[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Researches on Pyrimidines. CXLVIII. Action of Chlorine on Mercaptopyrimidines

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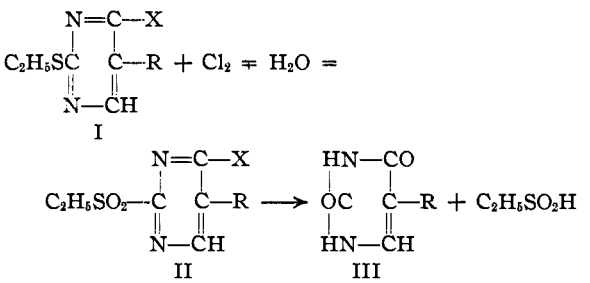
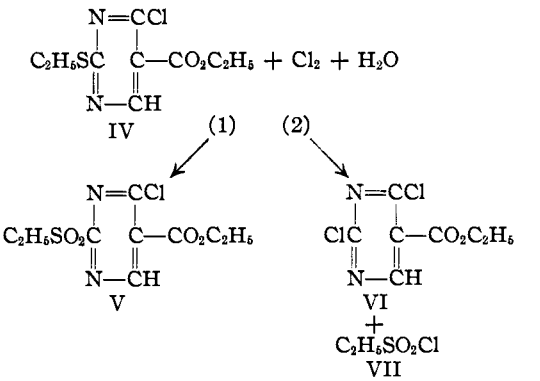
Although considerable work has been done on the application of mercaptopyrimidines to synthesis in the pyrimidine series,[2] no extensive investigation has been made of reactions in this heterocyclic series involving changes in the mercapto group. The chief reactions, in which the mercapto grouping functions, have been its replacement by a hydroxyl group by hydrolysis, and by its substitution with an amino radical by interaction with various amines.[2] Recent developments in the field of "vitamin chemistry" have induced the authors to undertake an exhaustive study of characteristic reactions of the mercapto grouping in different heterocyclic combinations. Because of the postulated existence of a pyrimidine nucleus in the sulfur containing vitamin B_1,[3] a better knowledge of the chemistry of different types of mercapto- and thiopyrimidines becomes very important. A study has been made, therefore, of the behavior of several mercaptopyrimidines toward such reagents as alkalies, sodium alkoxides, nitric acid and chlorine. In this paper the authors will discuss fundamental changes resulting from the action of chlorine upon some ethylmercaptopyrimidines.

When a 2-ethylmercaptopyrimidine (I) is suspended in water and treated with chlorine gas at a low temperature, a pyrimidine sulfone compound is formed (II).



This reaction was applied with success to a series of 2-ethylmercapto-4-ethoxy- (I, X = OC_2H_5), and 2-ethylmercapto-4-chloropyrimidines (I, X = Cl) where R was hydrogen, methyl and bromine. With a slight modification of experimental conditions we also succeeded in synthesizing the 2-ethyl sulfone derivative of 2-ethylmercapto-4-amino-5-carbethoxypyrimidine (I, X = NH_2, R = $CO_2C_2H_5$). The results of our experiments are recorded in Table II. When 2-ethylmercapto-4-chloro-5-carbethoxypyrimidine (IV) is treated with chlorine according to the above technique the pyrimidine VI and ethylsulfonyl chloride (VII) together with the corresponding pyrimidine sulfone (V), were obtained.



The relative amounts of the products of these two reactions depended largely upon the temperature. When the treatment with chlorine gas was carried out below 5°, a 60% yield of the sulfone (V) was obtained. Nevertheless, at this temperature, a 15–20% yield of the product of the second reaction was also obtained. When the chlorination was conducted at a higher temperature, 30–40°, reaction 2 predominated and 2,4-dichloro-5-carbethoxypyrimidine (V) (69–75%), and ethylsulfonyl chloride (VII) (47–75%) were obtained. Under these conditions the yield of the sulfone (V) was reduced to 7%.

That the sulfone (V) is not an intermediate in the formation of compounds (VI) and (VII) through a cleavage by chlorine is shown by its inertness toward chlorine in either water or benzene. This behavior is analogous to that observed in the case of diethyl-sulfone, which remained unaffected while the corresponding diethyl sulfoxide was readily cleaved by chlorine to ethylsulfonyl chloride and ethyl chloride.[4] This suggests that the pyrimidine sulfoxide derivative of the original mercaptopyrimidine is an inter-

(1) Sterling Professorship of Chemistry Research Assistant in Organic Chemistry, 1934–35.

(2) Johnson and Hahn, *Chem. Rev.*, **13**, 193 (1933).

(3) Windaus, *Z. physiol. Chem.*, **228**, 27 (1934); Williams, Buchman and Rueble, THIS JOURNAL, **57**, 1093 (1935).

(4) Spring and Winssinger, *Ber.*, **15**, 447 (1882).

mediate in both reactions 1 and 2.[5] Conditions have not yet been found which will yield pyrimidine sulfones from 2-ethylmercapto-4-oxypyrimidine (I, X = OH) by the action of chlorine.

That an ethylmercapto group occupying the 4-position of the pyrimidine nucleus may also be converted into a sulfone was shown with 2,4-diethylmercaptopyrimidine (I, X = SC_2H_5, R = H). This compound, on treatment with chlorine, gave smoothly the disulfone, 2,4-diethylsulfonylpyrimidine (II, X = $SO_2C_2H_5$, R = H). Although 2,4-diethylmercapto-5-methylpyrimidine (I, X = SC_2H_5, R = CH_3) gave a product insoluble in petroleum ether, it could not be crystallized or distilled. Similar results were obtained with 2-ethylmercapto-4-ethoxy-5-carbethoxypyrimidine.

To establish definitely the point of attack of the chlorine, as well as to establish the structure, our sulfones were subjected to hydrolysis. On refluxing with 20% hydrochloric acid, there were obtained, beside the corresponding dioxypyrimidine, sulfur dioxide and a small amount of ethylsulfonic acid.

Ethylsulfonic acid was found to be stable under the conditions of hydrolysis; this fact, coupled with the production of a 2,4-dioxypyrimidine (III) rather than a monoxypyrimidine, suggests that the immediate product of the hydrolysis was probably ethylsulfinic acid. Although most of this acid decomposed to sulfur dioxide a small amount underwent oxidation to ethylsulfonic acid during the working-up process.

Experimental Part

2 - Ethylmercapto - 4 - chloropyrimidines.—These compounds, 2-ethylmercapto-4-chloropyrimidine,[6] 2-ethylmercapto-4-chloro-5-methyl pyrimidine,[6] 2-ethylmercapto-4-chloro-5-bromopyrimidine,[6] and 2-ethylmercapto-4-chloro-5-carbethoxypyrimidine[7] have all been previously prepared in this Laboratory, but largely by the use of phosphorus pentachloride. For this investigation they were all prepared in the usual manner[8] from the corresponding 4-oxypyrimidine by action of phosphorus oxychloride.

2-Ethylmercapto-4-ethoxypyrimidines.—An alcohol solution of the 2-ethylmercapto-4-chloropyrimidine was added slowly to a well-cooled solution of sodium (10–20% excess) in dry ethanol. The reaction mixture was allowed to stand at room temperature for three or four hours and the reaction completed by heating on a steam-bath for ten minutes. The alcohol was then removed under diminished pressure. Water was added to the residue and the reaction product of 2-ethylmercapto-4-ethoxypyrimidine extracted with ether. After drying over calcium chloride, the ether extract was distilled. The results of the experiment are collected in Table I. 2-Ethylmercaptopyrimidine had been prepared previously by a different procedure.[9]

In the preparation of 2-ethylmercapto-4-ethoxy-5-carbethoxypyrimidine (I, X = OC_2H_5, R = $CO_2C_2H_5$) it was necessary to modify the above procedure since in alcohol solution there was a loss of ethylmercaptan. The corresponding 4-chloropyrimidine in boiling benzene was treated with an equivalent amount of sodium ethoxide prepared in benzene from powdered sodium and the calculated amount of dry ethanol. The rate of addition of the sodium ethoxide was adjusted so that the reaction mixture was never alkaline to moist litmus. After heating for an additional fifteen minutes, the reaction was worked up as described below for the diethylmercaptopyrimidines.

2,4-Diethylmercaptopyrimidine.—A solution of 2,4-dichloropyrimidine[10] in toluene was added to a suspension of sodium ethylmercaptide (10% excess) which had been prepared in toluene from powdered sodium and ethyl mercaptan. After heating on a steam-bath for four hours, water was added and the toluene layer was dried and distilled. 2,4-Diethylmercapto-5-methylpyrimidine was prepared by the same procedure from 2-ethylmercapto-4-chloro-5-methylpyrimidine and sodium ethylmercaptide (Table I).

Ethylsulfonylpyrimidines. General Procedure.—The liquid 2-ethylmercaptopyrimidine (1–5 cc.) was suspended in water (20–75 cc.) and chlorine gas vigorously passed into the mixture which was well cooled in ice. Heat was evolved but the temperature did not rise above 20°. Most of the mercaptopyrimidine went into solution which immediately became turbid and a heavy oil precipitated. This gradually solidified and the treatment with chlorine was continued until the reaction mixture had a distinct green color of excess chlorine. The solid sulfone was filtered off, and, after drying over phosphorus pentoxide, recrystallized from a mixture of benzene and petroleum ether. These sulfones were readily soluble in the common organic solvents except petroleum ether in which they were practically insoluble. The purified sulfones may be kept over phosphorus pentoxide for several months without decomposition. However, in moist air they decompose rapidly.

Occasionally difficulty was experienced in obtaining the sulfones as solids on the first preparation. Usually this was due to incomplete chlorination or insufficient cooling during the reaction. However, the solid sulfone was obtained when an ether extract, which had been washed with sodium thiosulfate and dried over calcium chloride, was evaporated. If the residue from the ether extract did not solidify, it was triturated with petroleum ether. Subsequent preparations of the sulfone were obtained as solids directly from the reaction by seeding with a solid sulfone.

2-Ethylsulfonyl-4-ethoxypyrimidine (II, X = OC_2H_5, R = H) was a liquid which, when pure, distilled without decomposition.

(5) The mechanism of these transformations is being investigated and the results will be discussed in a future paper.

(6) Wheeler and Johnson, *Am. Chem. J.*, **31**, 596 (1904).

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

(8) Wheeler and Johns, *Am. Chem. J.*, **38**, 597 (1907).

(9) Wheeler and Johnson, *ibid.*, **31**, 597 (1904).

(10) Hilbert and Johnson, THIS JOURNAL, **52**, 1152 (1930).

TABLE I

MERCAPTO-PYRIMIDINES

2-Mercapto-pyrimidines	B. p., °C.	Mm.	n_D/°C.	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
4-Ethoxy-5-carbethoxy-	175	8	1.5420 (24.5°)	90	$C_{11}H_{16}O_3N_2S$	10.93	10.86	12.51	12.49
4-Ethoxy-	123–124	11	1.5405 (24.5°)	88	$C_8H_{12}ON_2S$	15.20	15.14	17.41	17.52
4-Ethoxy 5-methyl-	135–136	12	1.5365 (24°)	90	$C_9H_{14}ON_2S$	14.13	14.00	16.17	16.23
4-Ethoxy-5-bromo-[a]	140	6	1.5787 (22.5°)	82	$C_8H_{11}ON_2SBr$	10.64	10.62	12.19	12.02
4-Ethylmercapto-	135–137	6	1.5974 (24°)	92	$C_8H_{12}N_2S_2$	13.98	14.05	32.02	32.14
4-Ethylmercapto-5-methyl-	158–161	11	1.5900 (23°)	80	$C_9H_{14}N_2S$	13.07	13.12	29.93	29.98

[a] Analysis for bromine (Br), calcd., 30.38; found, Br, 30.71.

TABLE II

PYRIMIDINE SULFONES

2-Ethylsulfonyl-pyrimidines	M. p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found	Halogen, % Calcd.	Halogen, % Found
4-Ethoxy-5-methyl-[a]	67–68	80	$C_9H_{14}O_3N_2S$	12.16	12.12	13.94	14.13	...	...
4-Chloro-5-methyl-	67.5–68	80	$C_7H_9O_2N_2SCl$	12.70	12.74	14.54	14.71	16.08	16.24
4-Ethoxy-5-bromo-	89.5–90.5	77	$C_8H_{11}O_3N_2SBr$	9.48	9.43	10.86	11.10	27.08	26.68
4-Chloro-5-bromo-	81–82	97	$C_6H_6O_2N_2SClBr$	9.81	9.78	11.25	11.57	[b]	
4-Ethoxy-	Liquid[c]	50	$C_8H_{12}O_3N_2S$	12.95	12.96	14.83	15.15	...	...
4-Chloro-	57–58	84	$C_6H_7O_2N_2SCl$	13.56	13.58	15.53	15.76	17.18	17.48
4-Chloro-5-carbethoxy-	72.5–73.5	60	$C_9H_{11}O_4N_2SCl$	10.05	9.98	11.58	11.70	12.71	12.36
4-Ethylsulfonyl-4-Amino-5-carbethoxy-	87–88	63	$C_8H_{12}O_4N_2S_2$	10.60	10.62	24.27	24.35	...	...
	143.5–144.5	93	$C_9H_{13}O_4N_3S$	16.20	16.23	12.37	12.59	...	...

[a] Calcd.: C, 46.92; H, 6.27. Found: C, 47.08; H, 6.18. [b] 0.2424 and 0.2106 g. gave 0.2850 and 0.2455 g. of silver halide, respectively; calcd., 0.2818 and 0.2443 g. [c] B. p. 183–185° (4 mm.), $n^{25}D$ 1.5225.

2 - Ethylsulfonyl - 4 - chloro - 5 - carbethoxypyrimidine.—To obtain this sulfone (II, X = Cl, R = $CO_2C_2H_5$) in practical yields it was necessary to carry out the chlorination in an ice–salt bath (−10°). The temperature of the reaction was not allowed to rise above 5°. Even at this temperature 15–20% of the cleavage product (reaction 2) was obtained by extracting the reaction mixture with petroleum ether (see below). This sulfone is very unstable and decomposes rapidly even over phosphorus pentoxide, giving a product insoluble in benzene.

The cleavage reaction of 2-ethylmercapto-4-chloro-5-carbethoxypyrimidine was carried out as follows. Five cubic centimeters (6.3 g.) of 2-ethylmercapto-4-chloro-5-carbethoxypyrimidine was suspended in 60 cc. of warm water (30–40°) and chlorine rapidly passed into the mixture. The temperature was kept within the above limits by cooling in water. When the oil had separated completely, the mixture was shaken with petroleum ether and the sulfone derivative which separated as a solid at the water–petroleum ether interface was removed by filtration (0.5 g., 7%). After washing with dilute sodium thiosulfate and drying over calcium chloride the petroleum ether extract was fractionated with the following results: fraction 1, b. p. 68–74° (18 mm.) 1.5–2.5 g. (47–75%); fraction 2, b. p. 118–120° (4 mm.) 3.9–4.2 g. (69–75%).

Fraction 1.—This was redistilled, b. p. 67–68° (17 mm.), $n^{21.5}D$ 1.4520 and identified as ethylsulfonyl chloride (VII) by formation of ethylsulfonamide[11] (m. p. 59–60°), ammonium ethylsulfonate[12] (m. p. 208–209°), and aniline hydrochloride.

Fraction 2.—This solidified on cooling and was recrystallized from ether, m. p. 36–37°, and was identified as 2,4-dichloro-5-carbethoxypyrimidine (VI) by analysis and hydrolysis with hydrochloric acid to uracil-5-carboxylic acid.[13]

Anal. Calcd. for $C_7H_6O_2N_2Cl$: N, 12.67; Cl, 32.09. Found: N, 12.63; Cl, 31.88.

2 - Ethylsulfonyl - 4 - amino - 5 - carbethoxypyrimidine (II, X = NH_2; R = $CO_2C_2H_5$).—Five grams of 2-ethylmercapto-4-amino-5-carbethoxypyrimidine (m. p. 102°) was suspended in 60 cc. of water and concentrated hydrochloric acid (8 cc.) added. A small amount of solid remained undissolved but went into solution when treated with chlorine. The chlorination was carried out in an ice-bath. The yield was 5.3 g.

Hydrolysis of Pyrimidine Sulfones.—The sulfones (1–2 g.) were refluxed with 20% hydrochloric acid and the evolved gases swept into solutions of potassium permanganate, bromine water, or iodine–potassium iodide solution. The test solutions were decolorized and gave tests for sulfate. The acid solution was then evaporated to dryness on a steam-bath. The residue was triturated with alcohol and the filtered solid identified as a dioxypyrimidine by analysis and by comparison with authentic

(11) James, *J. prakt. Chem.*, [2] **28**, 384 (1882).

(12) This was compared with the ammonium ethylsulfonate prepared from ethylsulfonic acid, m. p. 208–209° from alcohol–ethyl acetate mixture. N, calcd., 11.04; found, 11.10.

(13) Wheeler, Johnson and Johns, *Am. Chem. J.*, **37**, 392 (1907).

preparations. The alcohol filtrate was evaporated and the residue was freed of solid by triturating with alcohol or water, filtering and evaporating to dryness. This was repeated several times and the residual sirup treated with concentrated ammonium hydroxide. The solid obtained on evaporation was then recrystallized from an alcohol-ethyl acetate mixture and identified as the ammonium salt[12] of ethylsulfonic acid.

The sulfone (2 g.), 2-ethylsulfonyl-4-ethoxy-5-methylpyrimidine (II, X = OC_2H_5, R = CH_3), on refluxing for several hours with 2.5% sodium hydroxide in 90% alcohol gave 2,4-diethoxy-5-methylpyrimidine.[14] The diethoxypyrimidine (0.9 g.) was extracted with petroleum ether after removal of the alcohol under diminished pressure.

(14) Johnson and Schmidt-Nickels, THIS JOURNAL, **52**, 4514 (1930).

Summary

The action of chlorine gas on ethylmercaptopyrimidines has led to the preparation of nine ethylsulfones in the pyrimidine series.

It has been shown that this method is applicable to ethoxy-, chloro-, amino- and carbethoxyethylmercaptopyrimidines.

On acid hydrolysis the pyrimidine sulfones yield the corresponding oxypyrimidines.

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Acetylene Polymers and their Derivatives. XXIII. The Preparation and Polymerization of Oxyprenes

BY HARRY B. DYKSTRA

Recent studies[1] have revealed that of the various derivatives of butadiene-1,3 which are known, those having a single substituent in the 2-position have outstanding properties from the standpoint of rubber synthesis. The term orthoprene has been suggested for compounds of this type.[2] Only a few orthoprenes are known. Prior to the discovery of the haloprenes, chloro-2-butadiene-1,3[3] and bromo-2-butadiene-1,3,[4] isoprene and ethylbutadiene were the only members of this class which had been described. To this list have recently been added the butyl, *t*-butyl, hexyl, phenyl and benzyl butadienes,[5] and the formoxy, acetoxy, chloroacetoxy and butyroxy butadienes.[6]

The interesting properties of the orthoprenes, particularly those containing a negative substituent, have prompted the preparation and examination of other members of this class. The present paper is concerned with orthoprenes in which the substituent is an ether group. The designation "oxyprene" is suggested for these compounds. They are obtained by the series of reactions illustrated below for ethoxyprene (V).

$$\underset{\text{I}}{CH_2{=}CHC{\equiv}CH} + H_2O \longrightarrow \underset{\text{II}}{CH_2{=}CHCOCH_3}$$

$$\text{II} + C_2H_5OH \longrightarrow \underset{\text{III}}{C_2H_5OCH_2CH_2COCH_3}$$

$$\text{III} + HC(OC_2H_5)_3 \longrightarrow \underset{\text{IV}}{C_2H_5OCH_2CH_2C(OC_2H_5)_2CH_3} + HCOOC_2H_5$$

$$\text{IV} \longrightarrow \underset{\text{V}}{CH_2{=}CHC(OC_2H_5){=}CH_2} + 2C_2H_5OH$$

The hydration of vinylacetylene to methyl vinyl ketone[7] and the addition of alcohols to methyl vinyl ketone[8] are recorded elsewhere and will not be described in detail. The conversion of the ether ketones (III) into the ether ketals (IV) by means of orthoformic esters takes place almost quantitatively at room temperature in the presence of alcohol and hydrogen chloride. Physical and analytical data for the ether ketals are given in Table IA.

At sufficiently high temperatures, generally above 130°, the decomposition of the ketal (IV) to the oxyprene (V) is fairly complete, but at lower temperatures intermediate compounds involving the elimination of only one molecule of alcohol are formed. These are the unsaturated ketals (VI) formed when acidic catalysts are used, and the unsaturated ethers (VII) formed with basic catalysts. By further heating, these compounds, particularly VI, are in turn converted to the oxyprenes. Physical and analytical data for the intermediates VI and VII are given in

(1) Whitby and Gallay, *Can. J. Research*, **6**, 280 (1932); Carothers, *Ind. Eng. Chem.*, **26**, 30 (1934).

(2) Carothers and Berchet, THIS JOURNAL, **55**, 2813 (1933).

(3) Carothers, Williams, Collins and Kirby, *ibid.*, **53**, 4203 (1931).

(4) Carothers, Collins and Kirby, *ibid.*, **55**, 786 (1933).

(5) Carothers and Berchet, *ibid.*, **55**, 2813 (1933); Backer and Strating, *Rec. trav. chim.*, **53**, 524 (1934).

(6) Werntz, THIS JOURNAL, **57**, 204 (1935).

(7) Nieuwland, Calcott, Downing and Carter, *ibid.*, **53**, 4197 (1931); Carter, U. S. Patent 1,896,161 (1933); Conaway, U. S. Patent 1,967,225 (1934).

(8) Rothrock, U. S. Patent 2,010,828 (1935).