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Pyrimidine Research: The Molecular Rearrangement of 2-Ethylmercapto-4,5-dimethyl-6-thiocyanopyrimidine

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A further study in this Laboratory of the chemistry of pyrimidine-thiocyanates has led to interesting results which the authors now report in this paper. Following the technique of Wheeler, Johnson[3] and their co-workers, the authors have investigated the action of potassium thiocyanate upon 2-ethylmercapto-4,5-dimethyl-6-chloropyrimidine (II) which is prepared from the corresponding oxypyrimidine (I) and find that they interact smoothly to form a normal thiocyanate (III). The structure of this rhodanide is established by the fact that it reacts with thioacetic acid[3b,d,f,4] to give 2-ethylmercapto-4,5-dimethyl-6-thiopyrimidine (V).

This thiocyanopyrimidine III is quite stable, and exhibits a chemical behavior similar to that of 2-ethylmercapto-5-carbethoxy-6-thiocyanopyrimidine,[3d] 2-ethylmercapto-4-methyl-6-thiocyanopyrimidine,[3e] 2-ethylmercapto-5-phenyl-6-thiocyanopyrimidine,[3f] and 2-ethylmercapto-5-ethyl-6-thiocyanopyrimidine. It can be distilled under a pressure of 1.5 mm. without decomposition and without conversion into its isothiocyanate form (IV). The stability of the thiocyanate, however, is greatly influenced by the presence of certain reagents, and a molecular rearrangement to the isothiocyanate IV can be accomplished easily under catalytic influence at a temperature below its boiling point. This instability of molecular structure is quite remarkable; however, a complete rearrangement is never reached even after twenty-four hours of heating. Possibly we are dealing here with an equilibrium mixture of the two forms. The conditions under which the molecular transformation is brought about are described in the experimental part of this paper.

$$NH{-}C(SC_2H_5){=}N{-}C(CH_3){=}C(CH_3){-}CO$$
(I)

$$N{-}C(SC_2H_5){=}N{-}C(CH_3){=}C(CH_3){-}CCl$$
(II)

$$N{-}C(SC_2H_5){=}N{-}C(CH_3){=}C(CH_3){-}CSCN$$
(III)

$$N{-}C(SC_2H_5){=}N{-}C(CH_3){=}C(CH_3){-}CNCS$$
(IV)

$$NH{-}C(SC_2H_5){=}N{-}C(CH_3){=}C(CH_3){-}CS$$
(V)

Experimental Part

$NH{-}CS{-}NH{-}C(CH_3){=}C(CH_3){-}CO$, **2-Thio-4,5-dimethyl-6-oxypyrimidine.**—Three and two-tenths grams of sodium was dissolved in 80 cc. absolute alcohol and 5.3 g. of thiourea and 10 g. ethyl methyl-acetoacetate were added to the solution. The mixture was heated on a water-bath for three hours and the excess of alcohol then evaporated at 100°, yielding the sodium salt of the above pyrimidine. This was dissolved in cold water and acidified with acetic acid, when the thiopyrimidine separated in a crystalline condition. It was recrystallized from hot water and separated as colorless needles, melting at 279–280°. The yield was 10 g. or 92.6%. *Anal.* Calcd. for $C_6H_8ON_2S$: N, 17.94. Found: N, 18.07, 17.85.

2-Ethylmercapto-4,5-dimethyluracil, I.—This was made by a different method from that originally used by Wheeler and Merriam.[5] One and six-tenths grams of metallic sodium was dissolved in 70 cc. of absolute alcohol, 10 g. of the preceding 2-thiopyrimidine added to the solution, and the mixture warmed on a water-bath. To this solution ethyl iodide was added (1.25 mol) and the solution refluxed for two hours. On cooling, the mercapto-pyrimidine separated in colorless prismatic crystals, melting at 155–156°.

An additional quantity of the mercapto-pyrimidine was obtained from the mother liquor by the following procedure. It was evaporated to dryness on a water-bath, and the residue triturated with cold water. The insoluble solid was recrystallized from 70% alcohol, when the pyrimidine separated in colorless prisms, melting at 155–156°; total yield, 10 g. *Anal.* Calcd. for $C_8H_{12}ON_2S$: N, 15.21. Found: N, 15.0, 15.0.

$NH{-}C(SCH_3){=}N{-}C(CH_3){=}C(CH_3){=}CO$, **2-Methylmercapto-4,5-dimethyluracil.**—This pyrimidine was prepared by alkylation of the 2-thiopyrimidine above with methyl iodide. It crystallized from hot water in colorless needles, melting at 225–227°. The yield was 3.8 g.

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[1] Our researches on pyrimidines were started originally in the Sterling Chemistry Laboratory of Yale University under the direction of Professor Treat B. Johnson, Sterling Professor of Chemistry.

[2] The writers wish to acknowledge the assistance of Mr. Yao-Tseng Hwang who made micro-analyses of the compounds described in this paper.

[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); (f) Chi and Tien, *ibid.*, **55**, 4181 (1933); (g) Chi and Ma, *ibid.*, **55**, 4655 (1933).

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

[5] Wheeler and Merriam, *Am. Chem. J.*, **29**, 478 (1903).

Anal. Calcd. for $C_7H_{10}ON_2S$: N, 16.47. Found: N, 16.7, 16.6.

Ethyl-4,5-dimethyl-6-oxypyrimidine-2-thioglycolate, $\mathrm{NH—C(SCH_2COOC_2H_5)=N—C(CH_3)=C(CH_3)—CO}$.—To an alcoholic solution of the sodium salt of the 2-thiopyrimidine above one mol. proportion of ethyl chloroacetate was added, and the solution refluxed for two hours on a water-bath. The solution was then evaporated to dryness and the residue recrystallized from hot water. The above compound separated in colorless long needles melting at 132–133°. The yield was 4.5 g. *Anal.* Calcd. for $C_{10}H_{14}O_3N_2S$: N, 11.57. Found: N, 11.6, 11.5.

4,5-Dimethyl-6-oxypyrimidine-2-thioglycolic Acid, $\mathrm{NH—C(SCH_2COOH)=N—C(CH_3)=C(CH_3)—CO}$.—This was prepared by saponification of its ethyl ester with boiling dilute potassium hydroxide solution on a boiling water-bath for fifteen minutes. The acid was recrystallized from hot water, separating in colorless needles, melting at 128–129°. *Anal.* Calcd. for $C_8H_{10}O_3N_2S{\cdot}H_2O$: N, 12.07; H_2O, 7.76. Found: N, 12.01, 12.16. 0.6540 g. of substance on heating at 110° for one and one-half hours lost 0.04985 g. or equivalent to 7.62% of water of crystallization.

$\mathrm{NH—CO—NH—C(CH_3)=C(CH_3)—CO}$, **4,5-Dimethyluracil (1). By Desulfurization of 2-Thio-4,5-dimethyl-6-oxypyrimidine.**—Two grams of this pyrimidine was refluxed with 10 cc. of chloroacetic acid for three hours, when the sulfur was completely removed. The oxypyrimidine recrystallized from hot water in prisms, melting at 294–296°. It agreed in all its properties with the dimethyluracil originally prepared by Schlenker[6] and later by Wheeler and Merriam.[5] *Anal.* Calcd. for $C_6H_8O_2N_2$: N, 20.00. Found: N, 19.9. 0.7190 g. substance on heating at 110–120° for one and one-half hours lost 0.0820 g., equivalent to 11.40% of water of crystallization.

(2) **By Hydrolysis of 2-Ethylmercapto-4,5-dimethyluracil with Hydrobromic Acid.**—The resulting 4,6-dimethyluracil separated in colorless prisms and melted at 294°. The yield was 1.45 g. For analysis, it was dried at 120°. Calcd. for $C_6H_8O_2N_2$: N, 20.00. Found: N, 20.1.

2-Ethylmercapto-4,5-dimethyl-6-chloropyrimidine, II.—This was prepared by allowing twenty grams of 2-ethylmercapto-4,5-dimethyluracil to react with 80 cc. of phosphorus oxychloride at its boiling temperature for ten hours. After distilling off under diminished pressure the excess of phosphorus oxychloride, we obtained a heavy oil which was poured upon crushed ice to destroy complex phosphorus compounds and the chloropyrimidine finally extracted with ether. The ethereal solution was then washed with dilute sodium hydroxide and then with water, and finally dried over anhydrous sodium sulfate, and the solvent distilled off. The chloropyrimidine was fractionated under a vacuum and boiled at 142–144° at 10 mm. pressure or at 129–132° at 2 mm. pressure. The yield was 17 g. or 77% of the theoretical. *Anal.* Calcd. for $C_8H_{11}N_2SCl$: N, 13.83. Found: N, 13.87, 13.70.

2-Ethylmercapto-4,5-dimethyl-6-thiocyanopyrimidine, III.—Ten grams of the 6-chloropyrimidine and 5.3 g. of potassium thiocyanate were refluxed in 10 cc. of absolute alcohol on a water-bath for one and one-half hours. The insoluble potassium chloride formed during the reaction was filtered from the solution, while hot. On standing in an ice box overnight, the thiocyanopyrimidine separated in needles. After recrystallizing from 95% alcohol or petroleum ether, it melted at 64.5–65.5° and boiled at 160° at 1.5 mm. pressure. The yield was 50%. *Anal.* Calcd. for $C_9H_{11}N_3S_2$: N, 18.66. Found: N, 18.8, 18.7.

Proof of the Structure of the Pyrimidine Thiocyanate

That the above compound, melting at 64.5–65.5°, had the structure of a normal rhodanide, was proved by the following facts. (1) It could be recrystallized from ethyl alcohol without conversion into a thiourethan. (2) It did not react with concentrated ammonia and aniline to form thioureas. (3) It interacted with thioacetic acid to form the 6-thiopyrimidine V as described below.

2-Ethylmercapto-4,5-dimethyl-6-thiopyrimidine, V.—One gram of the thiocyanopyrimidine was dissolved in 7 cc. of cold thioacetic acid, and the solution refluxed on a water-bath for three hours. On cooling, the thiopyrimidine separated in long, rectangular plates which, on purification by recrystallization from absolute alcohol, melted at 187–188°. The yield was 0.75 g. *Anal.* Calcd. for $C_8H_{12}N_2S_2$: N, 13.99; C, 47.94; H, 6.04. Found: N, 13.8; C, 48.20; H, 5.99.

The compound melting at 187–188° was mixed with the 6-thiopyrimidine prepared from the interaction between the above 6-chloropyrimidine and sodium hydrosulfide, and its melting point was not depressed.

The Molecular Rearrangement of 2-Ethylmercapto-4,5-dimethyl-6-thiocyanopyrimidine into its Isomeric Isothiocyanate Modification

2-Ethylmercapto-4,5-dimethyl-6-isothiocyanopyrimidine, IV.—Ten grams of the thiocyanate was refluxed for twenty-four hours in 20 cc. of boiling xylene, when a dark brown solution was obtained. The solvent was distilled off under diminished pressure, yielding an oily residue. This was then extracted with cold petroleum ether (b. p. 30–50°) to remove the unchanged thiocyanate and the solvent then distilled off when the isothiocyanate was left behind as an oil, boiling at 150–152° under a pressure of 1.5 mm. This solidified on standing in an ice box overnight and melted at 28–30°. For further purification, it was recrystallized from petroleum ether when the pure isothiocyanate melting at 29.5–30° was obtained. The yield was 5.5 g. or 55% of the theoretical. *Anal.* Calcd. for $C_9H_{11}N_3S_2$: N, 18.66. Found: N, 18.5, 18.5.

Proof of the Structure of the Isothiocyanate

$\mathrm{N—C(SC_2H_5)=N—C(CH_3)=C(CH_3)—C—NHCSOCH_3}$, **2-Ethylmercapto-4,5-dimethyl-6-thionmethylurethan-pyrimidine.**—One gram of the isothiocyanate was warmed with 10 cc. of methyl alcohol for ten minutes. After the completion of the reaction, nothing separated on standing in an ice box. The excess of methyl alcohol being removed at 100° under diminished pressure gave a residue which refused to solidify. It was then treated with dilute sodium hydroxide, and the alkaline filtrate

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(6) Schlenker, *Ber.*, **34**, 2813 (1901).

filtered and then neutralized with dilute acetic acid and the mixture extracted with ether. On evaporating the ethereal solution the above urethan was obtained in crystalline condition. The yield was 0.7 g. It was purified by recrystallization from petroleum ether and melted at 75–76°. *Anal.* Calcd. for $C_{10}H_{15}ON_3S_2$: N, 16.34. Found: N, 16.2, 16.5.

$\mathrm{N{-}C(SC_2H_5){=}N{-}C(CH_3){=}C(CH_3){-}C{-}NHCSOC_2H_5}$, **2 - Ethylmercapto - 4,5 - dimethyl - 6 - thionethylurethan-pyrimidine.**—This was purified by recrystallization from alcohol and it melted at 129–130°. *Anal.* Calcd. for $C_{11}H_{17}ON_3S_2$: N, 15.49. Found: N, 15.3, 15.4.

$\mathrm{N{-}C(SC_2H_5){=}N{-}C(CH_3){=}C(CH_3){-}C{-}NHCSOCH_2CH_2CH_3}$, **2 - Ethylmercapto - 4,5 - dimethyl - 6 - thion - *n* - propyl-urethan-pyrimidine.**—This was purified by recrystallization from petroleum ether. It separated as colorless rectangular plates, melting at 61–63°. *Anal.* Calcd. for $C_{12}H_{19}ON_3S_2$: N, 14.73. Found: N, 14.9.

$\mathrm{N{-}C(SC_2H_5){=}N{-}C(CH_3){=}C(CH_3){-}CNHCSNH_2}$, **2-Ethylmercapto - 4,5 - dimethyl - 6 - thiourea - pyrimidine.**—One gram of the thiocyanate was rearranged into its isothiocyanate in boiling xylene solution and isolated as described above. Ten cubic centimeters of concentrated aqueous ammonia were then added to the petroleum ether solution of the isothiocyanate when this thiourea separated. It was recrystallized from ethyl acetate and melted at 209–210°. *Anal.* Calcd. for $C_9H_{14}N_4S_2$: N, 23.13. Found: N, 22.8, 22.9.

$\mathrm{N{-}C(SC_2H_5){=}N{-}C(CH_3){=}C(CH_3){-}CNHCSNHC_6H_5}$, **2 - Ethylmercapto - 4,5 - dimethyl - 6 - phenylthiourea-pyrimidine.**—One gram of the thiocyanate was rearranged into its isothiocyanate and a calculated amount of aniline was added to a petroleum ether solution of the isothiocyanate at room temperature. This urea formed immediately. For purification it was recrystallized from ethyl alcohol. It deposited as needles, melting at 139–141°. *Anal.* Calcd. for $C_{15}H_{18}N_4S_2$: N, 17.64. Found: N, 17.4, 17.5.

Experimental Conditions Influencing the Rearrangement of the Isothiocyanate

A.—On heating the thiocyanate at 70° without a solvent for two hours and at 90° for one hour we observed no signs of a change. Heating at 90° for two hours gives rise to a product difficult to solidify and melting at 43–49°; however, the original thiocyanate can be isolated from this.

B.—On heating the thiocyanate in benzene solution for twenty-four hours, there was no sign of change; and the original material could be recovered.

C.—By heating the thiocyanate in toluene solution for twenty-four hours, there was obtained a small fraction showing evidence of rearrangement; however, most of the original material could be recovered.

D.—Distillation of the thiocyanate under a vacuum at its boiling point (160°) does not bring about a rearrangement. The distillate can be solidified, recrystallized from petroleum ether, and proved to be the original thiocyanate.

E.—Heating the thiocyanate in xylene solution for twenty-four hours does not bring about complete rearrangement, and an equilibrium mixture is the result.

Summary

1. 2-Thio-4,5-dimethyl-6-oxypyrimidine has been prepared by condensing ethyl methylacetoacetate with thiourea in the presence of sodium ethylate.

2. The action of alkyl halides on 2-thio-4,5-dimethyl-6-oxypyrimidine in the presence of sodium ethylate gives the corresponding mercaptopyrimidines.

3. 2-Ethylmercapto-4,5-dimethyluracil interacts with phosphorus oxychloride to form 2-ethylmercapto-4,5-dimethyl-6-chloropyrimidine.

4. This chloropyrimidine interacts normally with potassium thiocyanate to form a true thiocyanate derivative, 2-ethylmercapto-4,5-dimethyl-6-thiocyanopyrimidine.

5. This pyrimidine thiocyanate distils at 160° at 1.5 mm. pressure, and can be rearranged to its isomeric form, the isothiocyanate, by digesting in boiling toluene or xylene. Both the thiocyanate and the isothiocyanate can be obtained as crystalline compounds.

6. The structure of the thiocyanate is established by interaction of the compound with thioacetic acid. This gives 2-ethylmercapto-4,5-dimethyl-6-thiopyrimidine, which can also be synthesized normally by the action of sodium hydrosulfide on the corresponding chloropyrimidine.

7. 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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