[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Chlorination[1] of 2,4-Diketotetrahydropyrimidines by Action of a Mixture of Superoxol[2] and Hydrochloric Acid

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In our study of halogenation technique to be used in an investigation dealing with the chemistry of nucleotides and nucleosides, it became necessary to develop a method for the chlorination of pyrimidines, which would function in the absence of free chlorine and at a low temperature. In this paper the author will present some of the preliminary results obtained in a solution of this problem.

It is well known that the presence of hydrochloric acid accelerates the speed of decomposition of hydrogen peroxide into oxygen and water. This simple decomposition, which involves a low concentration of chlorine, has been studied quantitatively by Maass and Hiebert[4] and Livingstone and Bray,[5] who obtained results supporting a unimolecular change at 25°; and more recently by Budge,[6] who studied the speed of decomposition over temperature ranges of 25, 30 and 35°.

Maass and Hiebert postulated that the mechanism of this reaction or change might be represented by the primary formation of a complex molecule, $H_2O_2 \cdot HCl$, and interpreted the intermediate changes of the decomposition as expressed below in equations a, b and c (1)

$$\text{(1)}\quad \text{a}\quad H_2O_2 \cdot HCl \longrightarrow H_2O + HOCl$$
$$\text{b}\quad HOCl + H_2O_2 \longrightarrow H_2O + O_2 + HCl$$
$$\text{c}\quad HOCl + HCl \longrightarrow H_2O + Cl_2$$

Accepting this interpretation as true, we have here theoretically an ideal chlorinating medium for the smooth conversion of 2,6-diketotetrahydropyrimidines into the characteristic 5,5-disubstituted 2,6-diketohexahydropyrimidine combinations. This change is illustrated by the quantitative conversion of uracil I into 2,6-diketo-5,5-dichloroxyhexahydropyrimidine III.[8] 5-Chlorouracil II is an intermediate product of this reaction.

(1) Researches on Pyrimidines, CLXXVIII.

(2) Merck 30% hydrogen peroxide.

(3) This research was partially supported by a grant from the Research Committee of the Council on Pharmacy and Chemistry, American Medical Association (Grant No. 423).

(4) Maass and Hiebert, THIS JOURNAL, **46**, 290 (1924).

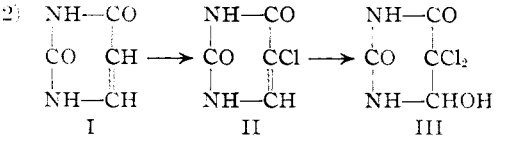
(5) Livingstone and Bray, *ibid.*, **47**, 2069 (1925).

(6) Budge, *ibid.*, **54**, 1769 (1932).

(7) It is also known that reaction c is reversible.

(8) Or 5,5-dichloroxyhydrouracil; see Johnson and Sprague, THIS JOURNAL, **59**, 2436 (1937).

(2)



I II III

This interesting change is accomplished according to our present technique by bubbling chlorine gas freely into a suspension of uracil I in water, or by oxidizing this pyrimidine with potassium chlorate in hydrochloric acid solution.[9] Both methods of operating are productive of excellent yields of the hexahydropyrimidine III, but are conducted under experimental conditions which are unfavorable for our present research.

The author finds that superoxol[2] mixed with strong hydrochloric acid provides an ideal reagent for bringing about such changes as expressed in Equation (2). The transformation to the hexahydropyrimidine derivative III is accomplished at ordinary temperature, and chlorine is introduced into the respective pyrimidine molecule at position-5 with production of quantitative yields of the desired 2,6-diketohexahydroxypyrimidine, and in very pure condition. In other words, nascent chlorine gas or potassium chlorate, or any inorganic salt of this nature, are unnecessary for accomplishing these transformations.

Results typifying some interesting changes brought about by the application of this technique with different pyrimidines studied in our preliminary research are recorded in Table I.

Experimental Part

All these reactions reported in Table I are conducted at ordinary temperature, and the yields of the reaction products are practically quantitative. No secondary reactions are met with to complicate the results. The general method of operating is very simple and is as follows: One gram of the pyrimidine is finely pulverized and stirred into 10 cc. of cold superoxol. No reaction apparently results. The same volume of cold, concentrated hydrochloric acid is then added to the peroxide mixture and this allowed to stand at ordinary temperature. There is no immediate evidence of any reaction, and there is no coloration of the liquid. Within five to ten minutes there is evidence of an increase in temperature followed by a slow evolution of oxygen. The reaction is allowed to proceed at its own rate, and during the evolution of oxygen the chlorination

(9) T. B. Johnson, *Am. Chem. J.*, **40**, 26 (1908).

TABLE I

ACTION OF SUPEROXOL AND HYDROCHLORIC ACID

Pyrimidine reactants	Reaction products	M. p., °C.	Nitrogen analysis, %	
Uracil NHCONHCH=CHCO	5,5-Dichloroxyhydrouracil NHCONHCHOHCCl$_2$CO·H$_2$O	215–218		
Thymine NHCONHCH=C(CH$_3$)CO	5-Methyl-5-chloroxyhydrouracil NHCONHCHOHC(CH$_3$)ClCO	202–203	16.00	15.75
4-Methyluracil NHCONHC(CH$_3$)=CHCO	4-Methyl-5,5-dichloroxyhydrouracil NHCOCHCOH(CH$_3$)CCl$_2$CO[a]	275–277	13.3	
5-Bromouracil NHCONHCH=CBrCO	5-Bromo-5-chloroxyhydrouracil NHCOCHCHOHC(Br)ClCO·H$_2$O[b]	195–200	10.71	
5-Nitrouracil NHCONHCH=CNO$_2$CO	5-Nitro-5-chloroxyhydrouracil NHCONHCHOHC(NO$_2$)ClCO[b]	165		
2-Ethylmercapto-6-oxypyrimidine NHC(SC$_2$H$_5$)=NCH=CHCO[c]	5,5-Dichloroxyhydrouracil	215–218		
Isocytosine NHC(NH$_2$)=CH=CHCO	2-Amino-6-keto-5,5-dichloroxyhexahydropyrimidine·hydrochloride NHC(NH$_2$)=NCHOHCCl$_2$CO·HCl		18.30	
Cytosine NHCONHCH=CHCNH$_2$	5,5-Dichloroxyhydrouracil	215–218		
Orotic acid NHCONHC(COOH)=CHCO[d]	5-Chlorouracil-4-carboxylic acid NHCONHC(COOH)=CClCO	+300	14.6	14.4
Uracil-5-carboxylic acid NHCONHCH=C(COOH)CO[e]	5,5-Dichloroxyhydrouracil and carbon dioxide	215–218		
5-Iodouracil NHCONHCH=CICO[f]	5,5-Dichloroxyhydrouracil	215–218		

[a] Behrend, *Ann.*, **236**, 22, 59 (1886). [b] Johnson, *Am. Chem. J.*, **40**, 19 (1908). [c] Johnson and Sprague, THIS JOURNAL, **60**, 1622 (1938). [d] Wheeler, *Am. Chem. J.*, **38**, 358 (1908); M. Bachstez, *Ber.*, **63**, 1000 (1930). [e] Wheeler, Johnson and Johns, *Am. Chem. J.*, **37**, 392 (1907). [f] Johnson, *ibid.*, **40**, 29 (1909).

product, in some cases, begins to deposit quickly. The reaction is generally complete after standing for ten to twelve hours. The crystalline reaction product is then filtered off and the total yield recovered by evaporation of the filtrate in a high vacuum, or by allowing to stand exposed to the air in a warm oven. The different reaction products reported in Table I can all be purified by recrystallization from hot water.

It is of special importance to call attention to the following facts: (1) uracil, 5-chlorouracil, cytosine and 2-ethylmercapto-6-oxypyrimidine are all productive of the same 5,5-dichloroxyhydrouracil. (2) Very striking is the difference in behavior of orotic acid and its isomeric uracil-5-carboxylic acid, the former undergoing direct chlorination without loss of its carboxyl group, while the latter isomer is converted quantitatively into 5,5-dichloroxyhydrouracil. (3) Hydrouracil is not attacked by the chlorinating mixture, while 5-iodouracil interacts with loss of iodine and formation of 5,5-dichloroxyhydrouracil and (4), isocytosine is not deaminized by the action of the superoxol mixture. Attention is called to the fact that orotic acid is attacked by bromine water with formation of 5,5-dibromobarbituric acid.[d]

Summary

2,6-Diketopyrimidines of the uracil type are attacked at ordinary temperature by superoxol and hydrochloric acid with formation of chlorinated hexahydropyrimidine compounds.

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