SYNTHESIS OF 8-HYDROXYMETHYL DERIVATIVES OF GUANINE AND THIOGUANINE

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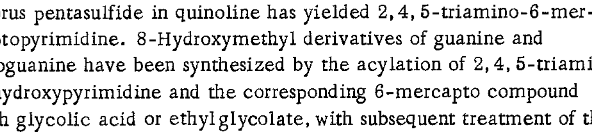
The reaction of 2, 4, 5-triamino-6-hydroxypyrimidine with phosphorus pentasulfide in quinoline has yielded 2, 4, 5-triamino-6-mercaptopyrimidine. 8-Hydroxymethyl derivatives of guanine and thioguanine have been synthesized by the acylation of 2, 4, 5-triamino-6-hydroxypyrimidine and the corresponding 6-mercapto compound with glycolic acid or ethylglycolate, with subsequent treatment of the resulting 5-hydroxyacetylamino derivatives with aqueous alkali.

Some derivatives of guanine, one of the bases of the nucleic acids, such as 8-azoguanine and thioguanine, possess a high antitumoral activity [1]. 8-Hydroxymethyl derivatives of guanine and thioguanine are of interest as potential antimetabolites and, in addition, these compounds can be used as intermediates for the synthesis of various 8-substituted guanines and thioguanines.

The synthesis of the compounds mentioned has been effected by the acylation of 2,4,5-triamino-6-hydroxypyrimidine (I) and the corresponding 6-mercapto compound (II) with glycolic acid or ethyl glycolate, followed by cyclization of the 5-hydroxyacetylamino derivatives (III and IV) to the corresponding purines (V and VI):



I, III, V R = OH; II, IV, VI R = SH

Compound I is readily accessible in large amounts [2, 3], while the known methods for synthesizing II involve many stages and give II in low yields [4, 5]. The most convenient method of preparing II may be the direct replacement of the hydroxy group in I by a mercapto group by means of phosphorus pentasulfide. This reaction has been used successfully to obtain some 4, 5-diaminomercaptopyrimidines [6].

The investigation of the reaction of I with phosphorus pentasulfide that we performed showed that it takes place slowly in pyridine, tetralin, and 4-picoline, giving unsatisfactory yields of II. However, when quinoline was used as the solvent the reaction took place smoothly with the evolution of heat. Thus, when I was heated with phosphorus pentasulfide in dry quinoline at 170° C for 7 hr, the yield of the sulfate of II was 74%. Free II was isolated from the sulfate in quantitative yield, and, after recrystallization from water in the presence of traces of a reducing agent, was stable to prolonged storage.

Fusing I and II with glycolic acid in vacuum at 160–165° C gave good yields of III and IV. Compound III was also obtained by boiling I with an excess of ethyl glycolate in an atmosphere of nitrogen. The structure of III and IV was confirmed by comparing their UV spectra with those of the known 5-formyl and 5-chloroacetyl derivatives of I [7].

Brief heating of the disodium salts of III and IV in vacuum at 210° C gave yields of more than 80% of V and VI. In principle, the cyclization of III and IV could give the isomeric α- and β-dihydroxanthopterins [7]. A comparison of the UV spectra of V and of α- and β-dihydroxanthopterins showed that they were different. Differences were also observed in the properties of the substances: in particular, in contrast to V, α- and β-dihydroxanthopterins dissolve in acetic acid.

EXPERIMENTAL

2,4,5-Triamino-6-mercaptopyrimidine (II). With stirring, 40 g of pure phosphorus pentasulfide was added to 200 ml of redistilled dry quinoline. The phosphorus pentasulfide was dissolved completely by heating to 140° C, and at this temperature 12 g (0.085 mole) of I was added in portions. The reaction was exothermic. The mixture was kept at 165–170° C for 7 hr and cooled, and the red precipitate was filtered off and then washed with pyridine and ether. Twenty-two grams of the crude product was boiled in 170 ml of water for 30 min, and 12 g of NaOH in 50 ml of water was added. The resulting solution was treated with decolorizing carbon, and the filtrate was acidified to Congo Red with 50% H_2SO_4 and left in the refrigerator overnight. The yellow crystalline precipitate was filtered off, washed with water and acetone, and dried in the air. The yield of II in the form of the sulfate was 17.1 g (74%). Found, %: C 17.81; H 4.11; N 25.93; S 23.52. Calculated for $C_4H_7N_5OS \cdot H_2SO_4 \cdot H_2O$, %: C 17.58; H 4.06; N 25.63; S 23.46.

To isolate the free base II, 4 g (0.015 mole) of the sulfate was dissolved in 80 ml of hot 5% aqueous NaOH, 2–3 drops of ammonium sulfide was added, the solution was treated with decolorizing carbon, and the hot filtrate was acidified with glacial acetic acid. After cooling in ice, the yellow lustrous precipitate was filtered off and washed with a small amount of ice water and acetone. The yield of II was 2.1 g (91.5%). The samples for analysis were recrystallized from water in the presence of traces of ammonium sulfide: light yellow crystals with mp 270° C (decomp.). Found, %: C 30.87; H 4.67; N 44.41; S 20.38. Calculated for $C_4H_7N_5OS$, %: C 30.56; H 4.49; N 44.55; S 20.40. UV spectrum: pH 1–λ_{max} 310 nm (log ε 4.34); pH 11–λ_{max} 240 nm (log ε 4.13), λ_{max} 320 nm (log ε 4.08).

2,4-Diamino-5-hydroxyacetamido-6-hydroxypyrimidine (III). a) Twenty-five grams (0.33 mole) of glycolic acid and 15 g (0.106 mole) of I were carefully ground in a mortar. The mixture was transferred to a Wurtz flask, 50 ml of water was added, and it was heated in an atmosphere of nitrogen at 120° C until the water had evaporated completely. The melt was kept in a vacuum at 165° C for 30 min, cooled, and treated with 200 ml of ice water; the precipitate was filtered off and washed with methanol and ether. After recrystallization from water, 15 g (78.5%) of III was obtained in the form of light yellow crystals with mp 260° C (decomp.). Found, %: C 36.23; H 4.37; N 35.07. Calculated for $C_6H_9N_5O_3$, %: C 36.15; H 4.53; N 35.14. UV spectrum: pH 1.0–λ_{max} 264 nm (log ε 4.17); pH 13.0–λ_{max} 260 nm (log ε 4.01).

b) A mixture of 2 g (0.142 mole) of **I** and 10 g (0.097 mole) of ethyl glycolate was heated in an atmosphere of nitrogen at 165–170° C for 5 hr. After cooling, the reaction mixture was mixed with 50 ml of ether, and the precipitate was filtered off, washed with ether, dried in the air, and recrystallized from water. The yield of **II** was 2 g (71%).

2,4-Diamino-5-hydroxyacetamido-6-mercaptopyrimidine (IV). 2.5 g (0.016 mole) of **II** and 3 g (0.04 mole) of glycolic acid were carefully mixed, 80 ml of water was added, the water was evaporated at 120° C in a current of nitrogen, and the residue was kept at 160° C for 20 min. Then the melt was treated with 50 ml of ice water and the solid matter was filtered off, washed with acetone, dried in the air, and recrystallized from water. The yield of **IV** was 2.6 g (75.8%) in the form of colorless crystals with mp 280° C (decomp.). Found, %: C 33.72; H 4.26; N 32.87; S 14.98. Calculated for $C_6H_9N_5O_2S$, %: C 33.48; H 4.21; N 32.54; S 14.90. UV spectrum: pH 1–λ_{max} 315 nm (log ε 4.25); pH 13–λ_{max} 222 nm (log ε 4.17), λ_{max} 297 nm (log ε 4.09).

8-Hydroxymethylguanine (V). The water was evaporated off in vacuum from a solution of 16.2 g (0.081 mole) of **III** in 81 ml of 1 N aqueous NaOH, and the residue was kept at 210° C and a pressure of 10 mm for 20 min. The light brown melt was dissolved with heating in 100 ml of 1 N aqueous NaOH, the solution was decolorized with carbon, and the hot filtrate was acidified with glacial acetic acid. After cooling, the voluminous yellow precipitate was filtered off, washed with water and acetone, and dried in a vacuum desiccator over H_2SO_4. The yield of **V** was 14 g (91%). For purification, the **V** was dissolved in boiling 10% hydrochloric acid, the solution was cooled, and the hydrochloride of V was filtered off and treated with 20% aqueous ammonia to give free V, light yellow crystals with mp 330° C (decomp.). Found, %: C 37.89; H 4.18; N 36.61. Calculated for $C_6H_7N_5O_2 \cdot 0.5H_2O$, %: C 37.86; H 4.21; N 36.81. The water of crystallization is readily driven off by drying in vacuum at 140° C. UV spectrum: pH 1.0–λ_{max} 258 nm (log ε 4.01); pH 7.0–λ_{max} 248 nm (log ε 3.81); pH 13–λ_{max} 248 nm (log ε 4.00), λ_{max} 270 nm (log ε 4.03).

8-Hydroxymethylthioguanine (VI). The water from a solution of 2.6 g (0.012 mole) of **IV** in 12 ml of 1 N aqueous NaOH was evaporated off in vacuum and the residue was kept at 210° C and a pressure of 10 mm for 20 min. The dark melt was dissolved in 30 ml of hot 1 N aqueous NaOH and treated with decolorizing carbon, and the filtrate was acidified with glacial acetic acid. After cooling, the yellow precipitate was filtered off, washed with water and acetone, and dried in a vacuum desiccator over H_2SO_4. The yield of **VI** was 2 g (81%). For analysis, a sample was recrystallized from a large amount of water; yellow crystals with mp 320° C (decomp.). Found, %: N 34.26; S 15.77%. Calculated for $C_6H_7N_5OS \cdot 0.5H_2O$, %: N 34.14; S 15.55. UV spectrum: pH1–λ_{max} 215 nm (log ε 4.48), λ_{max} 340 nm (log ε 4.23); pH 13–λ_{max} 230 nm (log ε 4.52), λ_{max} 320 nm (log ε 4.19).

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