[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Interaction of Chloromethyl Ether with 4-Methyluracil.[1,2] II

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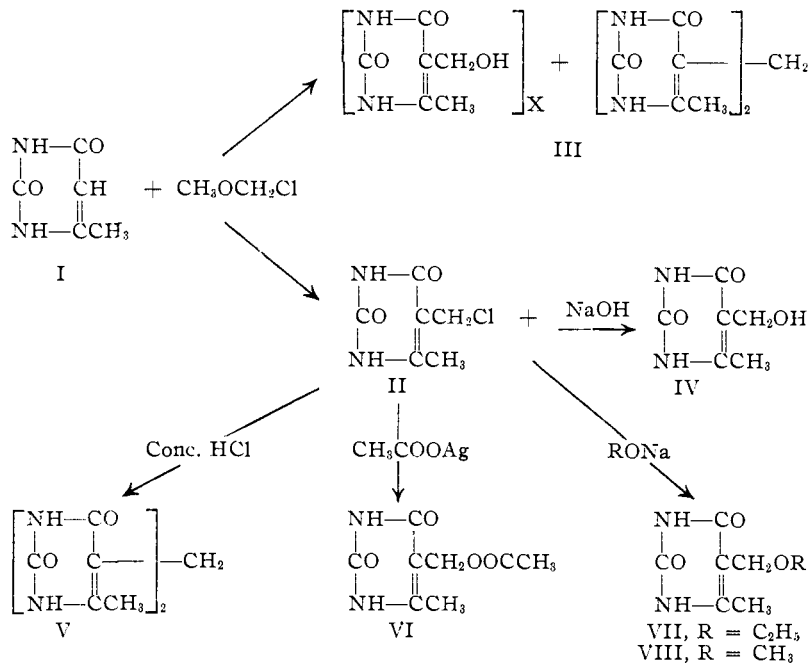
A problem of great interest in this Laboratory's program of pyrimidine research is the development of a practical method for synthesizing primary halide derivatives (RCH_2Cl) of compounds of the uracil type, substituted in position-5 of the pyrimidine cycle. Although it has been shown that the pyrimidine cycle is attacked in the 5-position by the action of chloromethyl ether on 4-methyluracil in glacial acetic acid solution, the introduction of the grouping (—CH_2Cl) into this pyrimidine was not effected under these conditions.[2] Direct treatment of 4-methyluracil with chloromethyl ether by heating under pressure, however, proved to be a successful method for introducing this primary halide group.

5-Chloromethyl-4-methyluracil II can be obtained in good yield by heating 4-methyluracil I with an excess of chloromethyl ether in a sealed tube at 100°. Small amounts of secondary products are also formed in this reaction, but the desired halogenated pyrimidine II is easily separated from them by extracting the crude reaction mixture with boiling dioxane, which dissolves the pyrimidine II. Analysis of the material insoluble in the dioxane indicated that it probably was a mixture III of a polymer of 5-oxymethyl-4-methyluracil[2] and bis-(4-methyl-2,6-dioxypyrimidyl-5)-methane.[2] This mixture could not be separated because of its extreme insolubility in all the common solvents. The formation of these pyrimidines is due to side reactions favored under the experimental conditions of the major reaction.[2,4]



The reaction between 4-methyluracil I and chloromethyl ether is an extremely sensitive one. The experiment was carried out several times under the conditions described above, but in a few cases a small amount of unchanged 4-methyluracil I was isolated from the reaction mixture along with the pyrimidine II and the "dioxane insoluble residue" III. It has not been possible to control the recovery of the 4-methyluracil in such experiments, although in every case, the reaction was applied under practically identical conditions. Additional evidence for the sensitiveness of this reaction was obtained by applying it at 80–85° and at 125–130°. The results obtained are recorded in Table I.

The chlorine in the pyrimidine II is ionic and interacts with silver nitrate in aqueous solution. The constitution of this compound II was established by its conversion into the known 5-acetoxymethyl-4-methyluracil[2] VI upon treatment with silver acetate. 5-Ethoxymethyl-4-methyluracil VII results by interaction of the pyrimidine II with boiling ethanol or by treatment with sodium ethylate in alcohol solution. The corresponding 5-methoxy derivative VIII is formed under

(1) Researches on Pyrimidines. CLXXIII. This paper was constructed from a dissertation presented by Miss Margaret M. Endicott in June, 1939, to the Graduate Faculty of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(2) Paper I, Researches on Pyrimidines CLXX, Endicott and Johnson, THIS JOURNAL, **63**, 1286 (1941).

(3) Yale University Fellow in Chemistry, 1938–1939.

(4) (a) C. Favre, *Compt. rend.*, **119**, 284 (1894); *Bull. soc. chim.*, [3] **11**, 879, 1095 (1894). (b) J. Kuenen, *Chem. Zentr.*, **72**, I, 772 (1901).

analogous conditions using methanol and sodium methylate.

When the pyrimidine II is dissolved in cold water the chlorine atom is replaced by a hydroxyl group. The formation of free hydrochloric acid in the aqueous solution catalyzes the decomposition of the 5-hydroxymethyl-4-methyluracil IV before it can be completely isolated from the solution. If, however, the hydrochloric acid is neutralized by an equivalent amount of alkali a good yield of the pyrimidine IV is obtained.

When the pyrimidine II is digested with concentrated hydrochloric acid it is changed practically quantitatively into bis-(4-methyl-2,6-dioxypyrimidyl-5)-methane V.[2] This transformation is quite analogous to the well-known pyrrole reaction applied by H. Fischer and his co-workers[5] for the preparation of dipyrrylmethanes. This behavior is in marked contrast to that of uracil derivatives containing a primary halide group in the 4-position of the pyrimidine cycle, namely, 4-chloromethyluracil and 4-chloromethyl-5-methyluracil.[6] Both of these pyrimidines can be heated with concentrated hydrochloric acid at 125–130° without alteration.

Experimental Part

5-Chloromethyl-4-methyluracil II

Preparations "A" and "B" (Table I).—Six grams of finely powdered 4-methyluracil I and 15 ml. (4.7 mols) of chloromethyl ether[7] were heated together in a sealed tube for twenty-four hours at 100°.[8] The tube was allowed to cool slowly to room temperature and when opened showed only slight pressure. The colorless reaction product was filtered from excess of chloromethyl ether, washed with ether and dried in the air. It was then extracted with boiling purified dioxane.[9] The material insoluble in dioxane and the dioxane extract were investigated as described below.

Dioxane Extract.—This contained the major part of the reaction product (see Table I) and deposited on standing the chlorinated pyrimidine II. This crystallizes in the form of small prisms arranged as rosets clinging to the walls of the crystallizing flask. Additional quantities were obtained by concentration of the dioxane filtrate *"in vacuo"* at 35–40° under careful protection from moisture which attacks the primary halide group. After three recrystallizations from dioxane (1 g. in 20 ml.), the compound turns yellow at 225° and decomposes with effervescence at 330–335°. It was dried in a vacuum desiccator for analysis.

Anal. Calcd. for $C_6H_7O_2N_2Cl$: N, 16.05. Found: N, 15.97, 15.95.

The pyrimidine is slightly soluble in boiling chloroform and acetone, and insoluble in ether, petroleum ether and benzene. It dissolves in water to form 5-oxymethyl-4-methyluracil.

Material Insoluble in Dioxane.—This represented a small portion of the reaction product, was chlorine free and did not melt below 340°. The analytical results indicated that it probably was a mixture III of the "insoluble polymer" of 5-oxymethyl-4-methyluracil $(C_6H_8O_3N_2)_x$ and bis-(4-methyl-2,6-dioxypyrimidyl-5)-methane[2] ($C_{11}H_{12}O_4N_4$). This could not be separated because of the insolubility of these pyrimidines in all the common solvents.

Anal. Calcd. for $(C_6H_8O_3N_2)_x$: N, 17.96. Calcd. for $C_{11}H_{12}O_4N_4$: N, 21.20. Found: N, 19.14, 19.31.

Preparations "C" and "D" (Table I).—These were carried out like preparations "A" and "B," but for some unexplainable reason the reaction did not go to completion. Some 4-methyluracil was recovered. The 5-chloromethyl-4-methyluracil was separated from the reaction mixture by extraction with dioxane, and treatment of the residue with boiling water dissolved the 4-methyluracil from the "dioxane insoluble" material. It was difficult to get a clean separation of the products by this method.

A more convenient method for determining the relative amounts of these reaction products was to digest the reaction mixture with boiling ethanol, thereby extracting the pyrimidine II as the corresponding 5-ethoxymethyl-4-methyluracil VII which is soluble in the alcohol and which was isolated as described below. The 4-methyluracil and "dioxane insoluble" material were separated as above.

Action of Hydrochloric Acid on 5-Chloromethyl-4-methyluracil II.—Five-tenths gram of this pyrimidine dissolved completely in 10 ml. of concentrated hydrochloric acid. This solution was refluxed for 1.5 hours during which time 0.31 g. of bis-(4-methyl-2,6-dioxypyrimidyl-5)-methane V,[2] separated (82% of theoretical). It did not decompose below 340°.

Anal. Calcd. for $C_{11}H_{12}O_4N_4$: N, 21.20. Found: N, 21.17, 21.10.

5-Acetoxymethyl-4-methyluracil VI.—This was prepared by refluxing the pyrimidine II (0.5 g.) with an equimolar quantity of freshly crystallized silver acetate (0.48 g.) in boiling glacial acetic acid (20 ml.) for one hour. The pyrimidine VI was formed quantitatively and was purified

TABLE I

SUMMARY OF PREPARATIONS OF 5-CHLOROMETHYL-4-METHYLURACIL

Reagents	Conditions for hrs.	Reaction product, g.	Insoluble in dioxane, g.	Chloromethylpyrimidine II, g.	4-Methyluracil, g.
6 g. 4-methyluracil, 15 ml. CH_3OCH_2Cl	100° for 24	8.03	0.38	6.69	..
	100° for 24	7.98	.32	7.05	..
	100° for 24	7.80	1.30	6.01	0.35
	100° for 24	7.52	0.31	6.12	.72
	125–130° for 24	4.41	.61	3.61	..
	80–85° for 24	6.04	.36	1.60	3.96

(5) H. Fischer, *et al.*, *Ann.*, **447**, 123, 158 (1926); **448**, 199 (1926); **469**, 85 (1927); **461**, 285 (1928); **468**, 58 (1929); **486**, 1 (1931).

(6) T. B. Johnson and L. Chernoff, THIS JOURNAL, **35**, 585 (1913); *ibid.*, **36**, 1742 (1914); *J. Biol. Chem.*, **14**, 307 (1913).

(7) The chloromethyl ether was an Eastman Kodak Co. product.

(8) CH_3OCH_2Cl heated under these same conditions was recovered unaltered.

(9) The dioxane was purified by refluxing over sodium for six hours. This treatment was repeated a second time over fresh sodium, and the dioxane finally distilled from fresh sodium.

by recrystallization from glacial acetic acid. It decomposes above 320°.

Anal. Calcd. for $C_8H_{10}O_4N_2$: N, 14.14. Found: N, 14.12, 14.06.

5-Oxymethyl-4-methyluracil IV.—A small amount of this pyrimidine IV (0.1 g.) precipitated immediately upon dissolving the chloropyrimidine II (0.5 g.) in cold water (10 ml.). It was purified by recrystallization from boiling water, dried in a vacuum desiccator and analyzed. It melted with decomposition at 313–315°.

Anal. Calcd. for $C_6H_8O_3N_2$: N, 17.96. Found: N, 18.03, 18.05.

Since this pyrimidine IV is unstable when heated with hydrochloric acid, concentration of the mother liquor did not result in the isolation of more of this pyrimidine, but only in its conversion to bis-(4-methyl-2,6-dipyrimidyl-5)-methane.

The following procedure was found to be more successful for this transformation: 0.5 g. of the chloropyrimidine II was dissolved in 15 ml. of cold water and 0.1 *N* sodium hydroxide added until the solution was neutral to litmus. After concentrating the solution, 0.37 g. of the pyrimidine IV (83%) crystallized. After recrystallization from boiling water it melted at 314–315°.

Anal. Calcd. for $C_6H_8O_3N_2$: N, 17.96. Found: N, 17.96, 17.93.

5-Ethoxymethyl-4-methyluracil VII and 5-Methoxymethyl-4-methyluracil VIII.—These two pyrimidines are most conveniently prepared by dissolving 5-chloromethyl-4-methyluracil in absolute ethanol and methanol, respectively. Solution of 1 g. of the pyrimidine II in 10 ml. of boiling absolute ethanol yielded on cooling 0.68 g. of the 5-ethoxypyrimidine VII. This yield was increased by 0.27 g. by neutralization of the free hydrochloric acid with the required amount of sodium ethylate and then evaporating the solution to dryness. The ethoxypyrimidine was then separated from the sodium chloride by extraction with acetone. This pyrimidine is soluble in boiling absolute ethanol (1 g. in 30 ml.), less soluble in boiling dioxane and acetone and insoluble in ether. The pyrimidine crystallizes from absolute ethanol in plates which on heating grow moist at 195–200° and finally decompose with effervescence to a yellow oil at 312–315°.

Anal. Calcd. for $C_8H_{12}O_3N_2$: N, 15.22. Found: N, 15.20, 15.27.

A quantitative yield of the 2-methoxypyrimidine VIII was obtained when the chloromethylpyrimidine II was treated with absolute methanol and sodium methylate (as above).[10] This compound crystallized from boiling methanol in the form of needles. These show a change, on heating, at 235° and finally decompose to a yellow oil above 330°. The pyrimidine is moderately soluble in dioxane and acetone, and insoluble in ether.

Anal. Calcd. for $C_7H_{10}O_3N_2$: N, 16.39. Found: N, 16.42, 16.50.

Summary

1. Chloromethyl ether interacts with 4-methyluracil in a sealed tube to give 5-chloromethyl-4-methyluracil.

2. This chlorinated pyrmidine is very reactive due to the high activity of the chlorine atom. Its reactions with water, absolute ethanol and methanol, concentrated hydrochloric acid and silver acetate are described.

(10) Dioxane proved to be a better solvent than acetone for extracting the methoxypyrimidine from the sodium chloride.

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[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Lignin and Related Compounds. LI. The Solvent Fractionation of Maple Ethanol Lignin

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Lignins obtained by the various available methods of isolation vary widely in physical characteristics such as solubility, homogeneity and average molecular complexity. The heterogeneous nature of certain isolated lignins, for example birch formic acid lignin, has been demonstrated by Lieff, Wright and Hibbert.[3] These authors fractionated their lignins by continuous solvent extraction, in this way obtaining several fractions having different solubility characteristics. Chemical analysis of the fractions showed marked differences in chemical composition, notably in the methoxyl and hydroxyl contents. Bailey[4] from his studies on aspen butanol lignin concluded that the isolated product was not homogeneous, and succeeded in fractionating this and other isolated lignins by use of the molecular still technique. His attempts to use solvent fractionation methods, however, were unsuccessful. Loughborough and Stamm[5] made a com-

(1) Holder of a Studentship awarded by the National Research Council of Canada, 1940–41.

(2) Holder of a Canadian Pulp and Paper Association Research Scholarship, 1940–41.

(3) Lieff, Wright and Hibbert, THIS JOURNAL, **61**, 1477 (1939).

(4) Bailey, *Paper Trade J.*, **111**, 27 (no. 7) (1940).

(5) Loughborough and Stamm, *J. Phys. Chem.*, **40**, 113 (1936).