[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

The Direct Thiation of Uracils

BY GERTRUDE B. ELION AND GEORGE H. HITCHINGS

Several dimercapto pyrimidines have been prepared by the chlorination of dihydroxypyrimidines and subsequent replacement of the chlorine atoms by mercapto groups through the action of alkali hydrosulfides.[1,2] The present report describes a method which allows the replacement of an hydroxyl or an alkylmercapto group by sulfhydryl in one step, through the action of phosphorus pentasulfide in an inert solvent. This method can be applied to a considerable variety of substituted pyrimidines but has some limitations which will be indicated.

The direct conversion of amides into thioamides is well known (*e. g.*, Kindler[3]). Henze and Smith[4] were able to substitute sulfur for oxygen in 5,5-disubstituted hydantoins and 5,5-disubstituted barbituric acids by heating with phosphorus trisulfide in an inert solvent. Carrington,[5] using phosphorus pentasulfide and "liver of sulfur," was able to thiate certain barbituric acid derivatives in stepwise fashion. The extent of the reaction was found to depend on the substituents in the 5-position.

Results

The method consists in heating the pyrimidine, suspended in an inert solvent such as tetralin, with an excess (commonly about 3 parts by weight) of phosphorus pentasulfide. The temperature and time of heating are varied somewhat depending on the nature of the compound to be thiated.

TABLE I

Expt.	Starting material	Temp., °C.	Time of reaction in hr.	Product	Yield, %	M. p., °C.
1	Uracil	160–180	1.5	2,4-Dithiouracil[1]	54[a]	235 dec.
2	2-Thiouracil	160–170	1.5	2,4-Dithiouracil	65	235 dec.
3	2-Thiothymine	185	2	2,4-Dithiothymine[2]	55	281
4	2-Ethylmercapto-4-hydroxy-5-methylpyrimidine	140–150	2	2,4-Dithiothymine	75[a]	281
5	6-Phenyl-2-thiouracil	170–180	1.5	6-Phenyl-2,4-dithiouracil	73	264–268 dec.
6	2-Mercapto-4-hydroxyquinazoline	170–180	0.5	2,4-Dimercaptoquinazoline[10]	85[a]	308–309 dec.
7	1,3-Dimethyluracil	120	3.5	1,3-Dimethyl-4-thiouracil	65[a]	132–133

[a] Crude product.

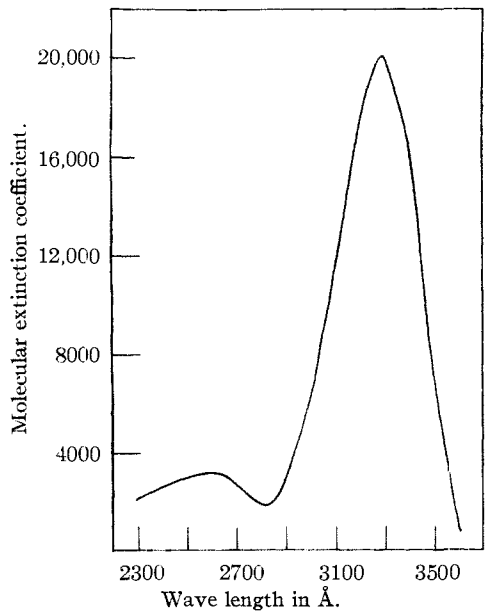

Fig. 1.—Ultraviolet absorption spectrum of 1,3-dimethyl-4-thiouracil at *p*H 1.0.

The data for 7 thiations are given in Table I. It will be observed that hydroxyl (Expt. 1) and ethylmercapto groups (Expt. 4) are replaced with approximately equal facility. The presence of alkyl (Expt. 3) or aryl (Expt. 5) substituents in the 4 or 5 positions has little effect; moreover, the condensed pyrimidine system 2-mercapto-4-hydroxyquinazoline behaved much like a substituted uracil. In general, however, the procedure works best with alkyl or aryl uracils or thiouracils. Barbituric acid and isobarbituric acid could not be thiated successfully nor could 5-nitrouracil or isocytosine.

The direct thiation of 1,3-dimethyluracil to give a dimethylmonothiouracil (Expt. 7) is of particular interest. The ultraviolet absorption spectrum of the product is given in Fig. 1. The marked resemblance of this spectrum to that of 4-thiouracil, and the considerable difference between the spectra of 2-thiouracil and 4-thiouracil[6] allow one provisionally to assign this compound the structure of 1,3-dimethyl-2-oxo-4-thiotetrahydropyrimidine. An attempt to prepare the 2-thio-4-oxo derivative by the condensation of 1,3-dimethylthiourea with formylacetic ester was unsuccessful when ring closure failed to take place. Since substituted ureas, in general, do not condense with β-ketonic

(1) Wheeler and Liddle, *Am. Chem. J.*, **40**, 547, 557 (1908).
(2) Wheeler and McFarland, *ibid.*, **43**, 19 (1910).
(3) Kindler, *Ann.*, **431**, 187 (1923).
(4) Henze and Smith, THIS JOURNAL, **65**, 1090 1943).
(5) Carrington, *J. Chem. Soc.*, 124 (1944).
(6) Elion, Ide and Hitchings, THIS JOURNAL **68**, 2137 (1946).

esters to form pyrimidines,[7] the synthesis of either isomer of dimethylthiouracil by systematic means does not appear likely.

Discussion

The direct replacement of an oxygen atom of 1,3-dimethyluracil by sulfur has several interesting implications. The product of this reaction is not attainable by any other known synthetic method. Furthermore, the ultraviolet absorption spectrum of this compound has a bearing on the general problem of the relationship between absorption spectra and tautomerism in the pyrimidine series. If, as seems probable, the sulfur has been assigned correctly to the 4 position, the marked resemblance of the spectrum of this compound to that of 4-thiouracil would seem to imply that the sulfur in the 4 position of the latter also exists primarily in the double bound form, rather than in the sulfhydryl form.

In this experiment the direct substitution of doubly bound sulfur for oxygen must have occurred. The greater reactivity of the oxygen in the 4 position here is to be contrasted with the more ready substitution of the oxygen in the 2 position of the dialkylbarbiturates.[5] The tautomerism of the latter group of compounds conceivably might have some bearing on the order in which the oxygen atoms are replaced.

Experimental

6-Phenyl-2,4-dithiouracil.—Three and one-half grams of 6-phenyl-2-thiouracil[8] was treated with phosphorus pentasulfide as indicated in Table I. The product was isolated by extraction with hot ethanol and was recrystallized from *n*-propyl alcohol, giving 2.75 g. (73%) of yellow needles, m. p. 264–268° (dec.): soluble in *ca.* 350 parts of hot ethanol, insoluble in cold ethanol, hot and cold water, ether and benzene.

Anal. Calcd. for $C_{10}H_8ON_2S$: C, 54.5; H, 3.64; S, 29.1. Found: C, 54.8; H, 3.55; S, 28.6.

1,3-Dimethyl-4-thiouracil.—A mixture of 3 g. of 1,3-dimethyluracil[9] and 9 g. of phosphorus pentasulfide was refluxed in 25 ml. of xylene and 35 ml. of toluene (120°) for three and one-half hours. The product was found in both solvent and residue. After recrystallization from 50 parts of hot water the product weighed 2.15 g. (64.5%). The yellow needles, m. p. 132–133°, were soluble in ether, xylene, toluene and hot water and somewhat soluble in cold water.

Anal. Calcd. for $C_6H_8ON_2S$: C, 46.7; H, 4.65; S, 20.5. Found: C, 46.6; H, 4.72; S, 21.1.

2,4-Dimercaptoquinazoline.—The residue from the phosphorus pentasulfide treatment was purified by solution in 0.4 *N* sodium hydroxide and precipitation with acetic acid. The yield was 85% of material decomposing 275–295°. Soxhlet extraction with absolute alcohol yielded yellow needles, m. p. 308–309° (dec.). Kötz[10] reports a decomposition point of 260°.

Anal. Calcd. for $C_8H_6N_2S_2$: C, 49.4; H, 3.09; S, 33.0. Found: C, 49.3; H, 2.59; S, 33.6.

Summary

In a variety of 2,4-substituted pyrimidines, oxygen or alkylmercapto groups can be replaced by sulfur by treatment of the compound with phosphorus pentasulfide at elevated temperatures. The formation of a monothiodimethyluracil from 1,3-dimethyluracil indicates that the reaction can proceed through replacement of a doubly bound oxygen atom by a sulfur atom.

(7) Johnson and Heyl, *Am. Chem. J.*, **37**, 628 (1907).

(8) Warmington, *J. prakt. Chem.*, [2] **47**, 208 (1893).

(9) Davidson and Baudisch, THIS JOURNAL, **48**, 2379 (1926).

(10) Kötz, *J. prakt. Chem.*, [2] **47**, 303 (1893).

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The Acid Catalyzed Isomerization of α-Pinene[1]

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It has been known for many years that α-pinene is readily converted into monocyclic terpenes and terpene alcohols when treated with dilute mineral acids.[3] The technical process for the production of synthetic pine oil practiced in this country and in Europe is based on this reaction. On the other hand, the course of this reaction has not been adequately explained; in fact, the literature does not offer any definite explanation, although general usage suggests the rupture of the cyclobutane ring by the direct addition of water.[4] However, the reaction takes place readily in the absence of water, although no alcohols are formed in this case. Heat alone gives dipentene, presumably other monocyclic hydrocarbons, the acyclic terpene *allo*-ocimene, and the pyronenes resulting from cyclization of the *allo*-ocimene.[5] Anhydrous organic acids also give monocyclic terpenes and the esters of the acids used.[6] Anhydrous hydrogen chloride as employed in the old camphor process gives considerable by-product monocyclic terpenes in addition to "pinene hydrochloride."[7] Active earths such as vermiculite give camphene as the principal product but also the monocyclic

(1) Presented in part before the Division of Organic Chemistry, American Chemical Society, Atlantic City, New Jersey, April, 1946.

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(3) Armstrong and Tilden, *Ber.*, **12**, 1752 (1879); Wallach, *Ann.*, **239**, 34 (1885).

(4) Wagner and Ginsberg, *Ber.*, **27**, 1644, 2270 (1894); **29**, 1195 (1896).

(5) (a) Berthelot, *Ann. chim.*, (iii) **37**, 223 (1853); **39**, 9 (1854); (b) Wallach, *Ann.*, **227**, 282 (1885); (c) Conant and Carlson, THIS JOURNAL, **51**, 3466 (1927); (d) Goldblatt and Palkin, *ibid.*, **66**, 655 (1944); (e) Fuguitt and Hawkins, *ibid.*, **67**, 224 (1945); (f) Savich and Goldblatt, *ibid.*, **67**, 2027 (1945).

(6) Reisman, *Bull. soc. chim.*, (iv) **41**, 94 (1927).

(7) *Cf.* Meerwein, *Ber.*, **53**, 1825 (1920).