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

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The starting point of this investigation on thiocyanates was ethyl 2-ethylmercapto-6-chloropyrimidine-5-acetate (I), which was prepared by interaction of phosphorus oxychloride with 2-ethylmercapto-6-oxypyrimidine-5-acetate.[3] The latter compound is easily obtained according to the method described by Johnson and Speh.[4] This chloropyrimidine reacts with potassium thiocyanate in benzene solution to form smoothly a normal rhodanide, II. Attempts to purify this latter pyrimidine derivative by distillation were unsuccessful as it was isomerized slowly into the isothiocyanate IV at its boiling point under 1 mm. pressure. That a normal thiocyanate structure is present is established by the behavior of the crude reaction product toward thioacetic acid. They interact to form ethyl 2-ethylmercapto-6-thiopyrimidine-5-acetate, III.

The isothiocyanate IV is easily prepared by refluxing the chloropyrimidine I with potassium thiocyanate in boiling toluene. This latter pyrimidine combines with alcohols, ammonia and aniline to form the corresponding thionurethans and thioureas, respectively. Prolonged exposure to the action of ammonia leads to the formation of 2-ethylmercapto-6-thiourea-pyrimidine-5-acetamide.

It has been the previous experience in our researches here that thiocyanates corresponding to formula II may be transformed into polymeric modifications by prolonged distillation. Such constructions apparently result from the polymerization of the isothiocyanate modification formed by isomerization. In the present case the isothiocyanate exhibits a behavior similar to that shown by Chi and Chen's 2-ethylmercapto-4-methyl-6-isothiocyanopyrimidine.[5] It is easily polymerized by prolonged heating at its boiling point, and the polymer is easily distinguished from the isothiocyanate form by its inactivity toward ammonia, amines and alcohol.

Experimental Part

$\overline{NC(SC_2H_5)=NCH=C(CH_2COOC_2H_5)CCl}$, I, **Ethyl 2-Ethylmercapto-6-chloropyrimidine-5-acetate.**—Twenty-two grams of 2-ethylmercapto-6-oxypyrimidine-5-ace-

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(3) Johnson, Peck and Ambler, THIS JOURNAL, **33**, 758 (1911).

(4) Johnson and Speh, *Am. Chem. J.*, **38**, 607 (1907).

(5) Chi and Chen, THIS JOURNAL, **54**, 2056 (1932).

tate and 75 cc. of phosphorus oxychloride interacted at 100° to give a sirupy product which distilled, after washing with water and drying, at 174° at 4 mm. pressure and 168° at 2 mm. The yield was 17 g. or 70.3% of theoretical.

Anal. Calcd. for $C_{10}H_{13}O_2N_2SCl$: N, 10.75. Found: N, 10.63, 10.68.

$NC(SC_2H_5)=NCH=C(CH_2COOC_2H_5)=CSCN$, II, **ethyl 2-ethylmercapto-6-thiocyanpyrimidine-5-acetate** is obtained by digestion of the preceding chloropyrimidine with potassium thiocyanate in benzene solution for about ten hours. It was never obtained in a pure state and a specimen of the oil distilled under 1 mm. pressure as follows: Fraction I, 175–180°; II, 181–186°; III, 187–195°; IV, 196–204°. Each fraction responded to the reaction of an isothiocyanate when treated with ammonia, yielding a thiourea compound. That a thiocyanate form was present in the crude reaction product was evidenced by its behavior toward thioacetic acid. With this reagent it reacted to form ethyl 2-ethylmercapto-6-thiopyrimidine-5-acetate, $NHC(SC_2H_5)=NCH=C(CH_2COOC_2H_5)CS$, III. This was purified by crystallization from 95% alcohol and separated in the form of needles melting at 130–131° to an oil.

Anal. Calcd. for $C_{10}H_{14}O_2N_2S_2$: N, 10.85. Found: N, 11.03, 10.61, 10.5.

This same pyrimidine is formed by interaction of sodium sulfhydrate with the chloropyrimidine I.

Molecular Rearrangement of Ethyl 2-Ethylmercapto-6-thiocyanopyrimidine-5-acetate

$NC(SC_2H_5)NCH=C(CH_2COOC_2H_5)CNCS$, IV, **Ethyl 2-Ethylmercapto-6-isothiocyanopyrimidine-5-acetate.**—This is formed by digesting the corresponding chloropyrimidine I with potassium thiocyanate in toluene for twenty hours. The pyrimidine was obtained as an oil which distilled at 190–200° at 4 mm.

Anal. Calcd. for $C_{11}H_{13}O_2N_3S_2$: N, 14.84. Found: N, 14.50.

A specimen of the isothiocyanate was *redistilled several times under diminished* pressure, and slowly converted into a polymerized modification. This distilled as a viscous oil boiling at 220° at 4 mm. pressure. On cooling, this product finally solidified and was purified further by crystallization from a mixture of benzene and ether. It separated, on cooling, in the form of prisms melting at 140–141°. The pyrimidine can be digested with alcohol for hours without change, and does not interact with ammonia or aniline.

Anal. Calcd. for $(C_{11}H_{13}O_2N_3S_2)_x$: N, 14.84; S, 22.64. Found: N, 14.78, 14.61; S, 22.51.

DERIVATIVES PREPARED BY INTERACTION OF THE CRUDE ISOTHIOCYANATE IV WITH AMINES AND ALCOHOL

Compound	Formula	Solvent	M. p., °C.	Nitrogen, % Calcd.	Found	
Ethyl 2-ethylmercapto-6-thioureapyrimidine-5-acetate	$C_{11}H_{16}O_2N_4S_2$	Bz	135–136	18.66	18.63	
2-Ethylmercapto-6-thioureapyrimidine-5-acetamide	$C_9H_{13}ON_5S_2$	Alc.	230	25.82	25.62	25.80
2-Ethylmercapto-6-thioureapyrimidine-5-acetic acid	$C_9H_{12}O_2N_4S_2$	Alc.	220–221	20.58	20.54	20.53
Ethyl 2-ethylmercapto-6-phenylthioureapyrimidine-5-acetate	$C_{17}H_{20}O_2N_4S_2$	Alc.	112.5–113	14.89	14.85	14.66
2-Ethylmercapto-6-thionethylurethanpyrimidine-5-acetic acid	$C_{11}H_{15}O_3N_3S_2$	Alc.	146–148	13.95	13.93	14.01

Summary

1. Ethyl 2-ethylmercapto-6-chloropyrimidine-5-acetate interacts with potassium thiocyanate to form first a normal thiocyanate. The latter easily undergoes a normal molecular rearrangement to give ethyl 2-ethylmercapto-6-isothiocyanopyrimidine-5-acetate.

2. Several derivatives of this isothiocyanate have been prepared by the action of amines and ethyl alcohol.

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The Alkyl Derivatives of Halogen Phenols and their Bactericidal Action. II. Bromophenols

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Introduction

Continuing the investigation of the bactericidal properties of the alkyl derivatives of halogen phenols[1] we prepared and studied a number of bromophenol homologs. A complete series of normal *o*-alkyl derivatives of *p*-bromophenol was synthesized comprising the compounds up to and including the 2-*n*-hexyl-4-bromophenol. We directed our attention primarily to the derivatives of *p*-bromophenol, since the exhaustive investigation of the two homologous series of *o*- and *p*-chlorophenol derivatives disclosed an antibacterial superiority of the *p*-chloro series over the *o*-chloro series in almost all instances. It was logical to assume that similar conditions would obtain in the group of bromophenol derivatives, and this opinion was borne out in certain individual test cases.

We were interested in determining the germicidal action of this series of compounds upon a number of representative resistant pathogenic microorganisms belonging to different bacteriological groups. On the basis of the previously observed group parallelism in the susceptibility of different microörganisms to the action of compounds of several homologous series of phenol derivatives,[2] the following test organisms were selected for the bacteriological evaluation of the bromophenol derivatives: the Gram-negative *Eberthella typhi*, the Gram-positive *Staphylococcus pyogenes aureus*, the acid-fast *Mycobacterium tuberculosis* (*hominis*) and the fungus *Monilia albicans*. The method of cultivating the microörganisms and of performing the tests will be described elsewhere.

(1) Klarmann, Shternov and Gates, THIS JOURNAL, **55**, 2576 (1933).

(2) Klarmann, "The Antibacterial Action of Certain Classes of Phenol Derivatives and Its Quasi-specific Character," paper presented before the section of Medicinal Chemistry of the American Chemical Society, Washington, March, 1933.