SYNTHESIS OF ANALOGS OF 5(4)-AMINOIMIDAZOLE-4(5)-CARBOXAMIDE

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UDC 547.784.1'782.9'781.5.07

In order to obtain 5(4)-aminoimidazole-4(5)carboxamide antagonists, the hydrazides of 5(4)-aminoimidazole-4(5)-carboxylic acid and 5(4)-aminoimidazole-4(5)hydroxamic acid were synthesized, and the reaction of 5(4)-bromo-4(5)sulfamoylimidazole with amines was studied.

In connection with the fact that 5(4)-aminoimidazole-4(5)-carboxamide (AICA) is one of the important precursors of purines, AICA antagonists are of definite interest for the study of biological activity. There are presently a number of communications regarding the antibacterial and antitumorigenic activities of AICA antagonists that were previously synthesized and studied by various authors [1-4].

In this paper we describe the synthesis of new AICA analogs in which the carboxamide group of the metabolite was replaced by a carbohydrazide group (I) and a carboxyhydroxylamide group (II), and the reaction of 5(4)-bromo-4(5)-sulfamoylimidazole (IV) with amines, which was carried out in order to obtain 5(4)-amino-4(5)-sulfamoylimidazole (III), was studied.

I X=$CONHNH_2$, Y=NH_2; II X=CONHOH, Y=NH_2;

III X=SO_2NH_2, Y=NH_2; IV X=SO_2NH_2, Y=Br; V X=H, Y=Br

5(4)-Aminoimidazole-4(5)carboxylic acid hydrazide (I) was obtained by stannous chloride reduction of 5(4)-nitroimidazole-4(5)-carboxylic acid hydrazide (VI), synthesized by the method in [2]. 5(4)-Aminoimidazole-4(5)hydroxamic acid (II) was synthesized by hydrazine hydrate reduction (on Raney nickel) of 5(4)-nitroimidazole-4(5)hydroxamic acid (VII), obtained via the method in [5]. 5(4)-Amino-4(5)-sulfamoylimidazole (III), was obtained by the reaction of 5(4)-bromo-4(5)-sulfamoylimidazole (IV), obtained by the method in [6], with ammonia under more severe conditions than those used in [6]. 5(4)-Bromoimidazole (V) was isolated instead of the expected III when IV was heated in ammonia-saturated alcohol in an autoclave at 180°. Compound V was similarly obtained by the reaction of IV with diethylamine. Compound IV remained unchanged when it was heated in alcohol at 180° without amine.

EXPERIMENTAL

5(4)-Aminoimidazole-4(5)-carboxylic Acid Hydrazide (I). A total of 1.5 g (0.0087 mole) of 5(4)-nitroimidazole-4(5)-carboxylic acid hydrazide (VI) and 6.52 g (0.028 mole) of $SnCl_2 \cdot 2H_2O$ were added with stirring at room temperature to 60 ml of ethanol and 2 ml of concentrated HCl. The mixture was held at room temperature for 3 h, and H_2S was passed through the solution until the tin had precipitated completely. The precipitate of SnS_2 was removed by filtration and washed with hot alcohol. The light-yellow filtrate was evaporated to dryness in vacuo at 65°. The residue was crystallized from isopropyl alcohol–water–ether to give 0.8 g (50%) of fine, colorless crystals with mp 217° (dec.). Found: C 27.9; H 4.5; N 39.0%. $C_4H_7N_5O \cdot HCl$. Calculated: C 27.3; H 4.5; N 39.5%.

S. M. Kirov Ural Polytechnic Institute, Sverdlovsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1421-1422, October, 1971. Original article submitted February 12, 1971.

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5(4)-Aminoimidazole-4(5)-hydroxamic Acid (II). Raney nickel was added to 1 g (0.0058 mole) of 5(4)-nitroimidazole-4(5)-hydroxamic acid (VII) in 30 ml of ethanol, and 1.2 ml (0.0248 mole) of hydrazine hydrate was added dropwise to the mixture at 70°. The mixture was held at this temperature for 4 h. The catalyst was removed by filtration, and the filtrate was evaporated to dryness in vacuo. The residue was crystallized from water to give 0.4 g (44%) of fine, colorless crystals with mp 180° (dec.). Found: C 30.2; H 5.1; N 34.2%. $C_4H_6N_4O_2 \cdot H_2O$. Calculated: C 30.0; H 5.0; N 34.0%.

Reaction of 5(4)-Bromo-4(5)-sulfamoylimidazole (IV) with Ammonia. A 1-g (0.00464 mole) sample of 5(4)-bromo-4(5)-sulfamoylimidazole (IV) was suspended in 45 ml of ammonia-saturated ethanol at −10°. The reaction mixture was heated in an autoclave at 180° for 12 h. The solvent was removed by distillation, and the residue was crystallized from water to give 0.4 g (61.5%) of V with mp 129-130° (mp 130-131° [7]). Found: Br 53.9%. $C_3H_3BrN_2$. Calculated: Br 54.4%. This product did not depress the melting point of an authentic sample obtained by the method in [7].

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