[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CHEKIANG, CHINA]

Researches on Pyrimidines. Synthesis of 5-Phenylcytosine

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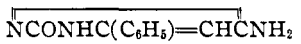
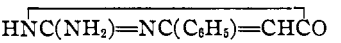
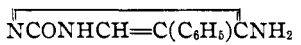
If we limit ourselves to carbon substituted pyrimidines there are only four phenyl derivatives of cytosine and isocytosine to be considered, namely, the phenyl constructions represented by formulas I, II, III and IV, respectively.



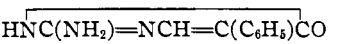
I



II

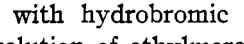


III



IV

Jaeger[1] and Warmington[2] independently prepared 4-phenylisocytosine II by the interaction of guanidine carbonate with ethyl benzoylacetate, and their observation was confirmed later by the work of Johnson and Hill.[3] The latter investigators also made the interesting observation that this pyrimidine II occurs in four isomeric crystalline modifications. Later Johnson and Hemingway[4] synthesized the 4-phenylcytosine I, but, so far as the authors are aware, 5-phenylcytosine III and 5-phenylisocytosine have not been prepared. The object of this short paper is to report our method of synthesizing the new phenylcytosine derivative represented by formula III.

Our method of procedure was to start with 2-ethylmercapto-5-phenyluracil and prepare first 2-ethylmercapto-5-phenyl-6-chloropyrimidine according to the technique of Chi and Tien.[5] This chloropyrimidine reacted smoothly with ammonia in alcohol solution at 150°, forming 2-ethylmercapto-5-phenyl-6-aminopyrimidine V,  . When digested with hydrobromic acid this aminopyrimidine was destroyed with evolution of ethylmercaptan, yielding the hydrobromide of the desired 5-phenylcytosine III in good yield. The free pyrimidine base was easily obtained by treatment of its hydrobromide with ammonia.

Experimental Part

2-Ethylmercapto-5-phenyl-6-aminopyrimidine, V.—This pyrimidine is formed by heating 2-ethylmercapto-5-phenyl-6-chloropyrimidine[5] with strong alcoholic ammonia at 150°. Usually about four hours of heating are necessary to bring about a complete reaction. The cooled reaction mixture is filtered to separate undissolved ammonium chloride and the alcohol solution finally evaporated to dryness. The residue left behind

(1) Jaeger, *Ann.*, **262**, 373 (1890).
(2) Warmington, *J. prakt. Chem.*, [2] **47**, 214 (1893).
(3) Johnson and Hill, THIS JOURNAL, **36**, 1202 (1914).
(4) Johnson and Hemingway, *ibid.*, **37**, 378 (1915).
(5) Chi and Tien, *ibid.*, **55**, 4181 (1933).

was then extracted with boiling benzene, and the filtered benzene solution diluted with petroleum ether. On cooling the desired aminopyrimidine separated in the form of colorless rhombic crystals. It was purified by recrystallization from a benzene–petroleum ether mixture and it melted at 87–88° to a clear oil. The yield from 16 g. of the chloropyrimidine was 8.5 g.

Anal. Calcd. for $C_{12}H_{13}N_3S$: N, 18.18. Found: N, 18.38, 18.39.

5-Phenylcytosine, III.—This pyrimidine was obtained in the form of its hydrobromic acid salt by hydrolysis of 2-ethylmercapto-5-phenyl-6-aminopyrimidine with hydrobromic acid. Five grams of the mercaptopyrimidine was dissolved in 20 cc. of hydrobromic acid (48%) and the mixture refluxed on a sand-bath for fifteen hours, when the evolution of ethylmercaptan had ceased. The hydrobromide separated on cooling. After evaporating the excess of acid the salt was then purified by crystallization from water. It separated in the form of colorless long needles which sintered at 270° and melted at 280–281° with decomposition. The yield of the hydrobromide was 3.5 g. It was dried in a vacuum desiccator and analyzed.

Anal. Calcd. for $C_{10}H_{10}ON_3Br$: N, 15.68. Found: N, 15.52, 15.32.

In order to obtain the free pyrimidine base (5-phenylcytosine), this hydrobromide was dissolved in water and the hydrobromic acid neutralized by adding aqueous ammonia solution. The pyrimidine separated at once in a crystalline condition. The base is insoluble in cold ammonia but soluble in sodium hydroxide solution. The pyrimidine is soluble in boiling water and 95% alcohol. It crystallizes from water in the form of colorless needles and from alcohol in the form of colorless rhombic prisms. The yield from 1 g. of the hydrobromide is 0.6 g. The pyrimidine does not melt or decompose below 310°. It was dried over concentrated sulfuric acid in a vacuum desiccator and analyzed.

Anal. Calcd. for $C_{10}H_9ON_3$: N, 22.46. Found: N, 22.52, 22.57.

Hydrochloride $C_{10}H_9ON_3 \cdot HCl$.—This salt is easily obtained by dissolving the 5-phenylcytosine in dilute hydrochloric acid and then allowing the solution to crystallize. It separated in the form of colorless needles which sintered at 270° and melted at 277–278°. For analysis, the salt was recrystallized from water and dried at 120°.

Anal. Calcd. for $C_{10}H_{10}ON_3Cl$: N, 18.80. Found: N, 18.85.

Summary

1. The action of alcoholic ammonia upon 2-ethylmercapto-5-phenyl-6-chloropyrimidine gives the corresponding aminopyrimidine, 2-ethylmercapto-5-phenyl-6-aminopyrimidine.

2. This mercaptopyrimidine is hydrolyzed by digestion with hydrobromic acid, giving 5-phenylcytosine hydrobromide.

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