SULFANYLAMIDE DERIVATIVES CONTAINING THE 1-ADAMANTYL GROUP

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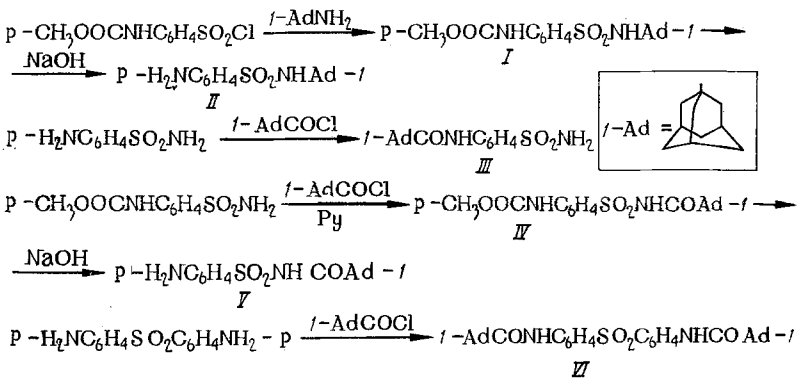
Several sulfanylamide derivatives containing 1-adamantyl or 1-adamantoyl groups at N^1 or N^4 were prepared to determine their chemotherapeutic activity.

The special features of the adamantane structure, associated with large volume, symmetry, and significant lipophilicity of its molecule, serve as the reasons for synthesis of many types of physiologically active materials containing the adamantyl group [1-6]. In addition, the possible biological activity is substantiated by both the cage surface (increased penetrability through hydrophobic membranes) and the molecular surface (specificity of reaction of the bulky nonpolar structure with the surface of the receptor).

This work describes the synthesis of several sulfanylamide derivatives containing an adamantyl radical in the amide or amine group; the compounds were prepared for clarification of the effect of this structural factor on antimicrobic activity:



Reaction of the acid chloride of carbomethoxysulfanilic acid with 1-aminoadamantane yielded N^4-carbomethoxy-N^1-(1-adamantyl)sulfanylamide (I), the basic saponification of which led to N^1-(1-adamantyl)-sulfanylamide (II). Reaction of the acid chloride of 1-adamantanecarboxylic acid in acetone with the sulfanylamide yielded N^4-(1-adamantoyl)sulfanylamide (III) (comp. [7]); the reaction of the same acid chloride with N^4-carbomethoxysulfanylamide in pyridine gave N^4-carbomethoxy-N^1-(1-adamantoyl)sulfanylamide (IV), the gradual saponification of which with a basic solution at 50°C led to N^1-adamantoylsulfanylamide (V). p,p'-Di-(1-adamantoylamino)diphenyl sulfone (VI) was also synthesized by acylation of p,p'-diaminodiphenyl sulfone with the acid chloride of 1-adamantanecarboxylic acid (comp. [8]).

The obtained compounds were examined at the Department of Chemotherapy of the Institute of Pharmacology and Chemotherapy for their antibacterial effect (in a synthetic nutrient) in relation to a series of representatives of Gram-positive and Gram-negative microbes. All of these compounds did not display antibacterial activity; also, they did not show an inhibiting effect on the growth of acid-resisting bacilli B-5 and tuberculosis microbacteria of the human type (strain H37Rv).

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EXPERIMENTAL*

N^4-Carbomethoxy-N^1-(1-adamantyl)sulfanylamide (I). To a solution of 2.6 g of 1-aminoadamantane in 12 ml of dry pyridine was added 4.32 g of p-phenylurethylansulfonyl chloride. After the exothermal reaction the mixture was heated for 3 h on a boiling water bath and cooled, 90 ml of water was added, and the precipitated solid was filtered, washed with water, dried, and saponified without further purification. Yield 4.5 g (71.7%). A sample after recrystallization from dichloroethane had mp 225-228°. Found, %: N 7.93, 7.95; S 8.85, 8.86. $C_{18}H_{24}N_2O_4S$. Calculated, %: N 7.69; S 8.79.

N^1-(1-Adamantyl)sulfanylamide (II). A mixture of 3.7 g of the intermediate product (I) from the preceding step and 77 ml of a 10% solution of sodium hydroxide was stirred for 8 h with boiling and a reflux condenser. After cooling, the precipitate was filtered, washed with water to a neutral reaction to phenolphthalein, dried, and recrystallized from benzene. The obtained material contained solvent of crystallization and therefore was dried in vacuum at 100°. Yield 2.7 g (86.8%). Needles having mp 182-182.5° are insoluble in water and soluble in cold acetone, alcohol, ethyl acetate, and dichloroethane. Found, %: N 9.44, 9.23; S 10.26, 10.18. $C_{16}H_{22}N_2O_2$. Calculated, %: N 9.14; S 10.47.

N^4-(1-Adamantoyl)sulfanylamide (III). To a solution of 2.04 g of the acid chloride of 1-adamantanecarboxylic acid in 10 ml of acetone was added 3.5 g of the sulfanylamide. The reaction mixture was stirred for 4 h at 40°. The precipitate was filtered, washed with acetone, a 3% solution of hydrochloric acid, and water. We obtained 3.01 g (87.5%) of material having mp 270° (dec., from a mixture of dimethylformamide-alcohol, 4:1); sparingly soluble in the normal solvents and soluble in the cold in dimethylformamide. Found, %: N 8.40, 8.56; S 9.60, 9.45. $C_{17}H_{22}N_2O_3S$. Calculated, %: N 8.38; S 9.59.

N^4-Carbomethoxy-N^1-(1-adamantoyl)sulfanylamide (IV). To a solution of 5.7 g of the acid chloride of 1-adamantanecarboxylic acid in 15 ml of dry pyridine was added 6.61 g of N^4-carbomethoxysulfanylamide. The reaction mixture was heated for 3 h with a reflux condenser on a boiling water bath. After cooling, to the mixture was added 100 ml of water, and the precipitated solid was filtered, washed with water, and dried. Yield 10.4 g (92.5%). The obtained material was used without further purification for the next step. After crystallization of the material from dichloroethane, the solvent of crystallization was removed by heating in vacuum. The material is insoluble in water and alcohol, and soluble at room temperature in alcohol, acetone, or ethyl acetate; mp 215-216°. Found, %: N 7.00, 6.97; S 8.21, 8.18. $C_{19}H_{24}N_2O_5S$. Calculated, %: N 7.14; S 8.17.

N^1-(1-Adamantoyl)sulfanylamide (V). A mixture of 1.5 g of the carbomethoxy derivative (IV) and 15 ml of a 10% solution of sodium hydroxide was stirred for 2 h at 50°. The precipitated solid was dissolved by carefully adding a 10% solution of sodium hydroxide. Hydrochloric acid was added to the obtained solution to a weakly acid reaction to Congo. The precipitate was filtered, dried, and recrystallized from dichloroethane. The material is insoluble in water and benzene, and soluble in alcohol, ethyl acetate, acetone, bases, and acids; mp 217-218° (from dichloroethane). Found, %: N 8.47, 8.39; S 9.35, 9.31. $C_{17}H_{22}N_2O_3S$. Calculated, %: N 8.38; S 9.59.

p,p'-Di-(1-adamantolylamino)diphenyl Sulfone (VI). To a solution of 2.48 g of p,p'-diaminodiphenyl sulfone in 20 ml of acetone was added 2 ml of pyridine and then in portions 5.96 g of the acid chloride of 1-adamantanecarboxylic acid. The reaction mixture was boiled for 1 h and after cooling the precipitate was filtered, washed with acetone, a 5% solution of hydrochloric acid, and water. We obtained 6.14 g (71.5%) of a material which is sparingly soluble in the usual solvents; mp 350° (dec., from a mixture of dimethylformamide-alcohol, 3:1). Found, %: 5.30, 5.37; S 5.61, 5.81. $C_{34}H_{40}N_2O_4S$. Calculated, %: N 4.89, S 5.59.

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* Melting points are uncorrected.