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OPTIMIZATION OF THE TECHNOLOGY OF 6-THIOGUANINE PRODUCTION

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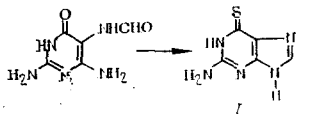
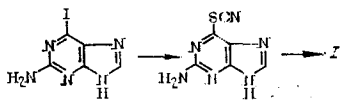
6-Thioguanine, or 2-amino-6-mercaptopurine (I), is a medicinal preparation with an antileucosis activity [2].

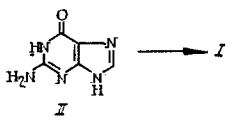
Several methods for the preparation of I are described in the literature [3-6, 8-10]. One of the proposed methods is based on the cyclization of substituted pyrimidines. Compound I is obtained in a 47% yield by heating 2,4-diamino-5-formamidino-6-oxopyrimidine with P_2S_5 in pyridine [4].



Another method consists in the preparation of I from 6-halopurines [8, 3]. 2-Amino-6-iodopurine is converted into I by treatment with KSCN, followed by alkaline hydrolysis; the yield is not indicated in the literature.



Because of the availability of the raw materials, the principal and most promising method for the preparation of I is the reaction of guanine (II) with P_2S_5 in a pyridine or quinoline medium [5, 6, 8, 9].



The yields of the unpurified product are 31-50%, based on II. However, when this method was used under pilot plant conditions at the Institute of Organic Chemistry of the Academy of Sciences of the Latvian SSR, compound I was obtained in a yield not exceeding 25%.

It was therefore our aim to develop an acceptable technology for the production of this preparation.

Since the halogen in 2-amino-6-halopurine can be replaced by a thiol group [3], an attempt was made to synthesize the required halogen derivatives from II or guanosine by means of $POCl_3$ or $SOCl_2$ in the absence and in presence of Et_3N. However, the halogen derivatives could not be isolated from the reaction mixture.

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TABLE 1. Planning Matrix and Experimental Results

		X_1, moles/mole	X_2, ml	X_3, ml	X_4, °C	X_5, h	Yield, y, %
Center of plan	0	2,5	50	5	160	5	
Variation spacing	Δ	0,5	10	5	20	1	
Replica 2^{2-5}	1	+	+	+	+	+	48,8
	2	−	+	+	−	−	42,3
	3	+	−	+	−	+	39,8
	4	−	−	+	+	−	37,1
	5	+	+	−	−	−	67,70 74,3 61,1
	6	−	+	−	+	−	50,9
	7	+	−	−	+	−	81,4
	8	−	−	−	−	+	57,3
	9	0	0	0	0	0	74,1
Experiments 1-8 b_i		7,088	0,088	−11,988	0,563	−4,788	b_0=54,788
Experiments 5-8 b_i^{II}		10,225	−5,025	—	1,825	−10,225	b_0^{II}=65,0

In developing a technology for the production of I, we first verified, and then as the result of the investigation improved, the method described in patents [5, 6]. As the starting material, we used 2,9-diacetylguanine (III), obtained by cleaving guanosine. Compound III is hydrolyzed by an NaOH solution, and II is isolated by subsequent acidification (yield 95%).

Verification of the method in [5, 6] for the preparation of I by heating II with P_2S_5 in pyridine at the boiling point showed that the yield of the pure product is only 20-25%. The yield could not be increased by either varying the ratios of the reagents or changing the order of mixing the initial components. A series of experiments have also been carried out in which pyridine was replaced by several other solvents: piperidine, morpholine, DMFA, picolines, DMSO, and sulfolane. Of the above solvents, only sulfolane (tetrahydrothiophene 1,1-dioxide) was found to be suitable. No side processes (resinification, reduction of solvent) were observed in its presence.

To clarify the influence of various factors on the reaction, we used the mathematical experiment planning method [7], and chose 1/4 replicas of the 2^{5-2} type. The following factors were used as variables: molar ratios of P_2S_5 and II (X_1), amount of sulfolane per 5 g of II (X_2), amount of pyridine added (X_3), thionation temperature (X_4), and time of reaction (X_5) (see Table 1).

The planning matrix and the results obtained are shown in Table 1. Two series of experiments were carried out (two 1/8 replicas) with addition of pyridine (Nos. 1-4) and without addition (Nos. 5-8). Coefficients b_i were calculated for all the experiments Nos. 1-8, and coefficients b_i^{II} for experiments Nos. 5-8. The results show that the supposition that the presence of pyridine in the solution is necessary has not been verified; on the contrary, the presence of pyridine negatively influences (b_3 = −11.988) and lowers the yield by more than 20% on an average.

The yield of I is appreciably influenced by the ratio of P_2S_5 and II (b_1 = 7.088, b_1^{II} = 10.225) and the duration of reaction (b_5 = 4.788, b_5^{II} = −10.225). The influence of the amount of solvent, sulfolane, is negative (b_2^{II} = −5.025), but with decrease in this amount, the reaction mixture becomes too viscous.

From these results, and also additional experiments, the following thionation regime could be finally selected: molar ratio of P_2S_5 and II 3.0-3.5:1, and II and sulfolane 1:19, time of reaction 3.5-4 h, and temperature 160-165°C. It was shown by a series of repeated experiments with increased charges that under these conditions the yield of pure I was 65-70% [1].

The problem of the isolation and purification of I was studied. During isolation, the pH of the medium is important: It should be equal to 7.0. If the medium is acidic or alkaline, the product acquires a pronounced yellow color, which is not permissible.

An attempt to directly thionate III was unsuccessful.

EXPERIMENTAL

The PMR spectra were run on a Bruker WH-90 apparatus, using HMDS as an internal standard, the mass spectrum on an MS-50 (Kratos) apparatus, and the UV spectrum on a Specord spectrophotometer.

Guanine (II). A 240-g portion (1 mole) of III is added to a solution of 106 g (2.65 moles) of NaOH in 2.5 liters of distilled water, and the reaction mixture is boiled for 1 h. First, all III is dissolved in the alkali, and then a copious white precipitate of II appears. When cool, the reaction mixture is neutralized with dilute HCl (1:2) to pH 7.0. The precipitate is filtered, washed with water and dried at 100-130°C. Yield, 148 g (95%, based on III) of a white finely crystalline product. According to the data of potentiometric titration, the content of II is not less than 98%.

6-Thioguanine (I). A 219-g portion (0.985 mole) of P_2S_5 and 600 ml of sulfolane are placed in a 2-liter flask, and 50 g (0.33 mole) of II are added, with stirring. The mixture is heated to 160-165°C, and held at this temperature, with stirring, for 4 h. At the end of the process, the mixture is cooled to room temperature and, with stirring, 1 liter of water is added from a dropping funnel, causing a vigorous evolution of H_2S. After the addition of water, the reaction mixture is heated for 2 h to 80-85°C to a complete removal of H_2S. It is then cooled, and the precipitate is filtered and washed with water. The precipitate is boiled twice with dilute (1:1) NH_4OH (1.5 and 0.2 liter) in the presence of activated charcoal. The combined filtrates are evaporated to the appearance of crystals of I, acidified with dilute (1:2) HCl to pH 7.0, and cooled to room temperature. The precipitate is filtered and washed with water. Yield, 40.4 g of crude product.

The crude product obtained is reprecipitated from concentrated NH_4OH solution by dilute (1:2) HCl, bringing the medium to pH 7.0. When cool, the precipitate is filtered, washed with water and ethanol, and dried at 100-130°C. Yield, 38.7 g of I (76% of theoretical yield, based on II). Found, %: C 35.78, H 2.95, N 42.10, S 19.20. $C_5H_5N_5S$. Calculated, %: C 35.93, H 3.01, N 41.92, S 19.4.

According to argentometric titration, the content of the principal compound is 99-101%.

The mass spectrum has an intense molecular ion peak m/z 167, without appreciable fragmentation to m/z 134. In the PMR spectrum (DMSO-d_6, internal standard HMDS) proton signals of the following fragments are observed: NH_2 at the 2 position — 6.52 ppm, CH at 8 position — 7.98 ppm, NH in 1 and 7 positions — 12.3 ppm.

UV spectrum at pH 1.0 (0.1 N HCl): λ_{max} 2.58, 374 nm (E_{max} 8100, 20,900), pH 11.0 (10^{-3} N NaOH): λ_{max} 242, 270, 322 nm (E_{max} 8700, 7200, 16,000).

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