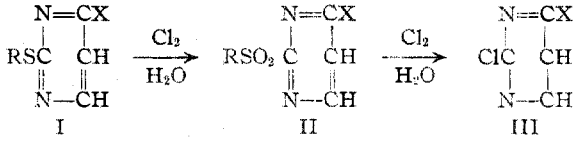
[CONTRIBUTIONS FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Researches on Pyrimidines. CLVIII. The Oxidation of Mercaptopyrimidines with Chlorine Water

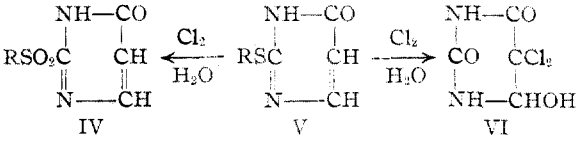
BY TREAT B. JOHNSON AND JAMES M. SPRAGUE[1]

In a recent publication from this Laboratory by the authors[2] it was shown that chlorine gas and certain 2-mercaptopyrimidines interact smoothly in aqueous solution at low temperature with production of the corresponding 2-alkylsulfonyl derivatives. This reaction is applicable to 2-mercaptopyrimidines conforming in constitution to Formula I. By raising the reaction temperature, however, the chlorination process proceeds further with replacement of the sulfonyl grouping of the pyrimidine II by chlorine. These changes are expressed by Formulas I, II and III.



(X = halogen, OCH_3 or OC_2H_5, SC_2H_5 and NH_2).

During study of this chlorination reaction in 1935 we experimented also with several 2-mercapto-4-oxypyrimidine compounds but were unable to prepare the 2-alkylsulfonyl pyrimidines corresponding to Formula IV. The products of reaction were always sulfur free and they were identified as 2,4-diketohexahydropyrimidines as is represented by Formula VI.



In other words, the chlorination reaction in aqueous solution proved to be specific, and serves to differentiate between 2-mercaptopyrimidines represented by structures expressed in Formulas I and V, respectively. In pyrimidines of type I the unsaturation of the pyrimidine cycle is not changed by chlorination, and the mercapto grouping is oxidized, giving a stable sulfonyl pyrimidine II. In the case of pyrimidines of type V the chlorination process is more complicated. Here we are dealing with three different reaction changes: (1) oxidation of the 2-mercapto grouping, (2) saturation of the double bond in positions 5 and 6 of the pyrimidine cycle and (3) hydrolysis in position-2 with formation of an alkyl sulfonic acid and a 2,4-diketohexahydropyrimidine derivative.

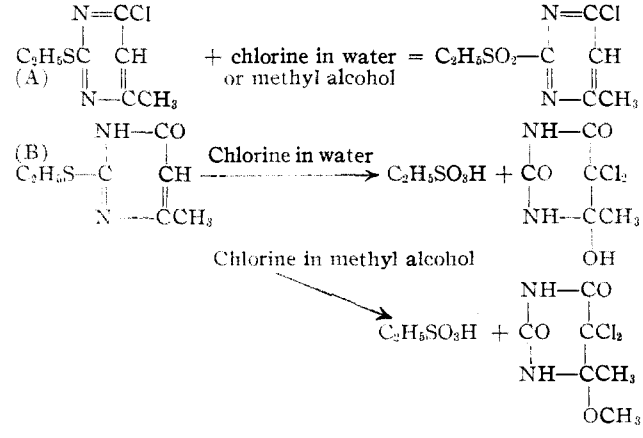
This specificity of reaction is also exhibited by chlorination of mercaptopyrimidines in alcohol solutions. The mercaptopyrimidines of type V behave as the corresponding 2,4-diketotetrahydropyrimidines, giving the same products, the 2,4-diketohexahydropyrimidines.[3] This characteristic difference in chemical behavior is illustrated in the equations expressed under sections A and B below.

Several mercaptopyrimidines of type V have been utilized in different research programs in progress in this Laboratory, and in every case thus far examined the respective mercaptopyrimidine has undergone the characteristic transformations expressed under section B. These 2,4-diketohexahydropyrimidines are converted quantitatively into 2,4-diketotetrahydropyrimidine derivatives by digestion with reducing agents.

Experimental Part

I. The Oxidation of the Mercaptopyrimidines to their Corresponding Sulfonyl Derivatives

$C_2H_5SO_2C{=}NCH{=}C(CH_3)C(NHCl){=}N$, 2-Ethylsulfonyl-4-chloroamino-5-methylpyrimidine.—Two grams of



2-ethylmercapto-4-amino-5-methylpyrimidine[4] was dissolved in 3 cc. of cold methyl alcohol and the solution acidified with 1 cc. of concentrated hydrochloric acid.

(1) Sterling Professorship of Chemistry Research Assistant 1936–1937.

(2) Sprague and Johnson, THIS JOURNAL, **57**, 2252 (1935).

(3) Johnson and Sprague, *ibid.*, **59**, 2436 (1937).

(4) Wheeler and Johnson, *Am. Chem. J.*, **31**, 597 (1904).

After diluting to 20 cc. with ice water chlorine gas was then bubbled slowly into the cold solution until the precipitation of a crystalline solid was complete. This reaction product (2 g.) was dried over phosphorus pentoxide and purified by crystallization from ethyl acetate. It melted at 125–126° and responded to qualitative tests for sulfur and chlorine.

Anal. Calcd. for $C_7H_{10}O_2N_3SCl$: N, 17.83; S, 13.61; Cl, 15.15. Found: N, 17.88; S, 13.77; Cl, 15.25; (active Cl, 15.05).

$C_2H_5SO_2\overline{C=NCH=C(CH_3)C(NH_2)=N}$, **Formation of 2-Ethylsulfonyl-4-amino-5-methylpyrimidine.**—The above chloroaminopyrimidine was suspended in dilute sodium bisulfite solution and the mixture agitated vigorously for several minutes. The insoluble material was then filtered off, dried in vacuum and purified by crystallization from ethyl acetate. It melted at 136–137° and proved to be identical with the pyrimidine obtained by the action of ammonia on 2-ethylsulfonyl-5-chloro-5-methylpyrimidine.[5]

Anal. Calcd. for $C_7H_{11}O_2N_3S$: N, 20.88; S, 15.94. Found: N, 21.03; S, 16.06.

On exposure of this pyrimidine to the action of chlorine in dilute hydrochloric acid the chloroamino compound (above) was formed and melted at 125–126°.

$C_2H_5SO_2\overline{C=NC(CH_3)=CHC(Cl)=N}$, **2-Ethylsulfonyl-4-chloro-6-methylpyrimidine.**—This was prepared by suspending 10 g. of 2-ethylmercapto-4-chloro-6-methylpyrimidine[6] in 75 cc. of ice water and then saturating the cold solution with chlorine gas. This pyrimidine chloride separated as an oil. After extraction with ether and drying over calcium chloride the oil was purified by distillation. It boiled at 189–191° at 3.5 mm.; $n^{25}D$ 1.5422.

Anal. Calcd. for $C_7H_9O_2N_2Cl$: N, 12.70. Found: N, 12.60.

$NH_2C=N-\overline{C(CH_3)=CHC(Cl)=N}$, **Formation of 2-Amino-4-chloro-6-methylpyrimidine.**[7]—This is formed smoothly by interaction of 2-ethylsulfonyl-4-chloro-6-methylpyrimidine with cold saturated alcoholic ammonia solution. It is also formed by heating the chloropyrimidine with strong aqueous ammonia at 100° for one hour. The yield is 80% of the theoretical. After purification by crystallization from hot alcohol it melted at 182–183°.

Anal. Calcd. for $C_5H_6N_3Cl$: N, 29.27; Cl, 24.74. Found: N, 29.40; Cl, 24.65.

$C_2H_5SO_2\overline{C=NC(CH_3)=CHC(NHCl)=N}$, **2-Ethylsulfonyl-4-chloroamino-6-methylpyrimidine.**—Four grams of 2-ethylmercapto-4-amino-6-methylpyrimidine was dissolved in 5 cc. of dilute hydrochloric acid and the solution diluted with 35 cc. of ice water. The above pyrimidine was formed on saturating the cold aqueous solution with chlorine gas. The pyrimidine crystallizes from benzene and melts at 133–134°. Analysis of the compound after drying *in vacuo* at 100°: Calcd. for $C_7H_{10}O_2N_3SCl$: N, 17.83. Found: N, 17.86.

(5) Sprague and Johnson, THIS JOURNAL, **58**, 426 (1936).
(6) Johns, *Am. Chem. J.*, **40**, 350 (1908).
(7) Gabriel and Colman, *Ber.*, **32**, 2922 (1899).

II. The Conversion of 2-Mercapto-4-oxypyrimidines into 2,4-Diketohexahydropyrimidines

$\overline{CONHCH(OCH_3)C(CH_3)ClCONH}$, **2,4-Diketohexahydro-5-methyl-5-chloro-6-methoxypyrimidine.**—Four grams of 2-ethylmercapto-4-oxy-5-methylpyrimidine[8] was dissolved in 50 cc. of methyl alcohol and the ice-cooled solution saturated with chlorine gas. The excess of alcohol was then removed below a temperature of 30° under diminished pressure. During this operation there was a distinct odor and lachrymator effect of ethyl sulfonyl chloride. The crystalline reaction product which separated (3 g.) was washed with cold water and petroleum ether, and then purified by crystallization from boiling water. The compound obtained was free from sulfur and crystallized from water in the form of needles melting at 220–221°.

Anal. Calcd. for $C_6H_9O_3N_2Cl$: N, 14.54; Cl, 18.42; methoxyl (OCH_3), 16.12. Found: N, 14.43; Cl, 18.60; methoxyl (OCH_3), 16.14.

This pyrimidine is very soluble in acetone, ethyl acetate, ethyl alcohol, ether and hot water. It is also soluble in dilute alkali solution from which it is precipitated by neutralization of the alkali with acids. On digesting the hexahydropyrimidine with hydriodic acid,[9] it is converted quantitatively into "thymine."

$\overline{CONHC(CH_3)(OCH_3)CClCONH}$, **2,4-Diketotetrahydro-5,5-dichloro-6-methyl-6-methoxypyrimidine.**—Four grams of 2-ethylmercapto-4-oxy-6-methylpyrimidine[10] was chlorinated according to the experimental technique described in the preceding experiment. Five grams of the hexahydropyrimidine was obtained. This was purified by crystallization from methyl alcohol and melted at 274–275°, with effervescence. The compound failed to give a test for sulfur.

Anal. Calcd. for $C_6H_8O_3N_2Cl_2$: N, 12.33, methoxyl (OCH_3), 13.67. Found: N, 12.33; methoxyl (OCH_3), 13.60.

On digesting this pyrimidine with tin and hydrochloric acid,[11] it is converted quantitatively into 5-chloro-6-methyluracil, $CONHC(CH_3)=CClCONH$. This crystallized from hot water in the form of needles.

Anal. Calcd. for $C_5H_5O_2N_2Cl$: N, 17.45. Found: N, 17.40.

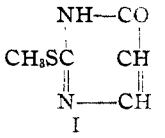
$\overline{CONHCH(OCH_3)CCl_2CONH}$, **2,4-Diketotetrahydro-5,5-dichloro-6-methoxypyrimidine.**—This is formed quantitatively by chlorination in methyl alcohol solution of 2-ethyl or 2-methylmercapto-6-oxypyrimidine.[12] The pyrimidine melts at 225–226°[3] and is converted into 5-chlorouracil by digestion with tin and hydrochloric acid.

Summary

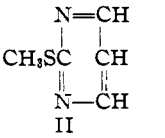
1. 2-Mercaptopyrimidines of types I and II, respectively, can be differentiated by their char-

(8) Wheeler and Merriam, *Am. Chem. J.*, **29**, 487 (1903); Wheeler and Johnson, *ibid.*, **31**, 595 (1904).
(9) Baudisch and Davidson, *J. Biol. Chem.*, **64**, 234 (1925).
(10) List, *Ann.*, **236**, 12 (1886); Wheeler and Merriam, *Am. Chem. J.*, **29**, 478 (1903).
(11) Johnson, *ibid.*, **40**, 27 (1908).
(12) Wheeler and Johnson, *Am. Chem. J.*, **29**, 483 (1903).

acteristic behavior toward chlorine gas in water and alcohol solutions.



I



II

2. Pyrimidines of type I are desulfurized completely with formation of 2,4-diketohexahydropyrimidine compounds.

3. Pyrimidines of type II are oxidized to the corresponding 2-alkyl sulfonyl pyrimidine compounds. The double bond in positions 5 and 6 of the pyrimidine cycle is not altered.

NEW HAVEN, CONN RECEIVED APRIL 4, 1938

[CONTRIBUTION FROM THE FLEISCHMANN LABORATORIES, STANDARD BRANDS INCORPORATED]

The Volatile Constituents of Roasted Coffee

BY WILLIAM R. JOHNSTON AND CHARLES N. FREY

Our interest in the staling of roasted coffee led us to attempt to isolate and identify some of the aroma and flavor constituents. It is evident that any effort to prevent or retard the staling of roasted coffee can be undertaken with better prospects of success if the identity and nature of the substances responsible for its flavor and aroma can be more completely ascertained.

When we started our investigation the best information on the subject was contained in the patents issued to Staudinger and Reichstein.[1] They outlined a method of isolating coffee volatiles by vacuum distillation and listed a number of compounds supposedly present in roasted coffee. Some of the compounds reported were: hydrogen sulfide, methyl mercaptan, furfuryl mercaptan, dimethyl sulfide, acetaldehyde, furfuraldehyde, diacetyl, acetyl-propionyl, furfuryl alcohol, acetic acid, guaiacol, vinyl guaiacol, pyridine, pyrazine and N-methylpyrrole. However, in British Patent 260,960, the statement is made that the compounds reported were not actually found in coffee but were split products obtained by analysis—the real products being unstable and difficult to isolate. This statement is somewhat confusing since some of the substances mentioned have been reported previously by earlier investigators as being present in coffee. For example, pyridine, furfuraldehyde, furfuryl alcohol and acetic acid actually have been isolated from roasted coffee. The older literature on this subject has been surveyed critically by Prescott and his co-workers.[2] With this contradiction in mind, we decided to use the work of Staudinger and Reichstein as a guide and attempt to isolate the volatile coffee components as nearly unchanged as possible. Their procedure includes distillation at 2–5 mm. pressure at 100–110° and the use of steam or liquid water to assist in removal of volatile substances from roasted coffee. We believed that this treatment was not ideal because previous work on staling had convinced us that very small amounts of oxygen were sufficient to cause appreciable deterioration of the coffee and in addition that moisture had a distinct accelerating effect on this deterioration. Consequently, we decided to utilize a high vacuum apparatus and to avoid the use of water during the distillation. By distilling at low pressures and working in the practical absence of oxygen we have been able to isolate as actual constituents of coffee several of the substances reported by Staudinger and Reichstein. We also have detected methylacetylcarbinol as a new constituent of roasted coffee.

Shortly after we had completed our investigation, two excellent papers by Prescott and his associates[2,3] supplied valuable new information on the constituents of roasted coffee. Prescott and his collaborators relied on solvent extraction of coffee brew and dry roasted coffee to isolate several new substances which were identified in the usual manner. The following substances were reported: furfuryl alcohol, furfuraldehyde, acetic acid, formic acid, diacetyl, diethyl ketone, kahweol, vanillone, *p*-vinylguaiacol, guaiacol, *n*-heptacosane, *p*-vinylcatechol, sylvestrene, eugenol, and a hydrocarbon melting at 116–117°. Of these substances, formic acid, diethyl ketone, vanillone, *n*-heptacosane, *p*-vinylcatechol, sylves-

(1) Staudinger and Reichstein, British Patents 246,454 and 260,960.

(2) Prescott, Emerson and Peakes, *Food Research*, **2**, 1-20 (1937).

(3) Prescott, Emerson, Woodward and Heggie, *ibid.*, **2**, 165-173 (1937).