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Pyrimidine Research. Synthesis of 4,5-Dimethylcytosine[1]

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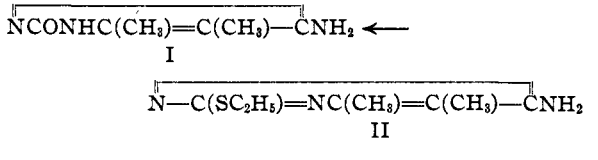
In this paper is described the synthesis of 4,5-dimethylcytosine which, so far as the authors are aware, is a new pyrimidine which promises to be of physiological importance. 2-Ethylmercapto-4,5-dimethyluracil[2] was allowed to react with phosphorus oxychloride to form 2-ethylmercapto-4,5-dimethyl-6-chloropyrimidine according to the technique of the authors.[3] This chloropyrimidine interacted smoothly with ammonia in alcohol solution at 140–150°, to form 2-ethylmercapto-4,5-dimethyl-6-aminopyrimidine II. When digested with hydrobromic acid, this aminopyrimidine II underwent hydrolysis with the evolution of ethylmercaptan and production of the hydrobromide of 4,5-dimethylcytosine I in excellent yield. The free pyrimidine base was then obtained by decomposition of its hydrobromide with ammonia.



Experimental Part

2 - Ethylmercapto - 4,5 - dimethyl - 6 - aminopyrimidine, II.—Three grams of 2-ethylmercapto-4,5-dimethyl-6-chloropyrimidine was heated with 15 cc. of strong alcoholic ammonia at 140–150° for six hours. After the completion of the reaction the insoluble ammonium chloride was filtered off from the cooled reaction mixture, the alcoholic solution concentrated on a steam-bath, and cooled in an ice mixture. The crystalline solid which separated was then dried on a porous plate, triturated with cold water, and the solid finally filtered off. This was then extracted with hot benzene, and the benzene solution evaporated to dryness. Purification of the product obtained here is accomplished by its crystallization from a petroleum ether–benzene mixture (containing 10 parts of petroleum ether and one part of benzene) giving the desired 6-aminopyrimidine in the form of glistening colorless scales. The base melted at 92–93° to a clear oil. The yield was 1.5 g. *Anal.* after drying in a vacuum desiccator. Calcd. for $C_8H_{12}N_2S$: N, 22.94. Found: N, 23.1.

4,5-Dimethylcytosine, I.—The above mercaptopyrimidine was dissolved in an excess of hydrobromic acid (48%) and the solution refluxed for twelve hours, when the evolution of ethylmercaptan was practically complete. After evaporating to dryness the hydrobromide was purified by crystallization from 95% alcohol. It separated in the form of small needles, which sinter at 278° and melt at 291° with decomposition. The yield of the hydrobromide is excellent. It was dried at 120° and analyzed for nitrogen. Calcd. for $C_6H_{10}ON_3Br$: N, 19.10. Found: N, 19.40.

In order to obtain the free pyrimidine base (4,5-dimethylcytosine) this hydrobromide was dissolved in water and the hydrobromic acid neutralized by adding aqueous ammonia solution in slight excess. The pyrimidine separated at once in a crystalline condition. It was purified by crystallization from hot water, when it separated in the form of long colorless prisms. It can also be purified by crystallization from 95% alcohol. The pyrimidine does not melt or decompose below 300°. *Anal.* Calcd. for $C_6H_9ON_3 \cdot H_2O$: N, 26.75. Found: N, 26.90. 0.0802 g. of substance, after being heated at 118° in a vacuum for ten hours, lost 0.0090 g. From which the water of crystallization was found to be 11.22%, as compared the theoretical value 11.47%.

Summary

1. Alcoholic ammonia acting upon 2-ethylmercapto - 4,5 - dimethyl - 6 - chloropyrimidine gives the corresponding aminopyrimidine-2-ethylmercapto-4,5-dimethyl-6-aminopyrimidine.

2. This mercaptopyrimidine undergoes hydrolysis by digestion with hydrobromic acid, giving 4,5-dimethylcytosine hydrobromide, from which the free base is easily obtained by neutralizing the hydrobromic acid with ammonia.

3. This cytosine derivative is a pyrimidine of physiological interest.

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(2) Wheeler and Merriam, *Am. Chem. J.*, **29**, 478 (1903).

(3) Chi and Kao, THIS JOURNAL, **58**, 769 (1936).