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Preparation of the biologically active substance 8-*N,N*-dimethylaminoethyl-7-thietanyl-1,3-dimethylxanthine and its salts

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The xanthine structure is the basis of the chemical structure of purine alkaloids, and it also plays an important role in the synthesis of new highly effective and low-toxic heterocyclic drugs. The diverse biological activity of xanthine derivatives has attracted the interest of many scientific groups for many years, leading to a comprehensive study of this core and the development of new biologically active compounds. In this study, we introduced thietanyl and dimethylaminoethyl substituents into the theophylline molecule and investigated the synthesis pathways of its salts.

The aim of the study synthesis and study of biological activity of a new purine derivative containing thietanyl and dimethylaminoethyl radicals.

Materials and methods. The study used the substance 8-chlorotheophylline (CAS number 85-18-7), as well as solvents and reagents of the "c.p." and "p.b.a." categories.

To confirm the structure of the synthesized compounds, IR and NMR spectra were recorded. The IR spectra of the compounds were recorded on an Infrared-FT-02 spectrometer in KBr disks. The NMR spectra were recorded on a Bruker DRX-500 instrument with a working frequency of 500.13 MHz (1H) and 125.76 MHz (13C).

The study of the effect on platelet aggregation was carried out using the Born method (Born G.G.V. Nature (London).-V.194.) on the AT-02 aggregometer ("Medtech", Russia). The determination of anticoagulant activity was carried out using the well-established clotting tests on the Solar CGL 2110 turbidimetric hemocoagulometer ("SOLAR", Russia).

Results and Discussions. Preparation of 8-**Chloro-7-thietanyl-1,3-dimethylxanthine (R1)**. Dissolved 0.96 g of sodium hydroxide in 50 ml of water. Added 4.30 g (10 mmol) of 8-chlorotheophylline to the solution. At a temperature of 40°C, 2.60 g (24 mmol) of epithiochlorohydrin was added with rapid stirring and the mixture was kept at a temperature of 40–50°C for 30 min. It was cooled to room temperature with stirring. The precipitate was filtered off, washed with 5% sodium hydroxide and water, and dried. The yield was 2.15 (50.0%).

8-*N,N*-Dimethylaminoethylamino-7-thietanyl-1,3-dimethylxanthine (R2). 1.43 g (5 mmol) of 8-chloro-7-thietanyl-1,3-dimethylxanthine was dissolved in 50 ml of isobutanol, 1.10 g (12.5 mmol) of *N,N*-dimethylaminoethylamine was added, and the reaction mixture was boiled for 5 hours. the mixture was cooled and left overnight in the refrigerator. The next day, the precipitate was filtered, washed with water, and dried. Yield: 1.10 g (77.0%).

8-*N,N*-Dimethylaminoethylamino-7-thietanyl-1,3-dimethylpurine hydrochloride (R3). 1.0 g of 8-*N,N*-dimethylaminoethylamino-7-thietanyl-1,3-dimethylpurine was placed in a 250 ml flat-bottomed flask and dissolved in 100 ml of acetone with slight heating. Cooled to room temperature, then on a magnetic stirrer, dropwise added a solution of hydrochloride diluted in alcohol pH to 3. After 2-3 h filtered, the filtrate was washed with acetone, left to dry. Yield 1.01 g (101.0 %).

8-*N,N*-Dimethylaminoethylamino-7-thietanyl-1,3-dimethylxanthine citrate (R4). 0.5 g (15 mmol) of 8-*N,N*-dimethylaminoethylamino-7-thietanyl-1,3-dimethylxanthine was dissolved in 25 mL of ethanol under heating. In parallel, 0.32 g (15 mmol) of citric acid was dissolved in 25 mL of ethanol. The resulting solutions were mixed and boiled with a reflux condenser for 15 min, cooled to room temperature, and then left in the refrigerator. After 24 h, the solution was filtered and washed with acetone, and left to dry. The yield was 0.20 g (40.0%).

8-*N,N*-Dimethylaminoethylamino-7-thietanyl-1,3-dimethylxanthine nicotinate (R5). 0.5 g (15 mmol) of 8-*N,N*-dimethylaminoethylamino-7-thietanyl-1,3-dimethylxanthine was dissolved in 25 mL of ethanol under heating. In parallel, 0.19 g (15 mmol) of nicotinic acid was dissolved in 25 mL of ethanol. The resulting solutions were mixed and boiled with a reflux condenser for 15 minutes, cooled to room temperature, and then left in the refrigerator. After 24 hours, the acetone was distilled off and left to dry. The yield was 0.51 g (102.0%).

Experimental biological part. The solutions showed varying degrees of effect on the plasma component of the hemostasis system, manifested by a change in the indicator of the internal pathway of blood clotting – APTV. At the specified concentration, the solutions did not affect the indicator of the concentration of fibrinogen and prothrombin time.

Solutions under laboratory codes R2 and R5 showed anti-aggregation activity exceeding the values of acetylsalicylic acid (by the level of reduction of maximum platelet aggregation). Compound R4 showed antiplatelet activity at the level of pentoxifylline, and compounds R1 and R3 showed antiplatelet activity at the level of acetylsalicylic acid.

Conclusions. As a result of the conducted research, a new substance 8-*N,N*-dimethylaminoethylamino-7-thietanyl-1,3-dimethyl-xanthine, as well as its salts – hydrochloride, citrate and nicotinate, the structures of which are confirmed by IR and NMR spectra, were obtained. As a result of the experimental work, the anti-aggregation and anticoagulation activity of the obtained new xanthine derivatives was revealed.