4(5)-(α-iminomethylthiomethyl)-5(4)-hydroxyimidazole (V) is the only product formed. In the PMR spectrum of this compound, there is one single signal of the methyl group protons at 2.5 ppm, which unequivocally confirms the structure of (V),




When an alcoholic solution of (V) is boiled with an amine, methyl mercaptan is liberated, and amidines (VI-VIII) are formed. Similarly, in the reaction of (V) with hydrazine hydrate, 5(4)-hydroxyimidazole-4(5)-amidrazone (IX) is formed. In the treatment of (IX) with sodium nitrite in dilute hydrochloric acid, 4(5)-[2'-tetrazolyl]-5(4)-hydroxylimidazole (X) is formed. Compound (V) is therefore the key compound in the synthesis of derivatives of 5(4)-hydroxyimidazoles with amidine and amidrazine groups in position 4 of the ring, and can also be used to prepare various 4(5)-heteryl-4(5)-hydroxyimidazoles. To obtain derivatives of 5(4)-hydroxyimidazoles with an ester group in position 4 of the imidazole ring, we studied hydrolysis in hydrochloric acid of various concentrations. The hydrolysis should yield products such as

S. M. Kirov Ural' Polytechnical Institute, Sverdlovsk. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 15, No. 7, pp. 58-60, July, 1981. Original article submitted May 23, 1980.

 0091/150X/81/1507-0498$07.50 

amide, acid and thioester. We found that when (V) is heated with 0.1 N hydrochloric acid, 4(5)-methylthiocarbonyl-5(4)-hydroxyimidazole (XI) is formed.

For all the compounds synthesized, we studied the ability to inhibit the synthesis of nucleic acids in cultures of ascite tumorigenic cells by a procedure described in [5]. The activity of compounds (III-IX) was studied in comparison with that of bredinin aglycone. From tests on NK/Ly and Fischer tumor cultures, we showed that the $ED_{50}$ for compound (II) is 1-10 μg/ml, and for compounds (VII-XI), 100-150 μg/ml. Compounds (III) and (IX) had no antitumorigenic activity.

The antiinfluenza activity of compounds (II) and (III) was studied at the All-Union Influenza Institute by V. I. Il'enko and O. F. Alferova on developing chicken embryos and mice. The bredinin aglycone has no antiinfluenza activity, and for the 5(4)-hydroxy-4(5)-thioamide, the protection index on the influenza virus B has a value of 30-35%.

## EXPERIMENTAL

The IR spectra of the compounds synthesized were obtained on the UR-20 (GDR) spectrophotometer in KBr tablets, the UV spectra of the solutions in 0.1 N hydrochloric acid were run on the Perkin-Elmer UV-402 spectrophotometer (Sweden). The PMR spectra were run on the Perkin-Elmer 12B apparatus (60 MHz) (Sweden) in DMSO-$d_6$ solutions, using TMS as internal standard. Thin-layer chromatography (TLC) was used in the following systems: n-butanol—acetic acid—water (4:1:1) (A) and n-propanol—0.2 N ammonia (3:1) (B) on Silufol UV plates.

4(5)-Hydroxyimidazole-4(5)-carbothioamide (III). A 72 g portion (0.325 mole) of $P_4S_{10}$ is added to a solution of 40 g (0.246 mole) of (I) in 400 ml of dioxane. The reaction mixture is boiled with continuous stirring for 4 h, cooled and filtered. The precipitate is dissolved in 1 liter of boiling 1 N hydrochloric acid, 1 g of activated charcoal is added and the mixture is filtered. The filtrate is evaporated under reduced pressure to 100 ml, cooled and filtered. The precipitate is recrystallized from water. Yield, 25 g (57%), mp 202-210°C, $R_f$ 0.7 (system A), 0.8 (system B). UV spectrum, $\lambda_{max}$, nm (log ε): 209 (3.78), 256 (3.65), 273 (3.70), 331 (4.60). Found, %: C 33.74; H 3.632; N 29.36; S 22.19. $C_4H_5N_3OS$. Calculated, %: C 33.57; H 3.50; N 29.37; S 22.38.

5(4)-Hydroxyimidazole-4(5)-carbonitrile (IV). A 5.72 g portion (0.029 mole) of $HgCl_2$ in 80 ml of ethanol and 8.1 ml (0.042 mole) of a 20% aqueous solution of methylamine are added to a suspension of (III) (0.021 mole) in ethanol. The reaction mixture is held for 30 min at 30°C, and the precipitate is filtered. The filtrate is evaporated under reduced pressure. The precipitate is crystallized from water. Yield, 0.39 g (15%), mp 215°C, $R_f$ 0.5 (system A), 0.65 (system B). UV spectrum, $\lambda_{max}$, nm (log ε): 229 (3.91), 263 (3.88). IR spectrum, ν, $cm^{-1}$: 2230 (C≡N). Found, %: C 43.82, H 2.31; N 38.56. $C_4H_3N_3O$. Calculated, %: C 44.05; H 2.75; N 38.53.

4(5)-(α-Iminomethylthiomethyl)-5(4)-hydroxyimidazole (V). A 0.46 g portion of methyl iodide is added to 0.5 g (0.03 mole) of sodium in a solution of sodium methylate in methanol, obtained from 0.08 g (0.03 mole) of sodium in 45 ml of methanol. The mixture is stirred at room temperature for 6 h. The precipitate is filtered and crystallized from water. Yield, 0.47 g (85%), mp 208-210°C, $R_f$ 0.6 (system A), 0.25 (system B). UV spectrum $\lambda_{max}$, nm (log ε): 215 (3.97), 327 (4.27). PMR spectrum (DMSO-$d_6$), δ, ppm: 2.5 s ($CH_3$), 7.310 (CH). Found, %: C 38.41; H 4.29; N 27.0; S 20.2. $C_5H_7N_3O_3S$. Calculated, %: C 38.30; H 4.46; N 26.8; S 20.4.

5(4)-Hydroxyimidazole-4(5)-[N-methyl]carboxamidine (VI). A 1.57 g portion (0.01 mole) of (V) is dissolved in 100 ml of 25% methylamine in methanol. The mixture is boiled for 1 h, cooled and filtered. The precipitate is crystallized from water. Yield, 0.70 g (50%), mp 260-265°C, $R_f$ 0.41 (system A), 0.22 (system B). UV spectrum, $\lambda_{max}$, nm (log ε): 287 (4.13). Found, %: C 43.00; H 5.93; N 40.7. $C_5H_8N_4O$. Calculated, %: C 42.80; H 5.73; N 40.0.

5(4)-Hydroxyimidazole-4(5)-[N,N-dimethyl]-carboxamidine (VII). A solution of 1.57 g (0.01 mole) of (V) in 100 ml of a 25% solution of dimethylamine in methanol is boiled for 5 h, cooled and filtered. The precipitate is crystallized from absolute methanol. Yield, 0.72 g (51%), mp 272-274°C. Found, %: C 46.76; H 6.57; N 36.58. $C_6H_{10}N_4O$. Calculated, %: C 46.70; H 6.50; N 36.40.

5(4)-Hydroxyimidazole-4(5)-carboxamidrazone (IX). A 5 ml portion hydrazine hydrate is added to a solution of 1.57 g of (V) in 100 ml of ethanol, and the mixture is boiled for 1 h.

The precipitate is crystallized from water. Yield, 1.05 g (80%), mp 198-200°C. UV spectrum, $\lambda_{max}$, nm (log ε): 285 (4.2). Found, %: C 35.20; H 5.01; N 49.2. $C_5H_7N_5O$. Calculated, %: C 35.00; H 4.95; N 49.5.

4(5)-[2'-Tetrazolyl]-5(4)-hydroxyimidazole (X). A solution of 1.41 g (0.01 mole) of (IX) in 14 ml of 1 N hydrochloric acid is cooled to a temperature below 0°C, and a solution of 0.7 g (0.0102 mole) of sodium nitrite in 2 ml of water is added. The mixture is stirred for 1 h, and filtered. The precipitate is recrystallized from water. Yield, 1.5 g (90%). $R_f$ 0.2 (system A); 0.27 (system B). UV spectrum, $\lambda_{max}$, nm (log ε): 230 (3.14), 280 (3.17). Found, %: C 29.10; H 3.07; N 51.79. $C_4H_4N_6O \cdot 0.5H_2O$. Calculated, %: C 29.08; H 3.10; N 52.0.

4(5)-Methylthiocarbonyl-5(4)-hydroxyimidazole (XI). A solution of 1.57 g (0.01 mole) of (V) in 14 ml of 0.1 N hydrochloric acid is stirred at 80°C for 30 h, cooled and filtered. The precipitate is crystallized from water. Yield, 0.79 g (50%), UV spectrum, $\lambda_{max}$, nm (log ε): 235 (3.11), 307 (3.17). PMR spectrum (DMSO-$d_6$), δ, ppm: 2.2 s ($CH_3$), 8.16 s (CH). Found, %: C 37.75; H 3.94; N 17.7; S 19.72. $C_5H_6N_2O \cdot H_2O$. Calculated, %: C 38.00; H 3.79; N 17.7; S 20.2.

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# EFFECT OF PHARMACOLOGICAL PREPARATIONS ON THE ALCOHOL CONSUMPTION OF ANIMALS UNDER CONDITIONS OF FREE CHOICE


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UDC 615.246.9.076.9:616:89-008.441.13-092.9


At the present time a complex of measures is used in the control of chronic alcoholism, an important one of which is pharmacotherapy. Expansion of the arsenal of agents that affect the attraction to alcohol, the syndrome of abstinence, the depth of acute alcohol intoxication, etc., requires a special investigation and selection of them. The search for new and effective pharmacological agents possessing the indicated properties is urgent, but it has been little developed from the methodological standpoint [1].

The most adequate model for the search for "antialcohol" agents, in our view, is the method of free choice. The use of this method permits the detection of preparations that prevent or suppress the pathological attraction to alcohol [2]. In addition, the method can also be used to seek pharmacological agents that affect the syndrome of abstinence [3].

In this work we made a comparative study of the action of 11 preparations from different pharmacological groups on addiction to alcohol in laboratory animals under conditions of free choice. Many of the investigated preparations are being used in the clinical treatment of alcoholism. Part of them (neuroleptics) are usually used for the treatment of alcohol psychoses, part (apomorphine, antabuse) to suppress the attraction to alcohol as a result of sensitization or a negative conditioned reflex.

In connection with the aforementioned, we were interested in comparing the experimental and clinical data in order to obtain more complete information on the spectrum of action of the preparations, which would also permit an evaluation of the informativeness of the method of free choice for the evaluation of the action of substances on addiction to alcohol.


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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 15, No. 7, pp. 60-63, July, 1981. Original article submitted April 21, 1980.




0091-150X/81/1507-0500$07.50