acid product, crystallized from water, melted at 183–184°, the melting point of 3,4-dimethoxy-6-bromobenzoic acid (6-bromoveratric acid). It was identified as this acid by a mixed melting point with the acid formed by oxidation of 6-bromoveratric aldehyde made by bromination of veratric aldehyde according to the directions of Pschorr.[9]

When the tribromo acid was treated with alcoholic potassium hydroxide an isomeric unsaturated bromo acid was obtained, and a small amount of a styrene derivative.

α-Bromo-3,4-dimethoxy-6-bromocinnamic Acid (198°).—Four grams of tribromo acid, finely pulverized, was stirred rapidly into 25 cc. of a 25% solution of potassium hydroxide in methyl alcohol. A colorless potassium salt began to separate at once. After ten minutes this was filtered out and dissolved in about 100 cc. of water. The solution deposited a small amount of solid, a styrene, which was filtered out and the solution cooled and acidified. The gelatinous precipitate was air dried and crystallized from boiling benzene from which it separates in fine pale lemon-yellow needles melting at 198°. The acid is readily soluble in acetone, boiling benzene and methyl alcohol, insoluble in ether.

Anal. Calcd. for $C_{11}H_{10}O_4Br_2$: C, 36.07; H, 2.73. Found: C, 36.16; H, 2.96.

The acid changes slowly to the higher melting isomeric acid (233°) on heating. It is, then, the less stable of the two isomers. The alcoholic filtrate from the separation of the potassium salt of the lower melting acid deposited, on acidification, a small amount of the impure high-melting acid.

The methyl ester of the acid (198°) was prepared by the usual procedure with diazomethane. It crystallizes from ether and from boiling methyl alcohol in fine white needles melting at 92°.

Anal. Calcd. for $C_{12}H_{12}O_4Br_2$: C, 37.89; H, 3.15. Found: C, 38.00; H, 3.24.

α-Bromo-3,4-dimethoxy-6-bromostyrene, $(CH_3O)_2C_6H_2BrCH{=}CHBr$.—The styrene derivative mentioned above separates from methyl alcohol in fine cream colored needles melting at 100°.

Anal. Calcd. for $C_{10}H_{10}O_2Br_2$: C, 37.26; H, 3.10. Found: C, 37.45; H, 3.67.

Concentrated sulfuric acid dissolves all these cinnamic acids, the solutions being of a pale yellow color as with other cinnamic acids studied. In the present case, however, the yellow solutions take on slowly a pale green or blue color which readily fades out.

Summary

3,4-Dimethoxybenzalpyruvic acid and its bromination products have been prepared for purposes of comparison with other substituted benzalpyruvic acids. 3,4-Dimethoxycinnamic acid and its bromination products have also been studied and contrasted with 3-methoxy- and with 2,4-dimethoxycinnamic acids.

NEW YORK, N. Y. RECEIVED NOVEMBER 22, 1934

(9) Pschorr, *Ann.*, **391**, 32 (1912).

[CONTRIBUTION FROM THE HENRY LESTER INSTITUTE OF MEDICAL RESEARCH, SHANGHAI, CHINA]

Researches on Pyrimidines. The Molecular Rearrangement of 2-Ethylmercapto-5-ethyl-6-thiocyanopyrimidine[1,2]

BY YUOH-FONG CHI AND YÜ-LIN T'IEN[3]

This paper describes the conditions of the molecular rearrangement of 2-ethylmercapto-5-ethyl-6-thiocyanopyrimidine (III) which is another example in our thiocyanate researches.[4,5,6,7,8,9,10] The thiocyanate (III) which is obtained from the corresponding chloropyrimidine (II)[11] prepared by the action of phosphorus chloride on the oxypyrimidine (I)[12] exhibits all the properties of a rhodanide, the structure of which is established by its interaction with thio-acetic acid[5,7,9,10,13] to give a dithiourethan (V). This thiocyanopyrimidine (III) is stable at its boiling point, and exhibits a similar behavior to 2-ethylmercapto-5-carbethoxy-6-thiocyanopyrimidine,[7] 2-ethylmercapto-4-methyl-6-thiocyanopyrimidine[8] and 2-ethylmercapto-5-phenyl-6-thiocyanopyrimidine.[9] It can be distilled at 158–160° under 5 mm. pressure without decomposition and without its conversion into its isomeric isothiocyanate (IV). Nevertheless, the stability of thiocyanopyrimidine (III) is greatly influenced by the presence of other reagents, and a molecular re-

(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) The authors desire to express their sincere thanks to The Lester Institute for their permission to undertake this research in their laboratories. They also wish to acknowledge help and criticisms from Professor Bernard E. Read.

(3) Holder of Fellowship from the China Foundation.

(4) Wheeler and Bristol, *Am. Chem. J.*, **33**, 448 (1905).

(5) Johnson and McCollum, *ibid.*, **36**, 136 (1906).

(6) Johnson and Storey, *ibid.*, **40**, 131 (1908).

(7) Johnson and Chi, THIS JOURNAL, **52**, 1580 (1930).

(8) Chi and Chen, *ibid.*, **54**, 2056 (1932).

(9) Chi and Tien, *ibid.*, **55**, 4181 (1933).

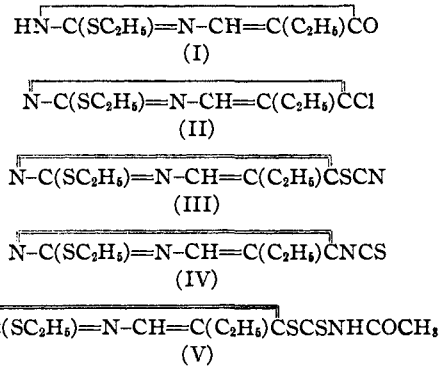
(10) Chi and Ma, *ibid.*, **55**, 4655 (1933).

(11) Johnson and Menge, *J. Biol. Chem.*, **3**, 105 (1906).

(12) Johnson and Menge, *loc. cit.*, p. 1508.

(13) Wheeler and Merriam, THIS JOURNAL, **23**, 283 (1901).

arrangement to the isothiocyanate (IV) can be brought about easily at a temperature very much below that of the boiling point of the thiocyanate (III).



(I) (II) (III) (IV) (V)

Experimental Part

Sodium Salt of Ethyl-formyl-*n*-butyrate.—This salt is prepared as follows. To 30 g. of sodium wire suspended in absolute ether, 150 g. of ethyl *n*-butyrate and 96 g. of ethyl formate were added drop by drop. As the reaction proceeded, the flask was chilled with ice water. After completion of the reaction, it was extracted with cold water. This aqueous solution of the sodium salt is used for the preparation of the oxypyrimidine.

2-Ethylmercapto-5-ethyl-uracil.—119 g. of pseudo-ethylthiourea hydrogen bromide was dissolved in the resulting aqueous solution of the sodium salt of ethyl-formyl-*n*-butyrate and a cold solution of 36 g. of potassium hydroxide dissolved in 50 cc. of water was added very slowly. The alkaline solution was allowed to stand overnight in an ice box. On acidifying the solution with acetic acid the oxypyrimidine separated at once as a flocculent precipitate. After purification by crystallization from 95% alcohol, it melted at 119–120° to a clear oil. The yield of pure oxypyrimidine was 52 g. or about 41% of the theoretical; soluble in hot water and very soluble in hot alcohol.

Anal. Calcd. for $C_8H_{12}ON_2S$: N, 15.21. Found: N, 14.49, 14.69, 15.02, 14.87.

2-Ethylmercapto-5-ethyl-6-chloropyrimidine.—Twenty-five grams of 2-ethylmercapto-5-ethyluracil was dissolved in 60 cc. of cold phosphorus oxychloride and the solution heated on an oil-bath for four hours. After the removal of the excess of phosphorus oxychloride under diminished pressure, there was left an oily product which would not solidify on cooling. The liquid was then poured on crushed ice to decompose the phosphorus complex. The chloropyrimidine was extracted with ether, dried over calcium chloride and purified by distillation under diminished pressure. It boiled at 160–162° under 22 mm. pressure. The yield of pure distillate was 23 g. or 85% of the theoretical.

Anal. Calcd. for $C_8H_{11}N_2SCl$: N, 13.83. Found: N, 13.34, 13.37.

2-Ethylmercapto-5-ethyl-6-thiocyanopyrimidine.—This thiocyanate can be obtained by the action of potassium thiocyanate on the above chloride in boiling alcohol, benzene or acetone solution. Fifteen grams of chloropyrimidine, boiling at 160–162° at 22 mm. pressure, and 8 g. of potassium thiocyanate were dissolved in 40 cc. of 95% alcohol and the solution refluxed on a water-bath for one hour, when the reaction was complete. The solution was filtered while hot and chilled; the thiocyanate crystallized out immediately in the form of colorless needles. The yield was 10.5 g. or 61% of the theoretical. After purification by recrystallization from alcohol, it melted at 46–47° to a colorless oil and distilled at 158–160° under 5-mm. pressure. The thiocyanate is soluble in benzene, toluene, xylene and alcohol, but insoluble in petroleum ether.

Anal. Calcd. for $C_9H_{11}N_3S_2$: N, 18.66. Found: N, 18.37, 18.60.

The alcoholic filtrate from the separation of the above thiocyanate was evaporated to complete dryness and the residue triturated with cold dilute sodium hydroxide. On acidifying this alkaline solution with acetic acid, 1.5 g. of a yellow oil separated out and solidified on standing. After recrystallization from 95% alcohol, it separated out in colorless rhombic prisms melting at 77–78° to a clear oil. The analytical values for nitrogen indicated that we are dealing here with 2-ethylmercapto-5-ethyl-6-thion-ethylurethan-pyrimidine.

Anal. Calcd. for $C_{11}H_{17}ON_3S_2$: N, 15.49. Found: N, 15.41, 15.55.

Proof of Structure of the Thiocyanate.—That the compound described above (melting at 46–47°) 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 thiourea when exposed to the action of concentrated aqueous ammonia, (2) it can be crystallized repeatedly from hot alcohol without conversion to a thiourethan, (3) the compound interacts with thioacetic acid to form the dithiourethan described below.

2-Ethylmercapto-5-ethyl-pyrimidine-6-acetyl-dithiourethan.—Four grams of 2-ethylmercapto-5-ethyl-6-thiocyanopyrimidine was dissolved in 10 cc. of thioacetic acid and the solution warmed on a steam-bath for two hours. After cooling, the dithiourethan separated in the form of yellow prisms. It was purified by crystallization from 95% alcohol, and separated on cooling in the form of yellow prisms, melting at 116–117° to a clear oil.

Anal. Calcd. for $C_{11}H_{15}ON_3S_3$: N, 13.95. Found: N, 13.72, 13.77.

This compound exhibited all the properties of a dithiourethan. It dissolved in cold alkali and was reprecipitated unaltered from such solution by the addition of acetic acid.

The Molecular Rearrangement of 2-Ethylmercapto-5-ethyl-6-thiocyanopyrimidine into its Isomeric Form

2-Ethylmercapto-5-ethyl-6-isothiocyanopyrimidine.—Ten grams of the thiocyanate was refluxed in 10 cc. of toluene for six hours. After distilling off the toluene, the isothiocyanate residue was extracted with petroleum ether and the solution finally evaporated, leaving the dried isothiocyanate as a red oil. This showed no signs of solidifying, and the yield was 8.5 g., corresponding to

85% of the theoretical. When this oil was subjected to distillation under diminished pressure, it underwent no decomposition. The main fraction distilling at 146–149° at 8-mm. pressure exhibited all the properties of a true isothiocyanate. This reacted immediately with aniline, ammonia and alcohol in accordance with the isothiocyanate structure. It would not solidify in a freezing mixture.

Anal. Calcd. for $C_9H_{11}N_3S_2$: N, 18.66. Found: N, 18.33, 18.55.

2-Ethylmercapto-5-ethyl-6-thiourea-pyrimidine.—The thiocyanate was rearranged into its isomeric form and a petroleum ether solution of the latter combined with an excess of concentrated aqueous ammonia. The corresponding thiourea was formed immediately and 2 g. of this was obtained from 3 g. of the thiocyanate. It was purified by crystallization from alcohol and melted at 143–144°.

Anal. Calcd. for $C_9H_{14}N_4S_2$: N, 23.13. Found: N, 22.94, 23.07.

2-Ethylmercapto-5-ethyl-6-phenyl-thiourea-pyrimidine.—Three grams of the rearranged thiocyanate gave 2.5 g. of this compound by treatment with aniline at ordinary temperature. This was purified by crystallization from 95% alcohol and separated in plates melting at 108–109°.

Anal. Calcd. for $C_{15}H_{18}N_4S_2$: N, 17.61. Found: N, 17.53, 17.69.

2-Ethylmercapto-5-ethyl-6-thionethylurethan-pyrimidine.—This was formed by warming the crude isothiocyanate with absolute alcohol. The alcohol was evaporated to dryness and the residue extracted with cold sodium hydroxide. On acidifying this alkaline solution with acetic acid, the urethan separated. After purification by crystallization from alcohol, it separated in the form of colorless rhombic prisms, melting at 77–78° to a clear oil.

Anal. Calcd. for $C_{11}H_{17}ON_3S_2$: N, 15.49. Found: N, 15.41, 15.48.

Experimental Conditions Influencing the Rearrangement of the Pyrimidine Thiocyanate.—A. Heating the thiocyanate (1) at 60° for twelve hours, (2) at 80° for eight hours, and (3) at 100° for three hours did not give any detectable amount of the isothiocyanate. At 140–150° rapid change takes place but the rearrangement is accompanied by secondary changes which lead to a reaction product which is very hard to purify.

B. Digestion of the pyrimidine in benzene did not produce a rearrangement until after twelve hours. Heating in toluene for six hours produces a rearrangement. At the boiling point of ethyl alcohol for two hours the pyrimidine thiocyanate undergoes a molecular rearrangement and the corresponding thiourethan was obtained.

Summary

1. A new process has been found for preparing the sodium salt of ethyl-formyl-*n*-butyrate by condensing ethyl *n*-butyrate and ethyl formate in the presence of sodium wire.

2. 2-Ethylmercapto-5-ethyl-6-chloropyrimidine has been prepared by a new procedure. Its corresponding oxypyrimidine reacts with phosphorus oxychloride in a characteristic manner.

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

4. This thiocyanate is rearranged to its isomeric form, the isothiocyanate, (1) by heating in boiling ethyl alcohol, (2) by digestion in boiling toluene or xylene solution.

SHANGHAI, CHINA RECEIVED NOVEMBER 22, 1934

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Reaction between Organic Magnesium Compounds and Alpha Bromo Ketones. II

BY E. P. KOHLER AND M. TISHLER

In our first paper[1] we showed that many α-bromo ketones react with organic magnesium compounds in accordance with the general equation

$$RCHBrCOR + R_1MgBr = RCH{=}C(OMgBr)R + R_1Br$$

In view of the great activity of Grignard reagents and the fact that at the end of the reaction the magnesium halide residue is in combination with oxygen, this metathesis is not surprising; in the absence of competing reactions it would be expected to occur whenever a Grignard reagent reacts with any α-halo ketone. Three other reactions are possible, however, even with saturated ketones, namely: elimination of halogen hydride, enolization and addition to the carbonyl group. And in the case of α,β-unsaturated ketones, addition to the conjugated system may also enter the competition.

It is easy to foresee that elimination of halogen hydride will occur only in the comparatively rare cases in which there is unusually active hydrogen in the β position. It is evident also that when the halo ketone is so constituted that neither enolization nor elimination of hydrogen halide is possible, and that the hindrance to addition is prohibitive,

(1) Kohler and Tishler, THIS JOURNAL, **54**, 1594 (1932).