RESEARCH ON THE PYRIMIDINE SERIES

V. Conversion of 4-Chloro-2-ethylthio-6-methylpyrimidine into 5-Chloro-6-methyluracil*

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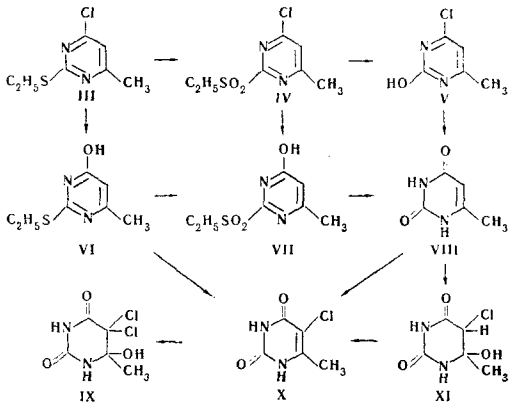
The reaction of 4-chloro-2-ethylthio-6-methylpyrimidine with 30% H_2O_2 in ethanol with heating forms 5-chloro-6-methyluracil instead of the expected 4-chloro-2-hydroxy-6-methylpyrimidine. Under similar conditions but in the presence of HCl, 6-methyluracil and 2-ethylthio-4-hydroxy-6-methylpyrimidine are also converted into 5-chloro-6-methyluracil.

According to Chinese workers [1, 2], 4-chloro-2-ethylthiopyrimidine (I) reacts at 88° with 30% H_2O_2 in ethanol to form the highly reactive 4-chloro-2-hydroxypyrimidine (II).

On working with 4-chloro-2-ethylthio-6-methylpyrimidine (III), we observed that when it reacted with 30% H_2O_2 under the given conditions [1, 2], the 2-ethylthio group was again replaced by hydroxyl. However, in contrast to 4-chloro-2-hydroxypyrimidine (II) the substance obtained hydrolyzes extremely slowly and reacts with ammonia and amines with difficulty.

It is known that 2-ethylthio-4-hydroxypyrimidine and uracil and a number of its derivatives react with H_2O_2 in the presence of concentrated hydrochloric acid at room temperature to form 5, 5-dichloro-6-hydroxy-2, 4-dioxohexahydropyrimidines of type IX [3]. At the same time, on heating, particularly in acid media, the 5, 5-dibromo analogs of IX are converted into 5-bromouracils [4].



These facts led us to the idea of the possibility of forming 5-chloro-6-methyluracil (X) by the action of 30% H_2O_2 on the pyrimidine III. In actual fact, the complete coincidence of the UV and IR spectra, of the acidity constants, of the neutralization equivalents, and of the results of paper and thin-layer chromatography of the reaction product and of authentic 5-chloro-6-methyluracil [5] unambiguously showed that the reaction of 4-chloro-2-ethylthio-6-methyluracil with 30% hydrogen peroxide in the presence of ethanol forms 5-chloro-6-methyluracil.

The conversion of 4-chloro-2-ethylthio-6-methylpyrimidine (III) into 5-chloro-6-methyluracil (X) cannot take place intramolecularly; it is obvious, also that the introduction of a chlorine atom into position 5 of the pyrimidine nucleus must be preceded by the hydrolysis of the chlorine atom in compound III, IV, or V, since none of these is a chlorinating agent.

In boiling 20% aqueous ethanol, III is practically stable for at least 1 hr, which considerably exceeds the time for performing the reaction described by the Chinese authors [1, 2]. Moreover, at room temperature it is possible to oxidize 2-ethylthiopyrimidines to the corresponding 2-ethylsulfonylpyrimidines [6]. Consequently, it may be assumed that the oxidation of the 2-ethylthio group in compound III takes place more readily than the hydrolysis of the chlorine atom.

It is known that 2-ethylsulfonylpyrimidines readily undergo nucleophilic substitution reactions. Here, either the activities of the chlorine atom and the ethylsulfonyl group in 4-chloro-2-ethylsulfonylpyrimidines are approximately the same or the latter is more active than the chlorine atom [7]. Thus, when 4-chloro-2-ethylsulfonylpyrimidine is boiled with hydrogen peroxide, 4-chloro-2-hydroxypyrimidine (II) is formed [1, 2]. On reaction with ethanolic alkalies or with sodium methoxide in the cold, 4-chloro-2-ethylsulfonyl-5-methylpyrimidine is converted into the corresponding alkoxy derivative [7].

Thus, it may be assumed that in the conversion of 4-chloro-2-ethylthio-6-methylpyrimidine (III) into 5-chloro-6-methyluracil (X), the III is first oxidized to IV which is subsequently hydrolyzed to V and then VIII.

It must also be noted that the results of paper and thin-layer chromatography showed the presence of 6-methyluracil in the reaction mixture when III reacted with 30% hydrogen peroxide in ethanol, its concentration first rising and then falling.

The low hydrolytic stability of IV and V and the presence of 6-methyluracil in the reaction mixture permits the assumption that the latter is the intermediate compound that undergoes chlorination. Moreover, 2-ethylthio-4-hydroxy-6-methylpyrimidine (VI) and 6-methyluracil itself are likewise converted into 5-chloro-6-methyluracil (X) under the action of 30% hydrogen peroxide in the presence of even one equivalent of hydrochloric acid in ethanol at 88°.

*For part IV, see [10].

The formation of X from VIII can be described by a number of reactions: a) direct chlorination of VIII by the chlorine formed in the reaction of hydrogen peroxide with the hydrogen chloride obtained by the hydrolysis of IV or V; b) addition of a molecule of HOCl to the multiple bond of VIII with the formation of XI, the dehydration of which leads to X. In addition X is also capable of adding a molecule of HOCl with the formation of IX. The latter can apparently chlorinate 6-methyluracil to X*.

Under the conditons that we studied, 5-chloro-6-methyluracil is evidently formed mainly by the chlorination of VIII with chlorine. The formation of IX and XI under these conditions is unlikely because of the low stability of HOCl at elevated temperatures. Furthermore, 5, 5-dichloro-6-hydroxy-6-methyl-2, 4-dioxohexahydropyrimidine reacts only very slowly with 6-methyluracil on being heated in water or in 30% hydrogen peroxide. This reaction is considerably accelerated in the presence of hydrogen chloride, but in this case the formation of IX takes place considerably more slowly than in the reaction of III with 30% hydrogen peroxide in ethanol.

Thus, it may be considered that 4-chloro-2-ethylthio-6-methylpyrimidine (III) is first oxidized to 4-chloro-2-ethylsulfonyl-6-methylpyrimidine (IV), which is hydrolyzed to 4-chloro-2-hydroxy-6-methylpyrimidine (V) and then to 6-methyluracil (VIII), and the latter is chlorinated by chlorine with the formation of 5-chloro-6-methyluracil (X).

It must be noted that in the oxidation of I under conditions analogous to those for the oxidation of III we observed the formation of a mixture of 5-chlorouracil and uracil in a ratio of approximately 1 : 4 (from the amount of chlorine and the results of chromatography), while the X is formed practically pure in 60% yield. It may be concluded from this that if the formation of 5-chlorouracils took place with the addition of a molecule of HOCl to the $C_5{=}C_6$ bond of VIII with the subsequent dehydration of the XI we should observe the reverse phenomenon: the yield of X should be lower than the yield of 5-chlorouracil because of the steric hindrance of the $C_6{-}CH_3$. Increase in the yield of X is evidently due to the influence of the methyl group, which raises the electron density in the ring at C_5; this promotes the electrophilic replacement of the $C_5{-}H$ with chlorine and thereby confirms the proposed mechanism for the formation of 5-chlorouracils.

EXPERIMENTAL

The UV spectra were taken on an SF-4-spectrophotometer at concentrations of 10^{-3}–10^{-4} M of the substances, in solutions of 0.1 N hydrochloric acid (pH 1), citrate-phosphate buffer (pH 7), and 0.1 N NaOH (pH 13). The IR spectra were recorded on an IKS-22 spectrophotometer in films on NaCl. The chromatography was carried out on Whatmann No. 1 paper using the following solvents: a) n-propanol—water (7 : 3), (system A) and b) n-butanol—acetic acid—water (5 : 2 : 3) (system B); and in a thin layer of alumina using a solvent system A.

4-Chloro-2-ethylthio-6-methylpyrimidine (III). A solution of 8.7 g (0.058 mole) of diethylaniline in 25 ml of phosphorus oxychloride was added to 10.0 g (0.058 mole) of 2-ethylthio-4-hydroxy-6-methylpyrimidine (IV) [9]. The mixture was heated under reflux for 1 hr 30 min, excess phosphorus oxychloride was distilled off in vacuum, and the residue was poured onto 50 g of finely-crushed ice. The chloropyrimidine was extracted with ether (3 × 50 ml) and the ethereal extract was washed with water, with 2% aqueous $NaHCO_3$, and with water again, and was dried over freshly calcined Na_2SO_4. After the ether had been driven off, the reaction product was distilled in vacuum twice. This gave 10.3 g (93%) of III with bp 87° (3 mm). According to the literature [9], bp 142° (15 mm). On a chromatogram the product migrated in the form of a single spot with, on paper, R_f 0.91 in system A and 0.92 in system B. UV spectrum (dioxane): λ_{max} 257 nm (log ε 4.25).

5-Chloro-6-methyluracil (X). This was obtained by the action of sulfuryl chloride on 6-methyluracil in the presence of ferric chloride [5]. Mp 325° (from water); paper chromatography: R_f 0.78 in system A and 0.70 in system B; pK_a 8.85. Found, %: C 37.21; H 3.23; Cl 21.97; N 17.64; equiv. 159. Calculated for $C_5H_5ClN_2O_2$, %: C 37.35; H 3.14; Cl 22.09; N 17.45; equiv. 160.6. UV spectrum: pH 1—λ_{max} 273 nm, (lg ε 3.94); pH 7—λ_{max} 273 nm (lg ε 3.89); pH 13—λ_{max} 284 nm (lg ε 3.83); ethanol—λ_{max} 270 nm (log ε 3.92). IR spectrum: 3100 cm^{-1}, m (ν_{NH}); 2980 s, 2900 m, 2700–2500 m (ν_{CH}); 1700 s, 1670 s, 1650 s (uracil C=O), 1620 m, 1590 m, 1560m (C=C, C—N); 1420 s (CH_3); 1320 s, 1310 m, 1140–1090 m, 980m, 880 m, 770 m (ring); 700 m, 660 m (C—Cl).

Reaction of 4-chloro-2-ethylthio-6-methylpyrimidine (III) with hydrogen peroxide. With stirring at 88°, 25 ml (0.22 mole) of 30% H_2O_2 was added to 10.0 g (0.053 mole) of III in 10 ml of ethanol. After the beginning of the exothermic reaction, the heating was stopped, whereupon the temperature of the reaction mixture rose spontaneously to 93°. After 15 min, the mixture was cooled to room temperature, and the precipitate that had deposited was filtered off, washed with water, acetone, and ethanol, and dried in a vacuum desiccator. This gave 4.5 g (59%) of a colorless crystalline substance with mp 325° (decomp.) (from water or dioxane). The test for sulfur was negative. On a chromatogram, the substance moved in the form of a single spot with R_f 0.78 in system A and 0.70 in system B on paper and R_f 0.46 in system A in a thin layer of alumina. pK_a 8.85. Found, %: C 37.40; H 3.25; Cl 21.98; N 17.45; equiv. 158.1. The IR and UV spectra fully coincided with the spectra of substance X, described below.

Reaction of 2-ethylthio-4-hydroxy-6-methylpyrimidine (VI) with hydrogen peroxide. A mixture of 3.2 g (0.018 mole) of VI, 5 ml of ethanol, 9 ml (0.079 mole) of 30% H_2O_2, and 1.5 ml (0.018 mole) of concentrated hydrochloric acid was heated with stirring until the exothermic reaction began. After 15 min, the mixture was cooled to room temperature and the precipitate that had deposited was filtered off, washed with acetone and ether, and dried in a vacuum desiccator. This gave 1.8 g (76%) of a colorless crystalline substance containing no sulfur with mp 325° (decomp.) (from water), a mixture with 5-chloro-6-methyluracil giving no depression of the melting point. The results of elementary analysis and of paper and thin-layer chromatography and potentiometric titration, and the UV and IR spectra, were completely analogous to those of the two preceding preparations.

When the reactions were carried out under analogous conditions but in the absence of hydrogen chloride, a white colorless substance with mp 300° (decomp.) was obtained in 50% yield. It migrated in the form of a single spot with R_f 0.67 in system A and R_f 0.60 in system B and in a thin layer of alumina with R_f 0.80 in system A. Found, %: C 47.39; H 4.90; N 22.37. Calculated for $C_5H_6N_2O_2$, %: C 47.60; H 4.76; N 22.20. UV spectrum: pH 1—λ_{max} 260 nm (log ε 3.98); pH 13—λ_{max} 273 nm (log ε 3.86). From the results of paper and thin-layer chromatography and the UV spectrum, the substance was identical with 6-methyluracil.

*As is well known, 5, 5-dibromo-6-hydroxy-2, 4-dioxohexahydropyrimidine brominates malonic acid and oxidizes thiourea, being converted into 5-bromouracil [8]. Like 5, 5-dibromo-6-hydroxy-2, 4-dioxohexahydropyrimidine, 5, 5-dichloro-6-hydroxy-6-methyl-2, 4-dioxohexahydropyrimidine (IX) liberates iodine from potassium iodide.

Reaction of 6-methyluracil with hydrogen peroxide. A mixture of 3.3 g (0.027 mole) of 6-methyluracil, 12.5 ml (0.07 mole) of 30% hydrogen peroxide, 5 ml of ethanol, and 2 ml (0.027 mole) of concentrated hydrochloric acid was heated with stirring. At 80°, a clear solution was formed, whereupon an exothermic reaction immediately began which was complete after 15 min. The mixture was cooled to room temperature, and the precipitate was filtered off, washed with acetone and ether, and dried in vacuum. This gave 1.4 g (36%) of a colorless crystalline substance with mp 325° (decomp.), completely identical with 5-chloro-6-methyluracil in respect of elementary analysis, paper and thin-layer chromatography, and UV and IR spectra.

When the analogous synthesis was carried out using double the amount of hydrochloric acid, 5-chloro-6-methyluracil was again obtained with a yield of 78%.

When 6-methyluracil was heated with 30% hydrogen peroxide in the presence of ethanol at 90° for 30 min, it was recovered unchanged almost quantitatively.

5,5-Dichloro-6-hydroxy-6-methyl-2,4-dioxohexahydropyrimidine (IX). With ice-water cooling, 50 ml of 30% hydrogen peroxide and 50 ml of concentrated hydrochloric acid were added to 5.0 g (0.04 mole) of 6-methyluracil. The solution that was formed after about 30 min was kept in the refrigerator for a day. The precipitate that had deposited was filtered off, washed with water, and dried in vacuum. This gave 8 g (94%) of a colorless crystalline substance with mp 276° (from aqueous ethanol). According to the literature [3], mp 275–277°.

Reaction of 5,5-dichloro-6-hydroxy-6-methyl-2,4-dioxohexahydropyrimidine (IX) with 6-methyluracil. A mixture of 1.0 g (0.008 mole) of 6-methyluracil, 1.7 g (0.008 mole) of IX, 7 ml of 30% aqueous ethanol, and 2 ml of concentrated hydrochloric acid was heated at 90° for 3 hr. After cooling, the precipitate that deposited was filtered off, washed with water, acetone, and ether, and crystallized from water. This gave 0.75 g of 5-chloro-6-methyluracil, completely identical with that obtained previously.

When the analogous experiment was carried out in the absence of hydrochloric acid only traces of 5-chloro-6-methyluracil were obtained in 3 hr. When IX was heated in water or hydrogen peroxide in the presence of hydrochloric acid, only after 2 hours was it possible to detect 5-chloro-6-methyluracil chromatographically in appreciable amounts. In the absence of hydrochloric acid, evidently, only the cleavage of the ring of the initial hexahydropyrimidine took place; 5-chloro-6-methyluracil was not detected on chromatograms.

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