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SYNTHESIS OF GUANINE FROM 3-METHYLXANTHINE

P. M. Kochergin, L. V. Persanova, E. V. Aleksandrova, L. A. Gutorov,* and V. S. Korsunskii*

A new preparative method of obtaining guanine from 3-methylxanthine has been developed.

Guanine [2-amino-6-hydroxypurine (VI)] is the starting material for the synthesis of the drugs thioguanine, acyclovir, gancyclovir, and several other biologically active substances [1, 2].

Natural sources for obtaining guanine include guano, fish scales, and yeast (yeast RNA), however the manufacture of this amine from these forms of raw material is complex, careful purification from contaminants is required, and it leads to a low yield of the final product.

Synthetic methods are known for obtaining guanine from derivatives of pyrimidine [3-8], imidazole [9-11], and purine [12, 13]. The drawbacks of the majority of the synthetic methods described for obtaining guanine are their multistage nature and the difficult availability of the starting substances.

Other studies have reported unsuccessful attempts to synthesize guanine from derivatives of pyrimidine and purine. Thus, on boiling 2,4,5-trimino-6-hydroxypyrimidine with formaldehyde a nitrogen-containing compound of unestablished structure was isolated in place of guanine [14]. On heating 2-methylmercaptohypoxanthine with alcoholic ammonia solution at 130°C no reaction occurred, only the starting material was isolated [15].

The point of our investigation was the development of a method of obtaining guanine from 3-methylxanthine, one of the purine derivatives available as an intermediate from the synthesis of the alkaloids theobromine and caffeine [16, 17].

For this purpose 7-benzyl-2-chlorohypoxanthine (IV) was obtained from the potassium salt of 3-methylxanthine (I) by the method of [18]. Several improvements were introduced into the method enabling the synthesis of (IV) to be simplified and its yield increased.

When studying the amination of compound (IV) it was noted that the chlorine atom in position 2 of the purine bicycle possessed a significantly lower lability than that in position 6 of 7-benzyl-2,6-dichloropurine (III) [18]. Consequently more forcing conditions are required to replace it by an amino group, viz. a temperature of 140-160°C and conducting the reaction in an autoclave. Ammonia may be used either in alcoholic or aqueous solution. For preparative purposes it is convenient to use a 25% aqueous solution of industrial manufacture. 7-Benzylguanine (V) is formed in high yield (80-82%) by reacting compound (IV) with ammonia. This compound had previously been obtained by more complex routes and in low yield from 3-benzylguanine [19], $N_{(2)}$-acetylguanine [19], and guanosine [20].

The debenzylation of the amine (V) occurs readily on catalytic reduction in aqueous alkaline solution at 85-90°C with atmospheric pressure of hydrogen in the presence of palladium. The yield of guanine was 88% calculated on amine (V) and 51-52% on the initial salt (I).

*Deceased.

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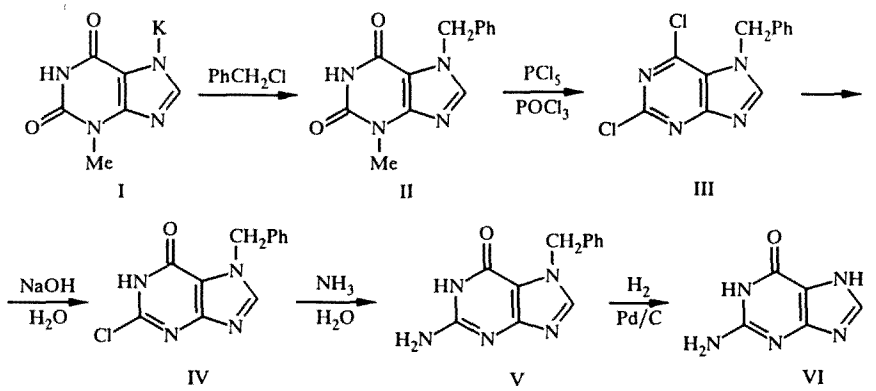

The new method of obtaining guanine developed by us is of preparative value [21]. Its advantages compared with known methods are not only the availability of the raw material but also the organization of production of this amine in a combined scheme with the synthesis of adenine and hypoxanthine [18]. The latter are also used in drug manufacture for 6-mercaptopurine, azathioprine, etaden, and new preservatives for blood and erythrocytes.

EXPERIMENTAL

The IR spectra of compounds were taken on a UR 10 instrument in Nujol mulls. The TLC of compounds was carried out on Silufol UV 254 plates, visualizing with iodine vapor. The system was $C_4H_9OH-AcOH-H_2O$, 4:1:5 (upper layer). In all stages of the synthesis of guanine (VI) the intermediates (II)-(V) were used as the crude products.

The data of elemental analysis of compounds (V) and (VI) for C, H, and N agreed with calculated values.

The potassium salt of 3-methylxanthine (I) used was of industrial manufacture, the salt was dried to constant weight at 120-130°C. The content of main substance was about 96%. R_f 0.39.

7-Benzyl-3-methylxanthine (II) was obtained from the salt (I) by the method of [18] with the differences that benzyl chloride was used at 1.3 mole per mole of salt (I). The crude product was washed with DMF, boiled in water for 30 min, washed with acetone, and dried at 120-130°C. Yield was 85% of mp 279-281°C (with decomposition). A pure sample had mp 283-285°C (with decomposition, from DMF). R_f 0.56.

7-Benzyl-2,6-dichloropurine (III) was obtained from compound (II) by the method of [18] with the difference that the product was isolated in two parts. At the end of the reaction the phosphorus oxychloride was not distilled off but the reaction mixture was left at 18-20°C for 14-16 h. The solid which separated was filtered off, thoroughly pressed out on the filter, and added in small portions with stirring to 4-5% aqueous ammonia solution with added crushed ice. The solid base (III) was separated , washed with water, and dried. Yield was 75-76% of mp 147-149°C. The phosphorus oxychloride was distilled from the filtrate to one third the initial volume, the solution cooled, and treated as described above. An additional 15-16% compound (III) was isolated of mp 132-142°C. This was purified by crystallization from 70% isopropanol (with carbon) to give 12-13% compound (III) of mp 146-148°C. The total yield of crude compound (III) was 87-88%. A pure sample had mp 152.5-154.5°C (from isopropanol). R_f 0.68.

7-Benzyl-2-chlorohypoxanthine (IV) was obtained by the method of [18]. Yield was 96% of mp 254-256°C (with decomposition). A pure sample has mp 255-256°C (with decomposition, from CH_3COOH). R_f 0.63.

7-Benzylguanine (V). A mixture of compound (IV) (20 g) and 25% aqueous ammonia solution (100 ml) was heated in an autoclave at 150-160°C for 5 h. After cooling the solid was separated, washed with water and with acetone, and dried. Compound (V) (16 g; 81%) of mp 370-380°C (with decomposition) was obtained. A pure sample decomposed at 375-380°C (from DMF). According to the data of [20] mp 380°C (with decomposition). R_f 0.44.

Guanine (VI). A mixture of compound (V) (10 g), sodium hydroxide (3 g), 5% palladium on carbon catalyst (10 g) and water (200 ml) was hydrogenated at 85-90°C at atmospheric hydrogen pressure until no more was absorbed. The mixture was cooled, filtered, and the catalyst washed with water and with dilute sodium hydroxide solution. The filtrate was acidified with acetic acid to pH 5-6, the precipitated solid was filtered off, washed with water and with acetone, and dried. Compound

(VI) (5.5 g. 88%) of mp 370-380°C (with decomposition) was obtained. An analytically pure sample decomposed at 375-380°C (from DMF). According to the data of [3] mp 380°C (with decomposition). The IR spectrum of the compound obtained was identical to the spectrum of an authentic sample of guanine.

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