[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

THE SYNTHESIS OF A NEW METHYLCYTOSINE

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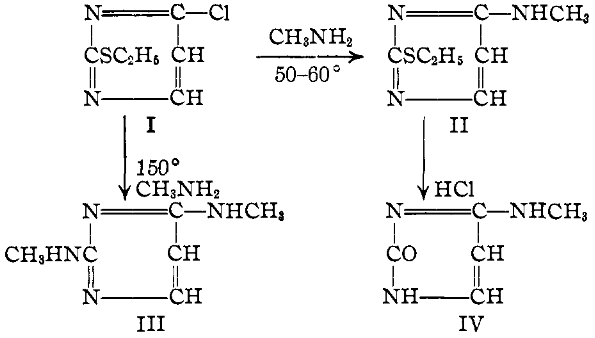
RECEIVED FEBRUARY 5, 1929 PUBLISHED MAY 6, 1929

Preliminary to a study of the action of diazomethane on certain nucleic acids and on the pyrimidine constituents[1] of the same it became necessary, for identification purposes, to synthesize a new methylcytosine, 2-oxy-6-methylaminopyrimidine, IV.

The method[2] which has been successfully employed utilizes as the starting material 2-ethylmercapto-6-chloropyrimidine, I. When this substance is treated with an absolute alcohol solution of methylamine in an autoclave the reaction proceeds in one of two ways, depending largely on the temperature factor.



At 50–60° the product is the hydrochloride of 2-ethylmercapto-6-methylaminopyrimidine, II, while at 150° the ethylmercapto group is displaced and the hydrochloride of 2,6-di-(methylamino)-pyrimidine, III, is formed. The free bases are easily obtained from the corresponding hydrochlorides by treatment with alkali.

The methylated cytosine, IV, is readily prepared, in the form of its hydrochloride, by digesting 2-ethylmercapto-6-methylaminopyrimidine, II, with concd. hydrochloric acid. The free base is obtained from the hydrochloride by careful treatment of the latter with potassium hydroxide in absolute alcohol. It gives a characteristic picrate and a positive color test[3] (purple) with bromine, indicative of the absence of a substituent in position 3.

Experimental Part

Hydrochloride of 2,6-Di-(methylamino)-pyrimidine.—Nine grams of 2-ethylmercapto-6-chloropyrimidine[2] was heated in an autoclave at 150° for four hours with

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[1] Preliminary paper, *Proc. Nat. Acad. Sci.*, **8**, 44 (1922).

[2] Wheeler and Johnson, *Am. Chem. J.*, **29**, 492 (1903).

[3] Wheeler and Johnson, *J. Biol. Chem.*, **3**, 183 (1907).

4 molecular proportions of methylamine in absolute alcohol solution. At the end of this period the autoclave was opened and a strong odor of ethyl mercaptan was observed. After removal of tarry material by filtration, the filtrate was evaporated to dryness and the residue crystallized several times from absolute alcohol. The hydrochloride melts at 262° and is soluble in water and alcohol, but insoluble in ether and acetone.

Anal. Calcd. for $C_6H_{11}N_4Cl$: N, 32.10; Cl, 20.33. Found: N, 31.88, 32.11; Cl, 20.50, 20.34.

2,6-Di-(methylamino)-pyrimidine, III.—Four grams of the hydrochloride of 2,6-di-(methylamino)-pyrimidine was dissolved in absolute alcohol and treated with an absolute alcohol solution of potassium hydroxide to faint alkalinity. The potassium chloride was filtered off and the filtrate evaporated to dryness. The residual base, after three crystallizations from a ligroin-absolute alcohol mixture, melted constantly at 132°. It is soluble in water and absolute alcohol, and insoluble in ligroin, acetone and ether.

Anal. Calcd. for $C_6H_{10}N_4$: N, 40.57. Found: N, 40.13, 40.21.

The Hydrochloride of 2-Ethylmercapto-6-methylaminopyrimidine.—Nine grams of 2-ethylmercapto-6-chloro-pyrimidine was heated in an autoclave for four hours at 50–60° with an absolute alcohol solution of 3.5 molecular proportions of methylamine. There was no perceptible odor of ethyl mercaptan upon opening the autoclave and the solution was clear, with entire absence of gummy material. It was evaporated to dryness and the residue triturated with ether. The precipitate of methylamine hydrochloride was filtered off and washed with ether. Dry hydrogen chloride was then passed into the ethereal filtrate until precipitation was complete; the precipitate was filtered and weighed (9 g.). After two crystallizations from an acetone–absolute alcohol mixture, the hydrochloride melted at 216°. It is soluble in water and absolute alcohol, but insoluble in ether and acetone.

Anal. Calcd. for $C_7H_{12}N_3S{\cdot}Cl$: N, 20.44; S, 15.57. Found: N, 20.58, 20.52; S, 15.62.

When this reaction was carried out at 105–110°, a mixture of 2,6-di-(methylamino)-pyrimidine and 2-ethylmercapto-6-methylaminopyrimidine was formed, with the latter considerably in predominance.

2-Ethylmercapto-6-methylaminopyrimidine, II.—When the above-described hydrochloride was dissolved in water and treated with concd. ammonium hydroxide, the free base was precipitated as an oil, which solidified on standing. It was filtered and then dissolved in a mixture of ligroin and absolute alcohol. From this solvent it separated as an oil which solidified when triturated with ligroin. The pure base thus obtained melts at 58°; it is insoluble in water, sparingly soluble in ligroin and very soluble in alcohol.

Anal. Calcd. for $C_7H_{11}N_3S$: N, 24.85. Found: N, 24.95, 24.77.

Hydrochloride of 2-Oxy-6-methylaminopyrimidine.—2-Ethylmercapto-6-methylaminopyrimidine was digested for eight hours with concentrated hydrochloric acid; the resulting solution was then evaporated to dryness and the residue crystallized from aqueous alcohol. It crystallizes in small prisms which decompose at 320°. It is soluble in water and insoluble in alcohol, acetone and ether.

Anal. Calcd. for $C_5H_8N_3OCl$: N, 26.01; Cl, 21.95. Found: N, 25.90, 26.07; Cl, 22.28, 22.21.

2-Oxy-6-methylaminopyrimidine, IV.—One and six-tenths g. of crude 2-oxy-6-methylaminopyrimidine hydrochloride, suspended in absolute alcohol, was treated with absolute alcoholic potash until the solution was faintly alkaline. The potassium chloride was filtered off and the filtrate evaporated to dryness. The base was purified by crystallization from aqueous acetone, out of which it separated in cubes which melted at 270°. It is soluble in water and alcohol and insoluble in acetone and ether. Unlike cytosine, this base is not hydrated. It gives the Wheeler–Johnson color test.[3]

Anal. Calcd. for $C_5H_7N_3O$: N, 33.60. Found: N, 33.38, 33.30.

The picrate of 2-oxy-6-methylaminopyrimidine crystallizes from water in slender prisms and melts at 220–225°.

Summary

1. The interaction of methylamine and 2-ethylmercapto-6-chloropyrimidine produces either 2-ethylmercapto-6-methylaminopyrimidine or 2,6-di-(methylamino)-pyrimidine, depending on the temperature employed.
2. A new methylcytosine, 2-oxy-6-methylaminopyrimidine, is formed by acid hydrolysis of 2-ethylmercapto-6-methylaminopyrimidine.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF UTAH]

THE STRUCTURE OF FURAZAN OXIDES. II

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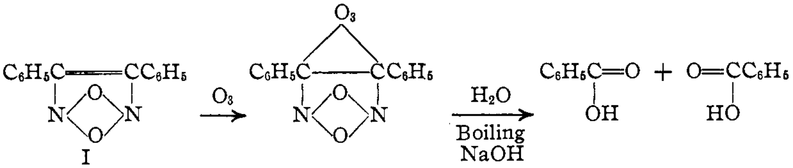
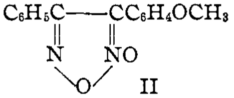
RECEIVED FEBRUARY 13, 1929 PUBLISHED MAY 6, 1929

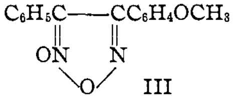
Furazan oxides (or furoxans) are attacked by ozone and the ozonized substances are decomposed with water and alkalies yielding acids. This behavior of these substances has been interpreted[1] on the basis of an ethylenic structure as follows



Meisenheimer, Lange and Lamparter,[2] however, have succeeded in isolating two substances which they believe to be isomeric furazan oxides. The isolation of two isomeric oxides does not permit an ethylenic formula, I, but necessitates an unsymmetrical structure, which in the case of Meisenheimer's oxides would have Formulas II and III.



II



III

The two isomeric oxides II and III were obtained by oxidizing the two *amphi*-dioximes of *p*-methoxybenzil. They appeared to be non-separable and isomorphous since recrystallization of a mixture from alcohol did not

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[1] Kinney and Harwood, THIS JOURNAL, **49**, 514 (1927).

[2] Meisenheimer, Lange and Lamparter, *Ann.*, **444**, 94 (1925).