TABLE II

RESULTS OF KETONIC HYDROLYSES

Ketone	Boiling range °C.	Mm.	Yield, %	Melting point semicarbazone, °C.	Ref.
$CH_3(CH_2)_2COCH_3$	99–102	747	70	110	15
$CH_3(CH_2)_4COCH_3$	148–151	747	75	126–127	15
$(CH_3)_2CHCH_2COCH_3$	114–120	746	36	132–135	15
$(CH_3)_2CH(CH_2)_2COCH_3$	141–142	746	60	142–143	16
$(CH_3)_2CH(CH_2)_3COCH_3$	162–164	746	77	153–154	17
$(CH_3CH_2)_2CHCOCH_3$	135–139	746	45	98–99	18
$(CH_3CH_2CH_2CH_2)_2CHCOCH_3$	104–107	22	64	109[a]	3

[a] Apparently a new compound. Analyzed by method of Veibel, *Bull. soc. chim.*, **41**, 1410 (1917). Calculated for $C_{12}H_{25}ON_3$: $^1/_3$N, 6.16. Found: $^1/_3$N, 6.11.

drops). The solution was titrated with 0.100 *N* hydrochloric acid until the blue color changed to yellow. Since aliquots taken toward the end of the reaction required small volumes of titrating solution, water was added so that approximately equal volumes of ethanol and water were present at the end-points of all titrations.

The structure of alkylation products was confirmed by ketonic hydrolysis. The mono-substituted acetoacetic esters were hydrolyzed with aqueous sodium hydroxide (5%). The esters were first stirred with the alkali (1.5 moles to 1 of ester) for four hours at room temperature, after which the mixture was refluxed for about six hours. The ketones were removed from the cooled solution by ether extraction, the extracts were dried, the solvent was removed and the residue was fractionally distilled. The α,α-disubstituted acetoacetic esters were very resistant to hydrolysis. The following procedure, of many that were tried,[14] gave the best results: a solution of ethyl α,α-dibutylacetoacetate (26 g., 0.107 mole) in methanol (100 ml.) and water (20 ml.) containing potassium hydroxide (8 g., 0.14 mole) was refluxed for four hours. Additional potassium hydroxide (8 g.) and water (10 ml.) were added and the refluxing was continued for eight hours longer. The mixture was distilled from a water-bath, and when 105 ml. of distillate had been removed the residue was transferred to a separatory funnel. Water (25 ml.) was added and the mixture was thoroughly shaken; three layers separated. The lower layer was potassium carbonate solution; the middle layer yielded α-butylcaproic acid (3.7 g.) on acidification; and fractionation of the upper layer gave α,α-dibutylacetone (11.6 g.). The results of the ketonic hydrolyses are summarized in Table II.

(14) The method of Connor and Adkins (THIS JOURNAL, **54**, 3420 (1932)) could not be tried because the equipment was not available. α,α-Dibutylacetoacetic ester was recovered unchanged after it was stirred for six hours at 150–170° with 85% phosphoric acid (Dehn and Jackson, THIS JOURNAL, **55**, 4284 (1933)). Attempts to induce an ester interchange by refluxing α,α-dibutylacetoacetic ester with formic or acetic acid and zinc chloride were unsuccessful.

Summary

1. A procedure is described for the alkylation of acetoacetic esters, by action of potassium *t*-amyloxide in *t*-amyl alcohol and alkyl bromides.

2. The method was found to be advantageous for the preparation of certain α,α-disubstituted acetoacetic esters.

(15) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, New York, N. Y., 1940, p. 221.
(16) Freylon, *Ann. chim.*, (8) **19**, 559 (1910).
(17) Wallach, *Ann.*, **381**, 86 (1911).
(18) Bardan, *Bull. soc. chim.*, **49**, 1875 (1931).

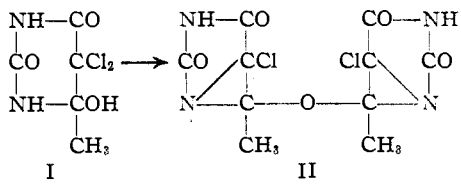
LOS ANGELES, CALIFORNIA
RECEIVED SEPTEMBER 17, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Reactions Characterizing the Oxide of 6-Methyl-6-oxy-5-chloro-1,5-bicyclouracil[1]

BY TREAT B. JOHNSON[2]

The formula adopted to interpret the constitution of the 1,5-bicyclouracil derivative, under discussion in this paper, is expressed graphically in no. II. This cyclo-pyrimidine is produced in excellent yield by digestion of 5,5-dichloro-6-hydroxy-6-methylhydrouracil (I) with concentrated hydrochloric acid.[3]



I II

The specific reactions pertaining to this first representative of a new type of pyrimidine compound, which the author is prepared to discuss at this time, are reported below under the two headings of (a) Reduction and (b) Oxidation Reactions, respectively.

Reduction Reactions

The 1,5-bicyclouracil derivative (II) loses its characteristic bicyclo structure on reduction and reverts to the constitution of a true uracil derivative. Interaction with stannous chloride and hydrochloric acid leads to the quantitative formation of 5-chloro-6-methyluracil, while warming with hydriodic acid and red phosphorus removes

(1) Researches on Pyrimidines. CLXXXI. Experimental work conducted in the Bethwood Research Laboratory, Bethany, Connecticut.

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

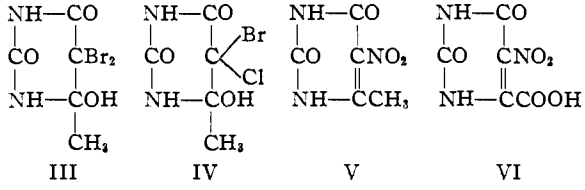
(3) Johnson, THIS JOURNAL, **65**, 1220 (1943).

all halogen from the bicyclo pyrimidine (II) with regeneration of 6-methyluracil. No other reduction products have been identified.[3]

Oxidation Reactions

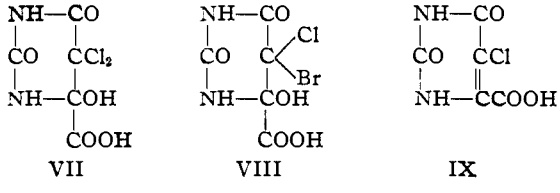
This section is confined to a discussion of the action of three different oxidizing reagents on the 1,5-bicyclouracil compound (II) namely: (a) superoxol and concentrated hydrochloric acid, (b) bromine water, and (c) concentrated nitric acid. Unexpected and characteristic reaction changes were disclosed as a result of this study.

The behavior of 6-methyluracil toward these three oxidizing reagents is well known. Hydrogen peroxide in the presence of hydrochloric acid, and bromine water react quantitatively at ordinary temperature to give 5,5-dichloro-6-hydroxy-6-methylhydrouracil (I),[3,4] and 5,5-dibromo-6-hydroxy-6-methylhydrouracil[5] (III), respectively. With bromine water 5-chloro-6-methyluracil yields 5 - bromo - 5 - chloro - 6 - hydroxy - 6 - methylhydrouracil[5] (IV). In neither case is the methyl group of the respective uracil molecule converted by oxidation to a carboxyl group. Nitric acid is known to react with 6-methyluracil smoothly with formation of 5-nitro-6-methyluracil cil (V), but at elevated temperatures oxidation takes place yielding 5-nitro-6-uracil-carboxylic acid[6] (VI).



III IV V VI

This comparison of differences in chemical behavior on interaction of the 6-methyluracil molecule with these three oxidizing reagents is instructive and interesting, when we consider the action of these same reagents on the 1,5-bicyclouracil derivative (II). In this case the author finds that the 6-methyl group in (II) is oxidized easily by all three reagents with destruction of the bicyclo structure and formation of 5,5-dichloroxyhydroorotic acid (VII), 5-chlor-5-bromoxyhydroorotic acid (VIII) and 5-chloroorotic acid (IX), respectively.



VII VIII IX

5,5-Dichloroxyhydroorotic acid (VII) is reduced quantitatively to 5-chloroorotic acid (IX) by means of hydriodic acid and red phosphorus. It is of special interest to note here that this same hydropyrimidine derivative (VII) is not formed by the action of superoxol and hydrochloric acid directly on orotic acid.[7] The end-product resulting under such experimental conditions is 5-chloroorotic acid (IX).[8]

Experimental Part

The Action of Superoxol and Concentrated Hydrochloric Acid on the Oxide of 6-Methyl-6-oxy-5-chloro-1,5-bicyclouracil. (II)

Formation of 5,5-Dichloroxyhydroorotic Acid (VII).—Five-tenths gram of the finely pulverized pyrimidine compound (II) was exposed to the action of an oxidizing mixture containing 5 ml. of superoxol and concentrated hydrochloric acid, respectively. After standing for five to six days at ordinary temperature a clear liquid was obtained with 0.2 g. of colorless prismatic crystals in suspension. These prisms melted sharply at 182° with violent effervescence. After recrystallization from boiling water it still melted at the same temperature, 182–183° with effervescence. The compound was dried for analysis at 100–110°. *Anal.* Calcd. for 5,5-dichloroxyhydroorotic acid (VII), $C_5H_4O_5N_2Cl_2$: C, 24.69; H, 1.65; N, 11.50. Calcd. for 5,5-dichloro-6-hydroxy-6-methylhydrouracil (I), $C_5H_6O_3N_2Cl_2$: C, 28.12; H, 2.81; N, 13.1. Found: (I) C, 24.67; H, 1.88; N, 11.0. (II) C, 24.55; H, 1.90; N, 11.41.

Reduction of 5,5-Dichloroxyhydroorotic Acid (VII) to 5-Chloroorotic Acid (IX).[9]—Two grams of this pyrimidine (VII) and 0.5 g. of red phosphorus were suspended in 2 ml. of hydriodic acid (sp. gr. 1.5) diluted with an equal volume of water, and the mixture digested at its boiling point for fifteen to twenty minutes. The solution was then diluted with 5 ml. of hot water, filtered and finally evaporated at 100° to a sirupy consistency and cooled.

On adding cold water a colorless crystalline substance separated, which was difficultly soluble in boiling water. When heated in a capillary tube it turned brown at about 255°, shriveled and decomposed with effervescence at 294–296°. This decomposition point varies depending upon the rate of heating. The substance contained chlorine, and did not respond to the characteristic Wheeler and Johnson color test for uracil.[10] This same pyrimidine is formed by the direct action of superoxol and hydrochloric acid on orotic acid.[8] *Anal.* Calcd. for $C_5H_3O_4N_2Cl$: N, 14.68. Found: N, 14.60, 14.62.

The Action of Concentrated Nitric Acid on the Oxide of 6-Methyl-6-oxy-5-chloro-1,5-bicyclouracil (II). Formation of 5-Chloroorotic Acid (IX).—Five-tenths gram of this bicyclo pyrimidine was partially dissolved in 10 ml. of cold, concentrated nitric acid, and the mixture allowed to stand in a stoppered flask at ordinary temperature; red fumes were evolved slowly during a period of six days. After allowing to stand in the laboratory for nearly two weeks, a crystalline deposit of 0.15 g. was filtered off which did not melt or decompose below 280°. This was purified by recrystallization from boiling water and separated in the form of prismatic crystals. These shriveled and turned brown on heating finally decomposing with effervescence when heated above 285°. The compound contained chlorine and was dried for analysis at 100–110°. *Anal.* Calcd. for 5-chloroorotic acid (IX), $C_5H_3O_4N_2Cl$: N, 14.68. Found: N, 14.55, 14.59.

(4) Behrend, *Ann.*, **236**, 22. 59 (1886).

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

(6) Behrend, *Ann.*, **229**, 32 (1885); *ibid.*, **240**, 4 (1887); Kohler, *ibid.*, **236**, 34 (1886).

(7) Biscaro and Belloni, *Chem. Zentr.*, **76**, II, 63 (1905); Wheeler, *Am. Chem. J.*, **38**, 358 (1907); Johnson and Schroeder, THIS JOURNAL, **53**, 1989 (1931).

(8) Johnson, *ibid.*, **65**, 1218 (1943).

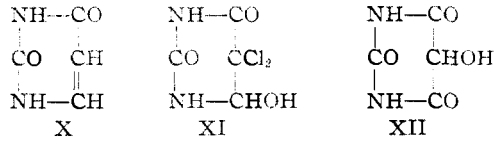
(9) 5-Chlorouracil-4-carboxylic acid.

(10) Wheeler and Johnson, *J. Biol. Chem.*, **3**, 183 (1907); see "Researches on Pyrimidines" (No. 180), by Johnson, *Science*, **98**, 90 (1943) for description of a modification of this color test.

Formation of 5-Chloro-5-bromoxyhydroorotic Acid (VIII).—This acid is formed in excellent yield by the action of bromine water at ordinary temperature on the oxide of 6-methyl-6-oxy-5-chloro-1,5-bicyclouracil (II). The pyrimidine is moderately soluble in hot water and crystallizes in the form of prismatic crystals melting at 192–193°. It was dried for analysis at 100–110°. *Anal.* Calcd. for $C_5H_4O_5N_2BrCl$: N, 9.63. Found: N, 9.63.

The Conversion of 5,5-Dihalogenated-6-hydroxyhydroorotic Acids to Dialuric Acid.—The two new hydroorotic acid derivatives, namely: 5,5-dichloroxyhydroorotic acid (VII) and 5-chloro-5-bromoxyhydroorotic acid (VIII) bear the same structural relationship to orotic acid as 5,5-dichloroxyhydrouracil (XI) does to the uracil molecule (X).

The author now finds that these two hydropyrimidines (VII) and (VIII) cannot be distinguished from 5,5-dichlorhydrouracil (XI) by application of the standard



X XI XII

Wheeler and Johnson color reaction for uracil.[10] By application of their well-known technique the 6-carboxyl groups in the two pyrimidines (VII) and (VIII) are removed by the action of barium hydroxide yielding at once dialuric acid (XII), and its characteristic purple-colored barium salt.

These are the first pyrimidines of the halogenated 6-hydroxyhydrouracil type, so far discovered, which have responded to this characteristic color reaction reported by Wheeler and Johnson as a specific color test for uracil and cytosine.[10]

Summary

1. The oxide of 6-methyl-6-oxy-5-chloro-1,5-bicylouracil is converted smoothly by reduction to a true uracil derivative.

2. The chemical action of three different oxidizing reagents has thus far been studied namely: superoxol and hydrochloric acid, bromine water and nitric acid.

3. The methyl group of this 1,5-bicyclopyrimidine compound is oxidized to carboxyl by the action of all three reagents, with regeneration of the normal pyrimidine structure, yielding characteristic derivatives of hydroorotic acid.

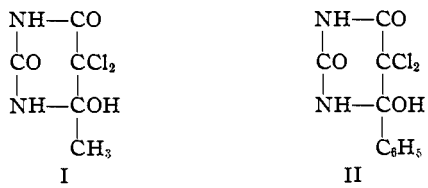
BETHANY, CONNECTICUT RECEIVED JULY 20, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

The Acid Hydrolysis of a 6-Aryl-5,5-dichloroxyhydrouracil[1]

BY TREAT B. JOHNSON[2]

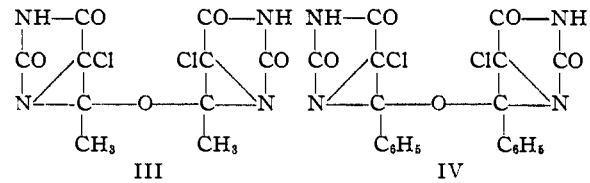
In the light of the results obtained during the previous experimentation on acid hydrolysis of 5,5-dichloro-5-hydroxy-6-methylhydrouracil[3] (I), it became of increased interest to the author to undertake a similar study with the simplest aromatic representative of this heterocyclic pyrimidine series, namely, 5,5-dichloro-6-hydroxy-6-phenylhydrouracil (II). Very little is known about the chemistry of such aromatic pyrimidine compounds as represented by (II).



I II

Judging from the experience of the author in other fields of pyrimidine research, it might be predicted that the study of such aryl derivatives as (II) would disclose further evidence in support of reaction mechanisms that have previously been postulated[3] regarding positions 1-, 5- and 6- in this type of hydrouracil compound. The pyrimidine (II) is easily prepared, without substitution of chlorine in the 6-phenyl group, by the action of superoxol and concentrated hydrochloric acid on 6-phenyluracil.[4] It is much less soluble in water than the corresponding 6-methylpyrimidine compound (I).

It has been shown by the author[3] that the 6-methylpyrimidine (I) undergoes a characteristic change when digested with strong hydrochloric acid yielding the first representative of a new type of pyrimidine compound to which has been assigned the constitution of the oxide of 6-methyl-6-oxy-5-chloro-1,5-bicyclouracil (III). In fact, the 1,5-bicyclouracil structure expressed in this formula (III) is favored by the oxide structure functioning in position 6- of the pyrimidine molecule.



III IV

The author now finds that 5,5-dichloro-6-hydroxy-6-phenylhydrouracil (II) is much less stable, under the influence of strong hydrochloric acid, than its corresponding 6-methyl-analog (I). No evidence has thus far been obtained by the author of the formation of a condensed 1,5-bicyclouracil compound (IV) by digestion of (II) with this mineral acid.

(1) Researches on Pyrimidines, CLXXXII.

(2) Experimental work conducted in the Bethwood Research Laboratory, Bethany, Connecticut.

(3) Johnson, THIS JOURNAL, **65**, 1220 (1943).

(4) Fischer and Roeder, *Ber.*, **34**, 3763 (1901); Wheeler and Merriam, *Am. Chem. J.*, **29**, 490 (1903); Johnson and Hemingway, THIS JOURNAL, **37**, 280 (1915).