METHODS OF DRUG SYNTHESIS, AND THE TECHNOLOGY OF DRUG PRODUCTION

IMPROVED CYANOACETYLUREA SYNTHESIS

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Cyanoacetylurea (I) is a key compound in the synthesis of such important drug preparations as sulfadimethoxine, theophyllin, caffeine, adenine, etc.

The industrial method for the preparation of I is based on the reaction of cyanoacetic acid (II) with urea in acetic anhydride at 75-85°C [1].

In spite of the comparatively simple technology for the preparation of I, the yield of the desired product, even under laboratory conditions, does not exceed 89-90%. In addition, because of the formation of acetylurea as a side product, the melting point of the technical product is 195-198°C, which is 10-12°C lower than that indicated for the pure product [2].

Several attempts to increase the yield and quality of the technical product by varying the reaction conditions are not applicable to industrial conditions, since they require the use of highly toxic and aggressive reagents [2], or give a decrease in the quality of the technical product [3].

We have observed that tarry products are formed in the cyanoacetylation of urea at temperatures above 60°C.

A significant quantity of acetylurea is obtained in the technical product if the reaction is carried out in a large excess of acetic anhydride or in solution containing a large quantity of acetic acid.

Since the cyanoacetylation of urea involves a mixed acetic-cyanoacetic anhydride (III), it seemed expedient to bring about the reaction by the use of the principle of displacement of equilibrium in the intermediate reaction of II with acetic anhydride to form III by removal of the volatile acetic acid [5].

If the cyanoacetylation reaction is conducted under vacuum at 45-55°C, a vigorous ebullition is observed in the reaction mixture accompanying the removal of the acetic acid. Resinified products of the reaction were not observed with this procedure. Chromatography of the technical product showed only traces of acetylurea. The yield of I with mp 203-205°C was 92-94%.

EXPERIMENTAL

To a solution of 53.5 g (0.5 mole) of sodium cyanoacetate at a temperature of less than 30°C was added with stirring 25.8 g (0.263 mole) of sulfuric acid, and the reaction mixture was kept for 30 min at 28-30°C.

To the above aqueous solution of II was added 30.3 g (0.5 mole) of urea and the water was removed by heating at an internal temperature of less than 65°C at 20-25 mm Hg. The dry residue was cooled to 40-45°C, and 80 ml (0.8 mole) of acetic anhydride was added.

Twenty ml (0.2 mole) of acetic acid was distilled from the reaction mixture at 45-50°C (internal temperature) and 20-25 mm Hg. Then an additional 40 ml (0.4 mole) of acetic anhydride was added at 50-55°C, and the reaction mixture was kept for 1 h at 55-60°C. From this mixture the acetic acid and acetic anhydride were removed under vacuum at an internal temperature of 60-65°C. Water (125 ml) was added to the residue, the mixture was stirred to give an homogeneous suspension, cooled to 20°C, and filtered. The solid was washed with water to the absence of sulfate and dried to constant weight at 100°C. The dried technical I weighed 60-63 g and contained 98.5-94.5% of the desired substance or 59-59.5 g of I with mp 205-206°C, which is 93-94% of the theoretical yield, calculated on sodium cyanoacetate.

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APPLICATION OF THE VILSMEIER REACTION TO THE SYNTHESIS OF DERIVATIVES OF PYRROLO[3,2-d]PYRIMIDINE-7-CARBOXALDEHYDE

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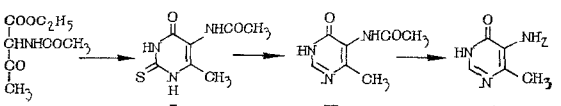
Our preceeding communication [1] described a method for obtaining 2-methyl-4-oxo-3,4-dihydropyrrole[3,2-d]pyrimidine-7-carboxaldehyde from 5-amino-2,6-dimethyl-4-oxo-3,4-dihydropyrimidine, using the Vilsmeier reaction to construct the pyrrole ring.

This method allows the synthesis of a series of pyrrolopyrimidine derivatives, among which are found compounds suppressing the growth of lactic acid bacteria, and showing tuberculostatic activity [2].

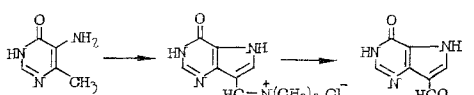
In the present work, the Vilsmeier reaction is applied to other 5-amino-6-methylpyrimidines having different substituents in position 2 of the pyrimidine ring.

5-Amino-6-methyl-4-oxo-3,4-dihydropyrimidine (III) was obtained by condensation of thiourea with acetylaminoacetoacetic ester, followed by reduction of the resulting 2-thioderivative (I) to the pyrimidine (II) and hydrolysis of the acetyl group.



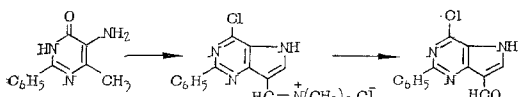
I II III

The interaction of III with phosphorus oxychloride in DMF solution gave the quaternary salt IV, which was hydrolyzed to 4-oxo-3,4-dihydropyrrolo[3,2-d]pyrimidine-7-carboxaldehyde (V).



III IV V

We studied the behavior of 5-amino-6-methyl-4-oxo-2-phenyl-3,4-dihydropyrimidine (VI) under Vilsmeier conditions. Its synthesis was accomplished by known methods from acetylaminoacetoacetic ester [3]. It should be noted that the reaction of VI with the Vilsmeier reagent, in addition to the desired pyrrole ring closure, gave substitution of the oxo group in position 4 by chlorine to form the intermediate dimethyl (4-chloro-2-phenylpyrrolo[3,2-d]-pyrimidine-7-yl)methyleneammonium chloride (VII), the hydrolysis of which gave 4-chloro-2-phenylpyrrolo[3,2-d]pyrimidine-7-carboxaldehyde (VIII). The structure of aldehydes V and VIII were confirmed by PMR spectral data, and by preparation of the phenylhydrazone and thiosemicarbazones.



VI VII VIII

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