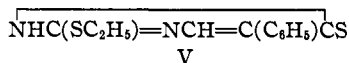
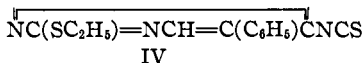
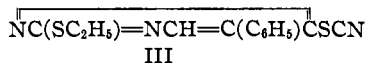
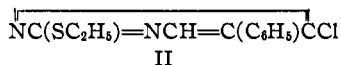
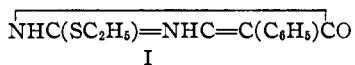


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Researches on Pyrimidines. The Molecular Rearrangement of 2-Ethylmercapto-5-phenyl-6-thiocyanopyrimidine^{1,2}

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A further study of the behavior of potassium thiocyanate toward imino chlorides of the pyrimidine type has led to interesting results which are now reported in this paper. Following the technique of Wheeler, Johnson³ and co-workers, the authors have investigated the action of 2-ethylmercapto-5-phenyl-6-chloropyrimidine³ (II) on thiocyanates and find that they interact smoothly to form a normal thiocyanate (III). The structure of this rhodanide is established by the fact that it undergoes a normal change when allowed to interact with a thiol acid^{3b,d,4} giving 2-ethylmercapto-5-phenyl-6-thiopyrimidine, V. This new thiocyanopyrimidine (III) exhibits a chemical behavior similar to that of 2-ethylmercapto-5-carbethoxy-6-thiocyanopyrimidine^{3d} and 2-ethylmercapto-4-methyl-6-thiocyanopyrimidine.^{3e} It can be distilled under a pressure of 2 mm. at 215° without decomposition and without molecular conversion into its isothiocyanate modification, IV. The stability of the rhodanide (III) is greatly influenced by the presence of certain reagents, and a molecular rearrangement to the corresponding isothiocyanate (IV) can be accomplished easily at a temperature very much below that of the boiling point of the pyrimidine thiocyanate. The conditions under which this change is brought about are described in the experimental part of this paper.



Experimental Part

2-Ethylmercapto-5-phenyluracil (I).—To an aqueous solution of the sodium salt of ethylformylacetate, prepared from 71 g. of ethyl phenylacetate and 38 g. of ethyl formate in the presence of 10 g. of metallic sodium in ether solution, 50 g. of pseudo-

(1) This paper is a report of one phase of a research program dealing with the chemistry of certain pyrimidine thiocyanates, which was started originally in the Sterling Chemistry Laboratory of Yale University under the direction of Professor Treat B. Johnson.

(2) This research has been accomplished and arranged for publication through the support of a grant from the Rockefeller Foundation. The authors desire to express here their appreciation and thanks for this liberal assistance.

(3) (a) Wheeler and Bristol, *Am. Chem. J.*, **33**, 448 (1905); (b) Johnson and McCollum, *ibid.*, **36**, 136 (1906); (c) Johnson and Storey, *ibid.*, **40**, 131 (1908); (d) Johnson and Chi, *THIS JOURNAL*, **52**, 1580 (1930); (e) Chi and Chen, *ibid.*, **54**, 2056 (1932);

(4) Wheeler and Merriam, *ibid.*, **23**, 283 (1901).

ethylthiourea hydrogen bromide was dissolved. A cold solution of 10.6 g. of sodium hydroxide dissolved in 20 cc. of water, was then added very slowly. The mixture was left overnight in an ice box. On acidifying this alkaline solution with acetic acid, the oxypyrimidine separated. After purification by crystallization from 95% alcohol, it melted at 153–154° to a clear oil. The yield of the pure oxypyrimidine was 33 g. It is soluble in hot water and alcohol.

Anal. Calcd. for $C_{12}H_{12}ON_2S$: N, 12.07. Found: N, 11.91, 11.86.

2-Ethylmercapto-5-phenyl-6-chloropyrimidine, II.—Twenty grams of 2-ethylmercapto-5-phenyluracil was dissolved in 60 cc. of cold phosphorus oxychloride and the solution heated in an oil-bath at 130–140° for nine hours. After the removal of the excess of phosphorus oxychloride under diminished pressure, there was left a sirup, which would not solidify on cooling. It was treated with cracked ice in order to decompose double phosphorus compounds, the temperature never being allowed to rise above 0°. It was then extracted with ether and the ethereal solution dried with anhydrous calcium chloride. After the ether was distilled off, it left a yellow oil which solidified on cooling. It distilled as follows: 72 mm. at 175°, 10 mm. at 218°, and 20 mm. at 231–232°. The product solidified in the receiver, and melted at 38–39°. The yield was 15 g. or 70%. It is insoluble in water but very soluble in alcohol, benzene, and petroleum ether. On account of its great solubility in most organic solvents, it cannot be purified by crystallization.

Anal. Calcd. for $C_{12}H_{11}N_2S_2Cl$: N, 11.18. Found: N, 11.16, 10.96.

2-Ethylmercapto-5-phenyl-6-thiocyanopyrimidine, III.⁵—This compound can be obtained by the action of potassium thiocyanate on the above chloride in boiling alcohol or benzene solutions. Fifteen grams of the chloropyrimidine, boiling at 175° at 2 mm. pressure, and 10 g. of potassium thiocyanate were dissolved in 40 cc. of absolute alcohol and the solution refluxed on a water-bath for one-half hour, when the reaction was complete. The solution was filtered while hot and chilled, when the thiocyanate separated immediately in the form of colorless needles. The yield was 16 g. or 97%. After purification by crystallization from benzene and ligroin (1:1), it separated as colorless flat needles and melted at 90° to a colorless oil. It distilled at 215° under a pressure of 2 mm. It can also be purified by crystallization from alcohol. The thiocyanate is insoluble in alkali but soluble in benzene, toluene and xylene, very soluble in hot alcohol and insoluble in petroleum ether.

Anal. Calcd. for $C_{13}H_{11}N_3S_2$: N, 15.38. Found: N, 15.30, 15.32.

Proof of Structure of the Thiocyanate.—That the compound described above (melting at 90°) is to be represented by a normal rhodanide or thiocyanate structure is established by the following experimental facts: (1) it does not undergo any change leading to the formation of a thiourea when exposed to the action of concentrated aqueous ammonia, (2) it can be crystallized from hot alcohol without conversion to a thiourea and (3) the compound reacts with thioacetic acid to form the thiopyrimidine described below.

2-Ethylmercapto-5-phenyl-6-thiopyrimidine, V.—Two grams of 2-ethylmercapto-5-phenyl-6-thiocyanopyrimidine was dissolved in 10 cc. of thioacetic acid and the solution warmed on a water-bath for six to eight hours. After cooling, the thiopyrimidine separated in the form of yellow needles. It was purified by crystallization from absolute alcohol, and separated on cooling in the form of yellow plates melting at 171° to a clear oil.

Anal. Calcd. for $C_{12}H_{12}N_2S_2$: N, 11.29. Found: N, 11.30, 11.28.

(5) The pyrimidine chloride and thiocyanate experiments were first performed by Miss Tse Yuh Ho and were described in her thesis submitted to the Faculty of the College of Arts and Sciences of the University of Chekiang as a partial fulfilment of the requirements for the B.S. degree from that institution in June, 1932.

This compound was identified as 2-ethylmercapto-5-phenyl-6-thiopyrimidine as follows. When mixed with the thiopyrimidine prepared by the action of sodium hydrosulfide upon the corresponding chloropyrimidine, the melting point was not altered.

The procedure used for preparing the thiopyrimidine by interaction of the chloropyrimidine and sodium hydrosulfide was as follows. Four grams of the corresponding chloropyrimidine and 1 g. of freshly prepared sodium hydrosulfide were dissolved in 15 cc. of absolute alcohol, and the solution heated to boiling for two hours. It was slightly acidified with one drop of glacial acetic acid. The solution was filtered to separate the insoluble sodium chloride, while hot, and when cooled the thiopyrimidine separated in the form of yellow needles. It was purified by crystallization from absolute alcohol and melted at 171°. The yield was 52%.

Anal. Calcd. for $C_{12}H_{12}N_2S_2$: N, 11.29. Found: N, 11.32.

The Molecular Rearrangement of 2-Ethylmercapto-5-phenyl-6-thiocyanopyrimidine into its Isomeric Form, IV

2-Ethylmercapto-5-phenyl-6-isothiocyanopyrimidine, IV.—Four grams of the thiocyanate was refluxed in 10 cc. of xylene for thirty hours, giving a red colored solution. After distilling off xylene, the isothiocyanate residue was extracted with petroleum ether and the solution concentrated and finally chilled, when the isothiocyanate separated in the form of colorless needles. The yield was about 70%. The compound was purified by crystallization from petroleum ether, and melted at 84–85° to an oil. On standing, the isothiocyanate becomes colored.

Anal. Calcd. for $C_{13}H_{11}N_3S_2$: N, 15.38. Found: N, 15.01.

Proof of Structure of the Isothiocyanate, IV

2-Ethylmercapto-5-phenyl-6-thioureapyrimidine $C_{13}H_{14}N_4S_2$.—The thiocyanate was rearranged into the isothiocyanate form as described above and a petroleum ether solution of the latter combined with an excess of concentrated aqueous ammonia. The corresponding thiourea was formed immediately and 2.4 g. was obtained from 4 g. of the thiocyanate. It was purified by crystallization from ethyl acetate and it separated in colorless needles melting at 204° to a clear oil.

Anal. Calcd. for $C_{13}H_{14}N_4S_2$: N, 19.31. Found: N, 19.22, 19.02.

2-Ethylmercapto-5-phenyl-thioureapyrimidine, $C_{19}H_{18}N_4S_2$.—Four grams of the rearranged thiocyanate gave 3.2 g. of this compound by treatment with aniline at ordinary temperature. This was purified by crystallization from a benzene–ligroin mixture and separated in yellow needles melting at 149°.

Anal. Calcd. for $C_{19}H_{18}N_4S_2$: N, 15.30. Found: N, 15.14, 15.02.

2-Ethylmercapto-5-phenyl-6-thionethylurethan-pyrimidine $C_{15}H_{17}ON_3S_2$.—Four grams of the thiocyanate was rearranged to the isothiocyanate modification and then dissolved in 10 cc. of absolute alcohol. The solution was heated for a few minutes, and on cooling the urethan separated in the form of colorless needles. The yield was 2.5 g. or about 53% of the theoretical. After crystallization from alcohol it melted at 85–85.5°.

Anal. Calcd. for $C_{15}H_{17}ON_3S_2$: N, 13.16. Found: N, 13.17, 13.18.

2-Ethylmercapto-5-phenyl-6-thionmethylurethan Pyrimidine, $C_{14}H_{15}ON_3S_2$.—This was formed by warming the crude isothiocyanate with 10 cc. of methyl alcohol. It crystallized from methyl alcohol in the form of colorless needles melting at 79–80° to a clear oil.

Anal. Calcd. for $C_{14}H_{15}ON_3S_2$: N, 13.77. Found: N, 13.87, 13.62.

Experimental Conditions Influencing the Rearrangement of the Pyrimidine Thiocyanate.—A. While the thiocyanate can be distilled under diminished pressure without change into the isothiocyanate modification, it can be rearranged at a temperature much lower than its boiling point. Heating of the thiocyanate at 120° for three hours gave an oil, in which there was not any detectable amount of the isothiocyanate modification. Digestion of the pyrimidine thiocyanate in benzene did not produce a rearrangement. Heating in xylene solution for ten hours produced no change; but the change was brought about by refluxing in xylene solution for thirty hours.

B. At the boiling point of ethyl alcohol the pyrimidine thiocyanate undergoes no change and can be crystallized repeatedly from this solvent without structure alteration. On heating in alcohol at 100° for six hours the thiocyanate also undergoes no change. On the other hand, when heated in alcohol solution at 140° (75° below its boiling point) the thiocyanate is transformed into the isothiocyanate and the latter combines with alcohol, giving the corresponding thionurethan. Two grams of the thiocyanate dissolved in 10 cc. of absolute alcohol was heated at 140° for two hours. After the tube was opened, the solution was left in an ice box for two weeks. The thionethylurethan separated extremely slowly. The yield was one gram. This crystallized from alcohol and melted sharply at 85°. Mixed with the thionethylurethan described above, the melting point was not altered.

Summary

1. 2-Ethylmercapto-5-phenyluracil has been prepared by condensing the sodium salt of ethylformylphenylacetate with pseudoethylthiourea hydrogen bromide in the presence of alkali.

2. This uracil derivative interacts with phosphorus oxychloride to form 2-ethylmercapto-5-phenyl-6-chloropyrimidine.

3. 2-Ethylmercapto-5-phenyl-6-thiocyanopyrimidine is formed by interaction of potassium thiocyanate with 2-ethylmercapto-5-phenyl-6-chloropyrimidine in boiling ethyl alcohol or benzene solutions.

4. This pyrimidine thiocyanate distills at 215° at 2 mm. pressure and is rearranged to its isomeric form, the isothiocyanate, (1) by heating with alcohol at 140° and (2) by digestion in boiling xylene. Both the thiocyanate and the isothiocyanate can be obtained as crystalline compounds.

5. The structure of the thiocyanate is established by interaction of the compound with thioacetic acid. This gives 2-ethylmercapto-5-phenyl-6-thiopyrimidine, which can also be synthesized normally by the action of sodium hydrosulfide on the corresponding chloropyrimidine.

6. The thiocyanate does not interact with alcohols, ammonia or aniline. The isothiocyanate reacts with these same reagents to form the corresponding thionurethans and thioureas, respectively.

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