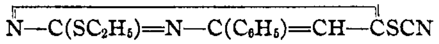
[CONTRIBUTION FROM NATIONAL RESEARCH INSTITUTE OF CHEMISTRY, ACADEMIA SINICA]

Pyrimidine Research: The Molecular Rearrangement of 2-Ethylmercapto-4-phenyl-6-thiocyanopyrimidine[1]

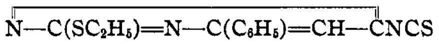
BY YUOH FONG CHI, YEE SHENG KAO AND YAO-TSENG HUANG

Further work in this Laboratory on pyrimidine-thiocyanates has led to new and interesting results. 2-Ethylmercapto-4-phenyl-6-thiocyanopyrimidine, represented by formula I, is a substance which can be distilled under a pressure of 1.5 mm. without decomposition, and without conversion into its isomeric isothiocyanate modification, represented by formula II. It exhibits all the characteristic reactions of a true rhodanide. The stability of this thiocyanate (I), however, is greatly influenced by the presence of certain reagents, and a molecular rearrangement to the isothiocyanate (II) can be accomplished easily, at a temperature much below its boiling point, by heating at 160–170° in toluene.



$N—C(SC_2H_5)=N—C(C_6H_5)=CH—CSCN$

I



$N—C(SC_2H_5)=N—C(C_6H_5)=CH—CNCS$

II

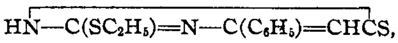
Experimental Part

2 - Ethylmercapto - 4 - phenyl - 6 - chloropyrimidine.—This chloropyrimidine, prepared according to the technique of Johnson and Hemingway,[2] boiled at 174–176°.

2-Ethylmercapto-4-phenyl-6-thiocyano-pyrimidine, I.—2-Ethylmercapto-4-phenyl-6-chloropyrimidine was refluxed for two hours with one molecular proportion of potassium thiocyanate in absolute alcohol. The reaction proceeded with great ease and on cooling the alcohol, this thiocyanate separated in colorless needles. It was purified by crystallization from a benzene–petroleum ether mixture or ethyl alcohol and melted at 88–89°. It distilled at 204° at 1.5 mm. pressure. The yield was 4.5 g. (82.5%).

Anal. Calcd. for $C_{13}H_{11}N_3S_2$: N, 15.39. Found: N, 15.3, 15.4.

Proof of the Structure of the Thiocyanate.—That the above compound, melting at 88–89°, has the structure of a normal rhodanide, was proved by the following facts. (1) It could be recrystallized from ethyl alcohol without conversion to a thiourethan; (2) it did not combine with ammonia or aniline to form thioureas and (3) it interacted with thioacetic acid to form the thiopyrimidine described below:



$HN—C(SC_2H_5)=N—C(C_6H_5)=CHCS$, **2-Ethylmercapto-4-phenyl-6-thiopyrimidine.**—This compound was formed when 2-ethylmercapto-4-phenyl-6-thiocyanopyrimidine was refluxed on a water-bath with 5 cc. thioacetic acid for two hours. It separated in characteristic yellow crystals and on recrystallization from absolute alcohol it deposited in yellow needles, melting at 206–207°. The yield was excellent.

Anal. Calcd. for $C_{12}H_{12}N_2S_2$: N, 11.29. Found: N, 11.2, 11.3.

The same ethylmercapto-4-phenyl-6-thiopyrimidine was also prepared as follows. Two grams of the corresponding 6-chloropyrimidine were refluxed on a water-bath with 1 g. of freshly prepared sodium hydrosulfide in 10 cc. of absolute alcohol. Sodium chloride separating in the reaction mixture was removed while hot. A drop of glacial acetic acid was added to the filtrate, when the thiopyrimidine separated in a yield of 1.2 g. After purification by recrystallization from absolute alcohol, it separated in yellow needles, melting at 206–207°. *Anal.* Calcd. for $C_{12}H_{12}N_2S_2$: N, 11.29. Found: N, 11.2, 11.3.

The Molecular Rearrangement of 2-Ethylmercapto-4-phenyl-6-thiocyanopyrimidine into its Isomeric Form

2 - Ethylmercapto - 4 - phenyl - 6 - isothiocyanopyrimidine, II.—Sixteen grams of the normal thiocyanate I was dissolved in 15 cc. of toluene and the solution heated in a bomb tube at 160–170° for ten hours. After cooling, the tube was opened without evidence of any pressure. After removing all solvent by heating under diminished pressure, the residue was extracted with a large quantity of petroleum ether to extract the rearranged pyrimidine, and the solvent distilled off. We obtained an oil which was purified by distillation. It boiled at 215–218° at 2 mm. pressure. *Anal.* Calcd. for $C_{13}H_{11}N_3S_2$: N, 15.39. Found: N, 15.38, 15.10.

2-Ethylmercapto-4-phenyl-6-thioureapyrimidine.—To a petroleum ether solution of the isothiocyanate, concentrated aqueous ammonia was added, when this thiourea separated immediately. After purification by recrystallization from alcohol, it melted at 212–213°. *Anal.* Calcd. for $C_{13}H_{14}N_4S_2$: N, 19.31. Found: N, 19.1.

2 - Ethylmercapto - 4 - phenyl - 6 - phenylthioureapyrimidine.—The isothiocyanate interacted in petroleum ether solution with aniline, forming the corresponding phenylthiourea. After recrystallization from ethyl acetate, it separated in colorless needles, melting at 215–216.° *Anal.* Calcd. for $C_{19}H_{18}N_4S_2$: N, 15.30. Found: N, 15.3, 15.5.

2 - Ethylmercapto - 4 - phenyl - 6 - thionmethylurethanpyrimidine.—Five-tenths gram of the normal thiocyanate was rearranged and isolated as described above. It was then heated with a few cc. of methyl alcohol for a few minutes, when the thionmethylurethan separated on standing. After purification by recrystallization from benzene–petroleum ether, it separated in colorless needles, melting at 130–131°. *Anal.* Calcd. for $C_{14}H_{15}ON_3S_2$: N, 13.77. Found: N, 13.8, 13.7.

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[1] This paper is a report of further work carried on in this Laboratory on the study of pyrimidine thiocyanates. The authors are indebted to Professor Treat B. Johnson of Yale University for his help in preparing the paper for publication.

[2] Johnson and Hemingway, THIS JOURNAL, 37, 381 (1915).

2 - Ethylmercapto - 4 - phenyl - 6 - thionethylurethanpyrimidine.—By digesting the isothiocyanate with ethyl alcohol for a few minutes, this thionethylurethan was formed smoothly. After recrystallization from benzene-petroleum ether, it separated in colorless needles, melting at 115–116°. *Anal.* Calcd. for $C_{15}H_{17}ON_3S_2$: N, 13.16. Found: N, 13.2, 13.1.

2 - Ethylmercapto - 4 - phenyl - 6 - thion - *n* - propylurethanpyrimidine.—This recrystallized from ethyl alcohol and melted at 97–98°. *Anal.* Calcd. for $C_{16}H_{19}ON_3S_2$: N, 12.61. Found: N, 12.6, 12.7.

2 - Ethylmercapto - 4 - phenyl - 6 - thion - *n* - butylurethanpyrimidine.—Prepared by action of butyl alcohol on the isothiocyanate. After recrystallization from ethyl alcohol or methyl alcohol, it melted at 89–90°. *Anal.* Calcd. for $C_{17}H_{21}ON_3S_2$: N, 12.10. Found: N, 12.1, 12.2.

Experimental Conditions Influencing the Rearrangement.—Heating the normal thiocyanate in benzene, toluene and xylene at their respective boiling points did not bring about any change. The thiocyanate could be distilled at 204° at 1.5 mm. pressure without decomposition and without conversion into the isothiocyanate. The rearrangement was, however, brought about by heating the thiocyanate at 160–170° in toluene under pressure.

Summary

1. 2-Ethylmercapto-4-phenyl-6-thiocyanopyrimidine, prepared from the corresponding chloro compound, was identified as the normal thiocyanate by its characteristic reaction with thioacetic acid.

2. Heating 2-ethylmercapto-4-phenyl-6-thiocyano-pyrimidine at 160–170° in toluene brought about a rearrangement to 2-ethylmercapto-4-phenyl-6-isothiocyano-pyrimidine.

3. The thiocyanate was non-reactive toward ammonia, aniline and alcohols. The isothiocyanate reacted with ammonia, aniline and alcohols, giving the corresponding thioureas and thiourethans, respectively.

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The Estimation of the Total Basic Amino Acids in Gelatin by Titration in Glacial Acetic Acid[1]

BY J. RUSSELL AND A. E. CAMERON

In the titration of gelatin in aqueous solution, no very significant data are obtainable with respect to groups with a *pK* above 12, due to the uncertainties introduced by the corrections for free base. Since arginine with a *pK* of 13 is found among the hydrolytic products of gelatin, it was very desirable that a method be found of supplementing the information obtained by aqueous titration. Acetic acid suggested itself as a very suitable solvent for further work, since it is a strongly acid solvent and the work of Conant[2] has shown that in it guanidine acts as a titratable strong base.

It was at first found impossible to proceed, since gelatin was insoluble in glacial acetic acid. However, the expedient was adopted of first dissolving the gelatin in a small amount of water and diluting with glacial acetic acid. The titrations were thus finally carried out in acetic acid with about 2% water present.

Portions of the solutions, containing 0.2 g. of dry gelatin, were pipetted into the titration vessel. Four palladium black electrodes were used. A half cell of chloranil–tetrachlorohydroquinone mixture in molar sulfuric acid in glacial acetic acid with a salt bridge of a saturated acetic acid solution of lithium chloride completed the cell. Hydrogen, saturated with acetic acid, was passed in at the bottom of the vessel through a porous bubble head. The exit gas passed out through a bubble bottle so that a slight positive pressure of hydrogen was maintained in the titration vessel at all times. The paraffined corks carrying the electrodes and salt bridge were sealed into the flask necks with paraffin. A swirling motion was given the flask by an electric motor to stir the solution and give the most satisfactory readings.

Freshly plated palladium black electrodes were employed in each titration. Attainment of the initial equilibrium was slow. Therefore, whenever possible, the solutions were allowed to remain overnight with hydrogen bubbling through, before beginning the titration. Four electrodes agreed uniformly within one millivolt even after precipitation of gelatin was taking place. The only effect of the precipitated gelatin was to retard the attainment of electrode equilibrium.

An approximately 0.01 *M* perchloric acid solution was prepared by adding 1 ml. of 70% aqueous acid to a liter of glacial acetic acid. Standard sodium acetate solution was prepared by dissolving a weighed amount of dried sodium carbonate in acetic acid and making up to volume. Samples of this solution were pipetted out and titrated with the perchloric acid for standardization.

The gelatin solutions employed were made up using 5 ml. of water to melt them in each case, and making up to 250 ml. total volume with glacial acetic acid.

The gelatin, measurements for which are reported in this

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(1) Presented before the Leather and Gelatin Division at the New York meeting of the American Chemical Society, April, 1935.

(2) J. B. Conant and N. F. Hall, THIS JOURNAL, **49**, 3047 (1927).