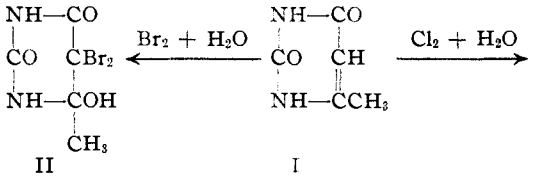
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

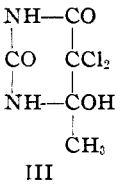
The Reaction of Hydrochloric Acid with 6-Methyl-5,5-dichloroxyhydrouracil[1]

BY TREAT B. JOHNSON[2]

Robert Behrend,[3] in his early classical researches on the chemistry of 6-methyluracil I, investigated the behavior of this pyrimidine when exposed to the action of bromine and chlorine in the presence of water. It was found to undergo practically a quantitative conversion into the hexahydro pyrimidine derivatives, *viz.*, 6-methyl-5,5-dibromoxy- and 6-methyl-5,5-dichloroxyhydrouracils expressed by the formulas II and III, respectively.

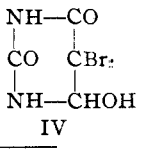


II I

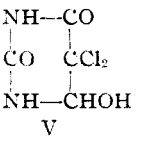


III

We now recognize this change brought about by the action of halogens as characteristic of representatives of the true uracil type; and the study of such hydrouracil compounds still promises to yield results of special interest during the progress of pyrimidine research in this Laboratory. The pyrimidine IV prepared by the action of bromine on uracil is the key reagent serving as the basis of the specific color test for this pyrimidine and cytosine.[4] It is important to note here that the corresponding chlorine compound V, first synthesized by the author,[5] can be substituted for the bromine compound IV for the successful application of this uracil color test. The two pyrimidines IV and V are equally sensitive to the action of barium hydroxide.



IV



V

While the two hydrouracil derivatives IV and V exhibit a close similarity in their chemical behavior, it has been the experience of the author that the 4-methylhydrouracils II and III differ decidedly in their relative reactivity under comparable experimental conditions. Behrend[3] was conscious of this fact and states in his early paper that the bromine compound II is easily decomposed by warming with alcohol giving 5-bromo-6-methyluracil, while the corresponding chlorine compound III is not altered by this treatment and can be recrystallized repeatedly from alcohol without change. He also found that the bromine compound II is easily converted to 5-bromo-6-methyluracil by warming with water, while the chlorine compound III can be exposed to long digestion at 100° without alteration.

Behrend extended his experimental study of 6-methyl-5,5-dichloroxyhydrouracil III by heating it with alcohol and also water over a temperature range of 140 to 150°, but without the formation of the expected 6-methyl-5-chloruracil in either case. Alcoholysis or hydrolysis led to the formation of ammonia and other difficultly soluble products which were not identified.[6] So far as the author is aware, no explanation, to date, has been given of the nature of these hydrolytic changes. The author's interest in the chemistry of this class of pyrimidines has induced him to undertake a comparative study of the reactivity of the two pyrimidines II and III, and a report is now rendered on the chemical deportment of both compounds when exposed to the action of strong hydrochloric acid.[7]

The author now finds that the two 4-methylhydrouracils II and III differ decidedly in their behavior toward hydrochloric acid. The bromine compound II reacts to undergo the normal change expected yielding a true uracil derivative,

(1) Researches on Pyrimidines, CLXXIX.

(2) The author expresses here his acknowledgment of the assistance given by Mr. C. O. Edens in the performance of analytical work reported in this paper.

(3) R. Behrend, *Ann.*, **229**, 18 (1885); **236**, 57 (1886); List, **236**, 22 (1886).

(4) "Color Test for Uracil," by Wheeler and Johnson, *J. Biol. Chem.*, **3**, 183 (1907).

(5) Johnson, *Am. Chem. J.*, **40**, 19 (1908).

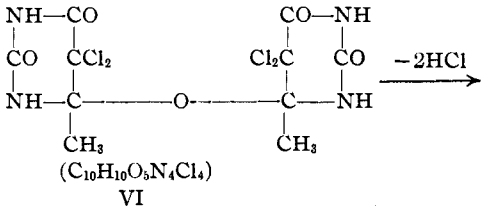
(6) Behrend, *Ann.*, **236**, 61 (1886). *Quotation:* "Unter Bildung von Ammoniak und anderen zum theil schwer löslichen, noch nicht näher untersuchten Producten" . . . "doch wird kein Chlormethyluracil gebildet."

(7) Behrend's experiments with alcohol and water at 140–150° will be repeated (T. B. J.).

viz., 6-methyl-5-bromouracil. The chlorine compound III, on the other hand, reacts with hydrochloric acid without formation of 6-methyl-5-chlorouracil, but is transformed almost quantitatively into a new compound of unknown structure and having the empirical formula $C_{10}H_8O_5N_4Cl_2$. This same substance is also formed by digesting the chlorine compound III with acetic anhydride. The reaction is expressed in the equation below.

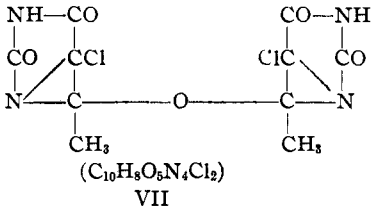
$$2C_5H_6O_3N_2Cl_2 \rightleftharpoons C_{10}H_8O_5N_4Cl_2 + H_2O + 2HCl$$

The composition of the new compound indicates that the 4-methylhydrouracil III first undergoes a condensation with elimination of one mole of water with formation of an heterocyclic ether construction VI, analogous to the production of α,α'-dimethyl-β,β'-furan-dicarboxylic acid by the action of hydrochloric acid on γ-diacetosuccinic acid.[8] The further loss of two molecules of hydrochloric acid from such an heterocyclic ether VI would account for the subsequent formation of a compound represented by the empirical formula $C_{10}H_8O_5N_4Cl_2$. That we are dealing here with a dimolecular condensation product, as expressed by this formula, is confirmed by the analytical values obtained for its molecular weight (339 and 341).



$(C_{10}H_{10}O_5N_4Cl_4)$

VI

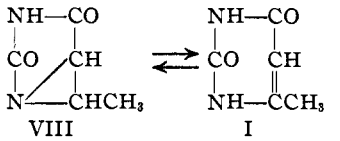


$(C_{10}H_8O_5N_4Cl_2)$

VII

To represent the constitution of this new compound we have tentatively assigned to it the structural formula VII. This is a representative of an entirely new type of pyrimidine compound, and, if correctly interpreted, it is the first pyrimidine to be described in the literature possessing the cyclic structure of the unknown 6-methyl-1,5-bicyclouracil VIII. The pyrimidine ether VII is soluble in alkali and is reprecipitated unchanged by addition of acids.

(8) Knorr, *Ber.*, **22**, 155, 172 (1889); **27**, 1157 (1894); Harrow, *Ann.*, **201**, 157 (1880).



VIII I

Experimental Part

The Oxide or Ether of 6-Methyl-6-oxy-5-chloro-1,5-bicyclouracil, VII.—This bicyclouracil derivative, which is an ether formation of the hypothetical 1,5-bicyclouracil compound, is obtained in excellent yield by dissolving 6-methyl-5,5-dichloroxyhydrouracil III in strong hydrochloric acid, and boiling the resulting solution for one or more hours. Many hydrolysis experiments have been conducted successfully by the author using proportions of 2 g. of the pyrimidine III dissolved in 20, 25, 40 and 50 cc. of concentrated hydrochloric acid. Variable periods of digestion have been applied, *viz.*, from one to fifteen hours. The reaction, however, is practically complete within one and one-half hours, and the fact that the yield is little diminished by long digestion indicates the strong resistance of the substance to further hydrolytic change. The bicyclo compound deposits slowly from the boiling solution, and on cooling at the end of the reaction period separates in the form of flat prisms. It is purified easily by crystallization from hot water or acetic acid, and the yield produced from 2 g. of the pyrimidine III averages 1.2 to 1.7 g. melting from 266–270° with decomposition. The purified product melts at 270–275° with decomposition. The ether dissolves in alkali without alteration and is reprecipitated by acids. Analysis after drying to constant weight at 100–110° gave

	C	H	N	Cl
Calcd. for $C_5H_5O_2N_2Cl$:	37.38	3.11	17.44	22.11
Calcd. for $C_{10}H_8O_5N_4Cl_2$ (VII):	35.80	2.40	16.71	21.18
Found:	35.50	2.60	16.51	21.07
Found:	35.51	2.55	16.40	21.06
Found:	35.60	2.70	16.44	21.10
Found:			16.61	
Found:			16.48	

Molecular Weight Determination by the Ebullioscopic Method.—Conducted with anhydrous methanol in Menzies and Wright apparatus.[9]

Anal. Calcd. for $C_{10}H_8O_5N_4Cl_2$: mol. wt., 335. Found: mol. wt., 339 and 341.

This same compound VII was also formed as follows. One gram of 6-methyl-5,5-dichloroxyhydrouracil III was dissolved in 10 cc. of acetic anhydride and the solution refluxed at its boiling point for one hour. After cooling, the insoluble reaction product was separated and purified by crystallization from hot water. It melted at 270–275° with effervescence.

Anal. Calcd. for $C_{10}H_8O_5N_4Cl_2$: N, 16.71. Found: N, 16.65, 16.70.

Experiments with 6-Methyl-5,5-dibromoxyhydrouracil II

Action of Hydrochloric Acid.—Digestion of 2 g. of this pyrimidine II with 30 cc. of concd. hydrochloric acid led to immediate destruction of the pyrimidine with evolution

(9) Menzies and Wright, THIS JOURNAL, **43**, 2309 (1921).

of nascent bromine. After refluxing until all free bromine was expelled the insoluble reaction product was separated and recrystallized from hot water. It melted with decomposition at 260–261° and was identified as 6-methyl-5-bromouracil. The yield was quantitative.

Anal. Calcd. for $C_5H_5O_2N_2Br$: C, 29.26; H, 2.63; N, 13.65. Found: C, 29.26; H, 2.43; N, 13.88.

This same decomposition was accomplished by boiling a solution of the pyrimidine II in acetic anhydride. The yield was quantitative.

Behavior of the Ether VII on Reduction

1. **Action of Tin Chloride and Hydrochloric Acid.**—One half a gram of the bicyclouracil compound VII was digested at 100° in 15 cc. of dilute hydrochloric acid with 2 g. of stannous chloride for six hours. The mixture was then allowed to cool when colorless crystalline material deposited. This was identified as a mixture of 6-methyl-5-chlorouracil and the unreduced bicyclo compound VII. The difference in water solubility permitted easy separation and the 6-methyl-5-chlorouracil was obtained in the form of prisms which did not melt below 300°. The recovered bicyclo compound VII crystallized from boiling water and melted at 270–275° with decomposition.

Anal. Calcd. for $C_{10}H_8O_5N_4Cl_2$: N, 16.71. Found: N, 16.74, 16.69.

2. **Action of Hydriodic Acid.**—One gram of the bicyclo compound VII, melting at 270–275° was boiled for fifteen minutes with 10 cc. of hydriodic acid of sp. gr. 1.5 and an excess of red phosphorus. The resulting solution was then diluted with 30 cc. of water and filtered while hot. A colorless solution resulted which deposited a small amount of crystals that were filtered off and identified as 6-methyl-5-chlorouracil. The acid filtrate was concentrated by evaporation at 100° to a small volume and cooled when 6-methyluracil I separated. This was purified by crystallization from hot water and did not melt below 300°. It was free from chlorine.

Anal. Calcd. for $C_5H_6O_2N_2$: C, 47.63; H, 4.76; N, 22.22. Found: C, 47.62; H, 4.66; N, 22.33.

Action of Ammonia on 6-Methyl-5-dichloroxyhydrouracil III.—Two grams of this pyrimidine was dissolved in 50 cc. of concentrated aqueous ammonia and the solution preserved at ordinary temperature in a stoppered bottle. After standing one week the solution was evaporated at 100° to expel the excess of ammonia and the filtrate cooled. Pure 6-methyl-5-chlorouracil separated and was the only product identified, and did not melt below 300°. We obtained no evidence of the formation of the bicyclo compound VII.

Summary

1. 6-Methyl-5,5-dichloroxyhydrouracil III is converted by the action of hydrochloric acid into a dichloro ether derivative of the hypothetical 6-methyl-6-oxy-1,5-bicyclouracil VII.

2. The corresponding 6-methyl-5,5-dibromoxyhydrouracil II is transformed by action of hydrochloric acid into 6-methyl-5-bromouracil. No evidence of the formation of a bicyclouracil derivative was obtained.

3. These same respective changes can also be brought about by the action of acetic anhydride.

NEW HAVEN, CONNECTICUT RECEIVED MARCH 11, 1943

[CONTRIBUTION FROM RESEARCH LABORATORIES OF NOCOCOL CHEMICAL MFG. CO., INC.]

Preparation of Aminobenzoic Acid Esters of Substituted Monoalkyl Amino Alcohols. II

BY WILLIAM F. RINGK[1] AND ELIAS EPSTEIN

In a previous paper,[1a] the author described the amino benzoates of β-alkylamino-α,α-dimethylethanols where the alkyl group contained from 1 to 5 carbon atoms.

This paper deals with members of the same series in which the nitrogen alkyl group contains 6 to 8 carbon atoms which were made for comparison with members of another series.

In general, the amino alcohols were prepared as previously described, with the following exceptions: the solvent used was 50% isopropanol solution and the mixtures were refluxed for about sixty hours. The yields were approximately 45%. Table I gives the physical constants of the amino alcohols and the molecular refractions.

The amino alcohols were condensed with *p*-nitrobenzoyl chloride in an aqueous alkaline medium as described in our previous paper. The nitro esters are all yellow solids which give positive nitroso tests.

TABLE Ia

β-ALKYLAMINO-α,α-DIMETHYLETHANOLS

$[RNHCH_2C(CH_3)_2OH]$

Alkyl group	B. p., °C.	d^{20}_{20}	$n^{20}D$	*MR*, calcd.	*MR*, found	Diff.
n-Hexyl	224–228	0.8618	1.4406	53.35	53.05	−0.30
n-Heptyl	242–246	.8567	1.4424	57.95	57.85	− .10
Octyl-2	245–248	.8560	1.4410	61.56	62.09	− .53
2-Ethylhexyl	245–248	.8560	1.4436	61.56	62.42	− .86

(1) Present address: Benzol Products Company, Newark, N. J.

(1a) Goldberg, Ringk and Spoerri, THIS JOURNAL, **61**, 3562 (1939).