[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

THE PREPARATION OF URACIL FROM UREA

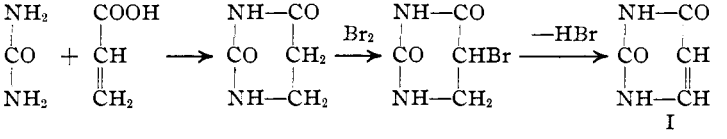
BY DAVID DAVIDSON AND OSKAR BAUDISCH

RECEIVED MAY 27, 1926 PUBLISHED SEPTEMBER 4, 1926

Introduction

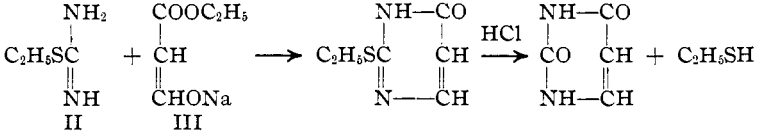
This paper deals with a convenient method of preparation of the pyrimidine uracil I directly from urea.

Uracil was isolated from the hydrolytic products of yeast nucleic acid by Ascoli[1] in 1900. Its wide distribution in plant and animal nucleic acids was demonstrated by the work of several investigators.[2] The discovery of uracil in nature was soon followed by its laboratory synthesis by Fischer and Roeder,[3] as illustrated below. A practical synthesis of uracil was then brought



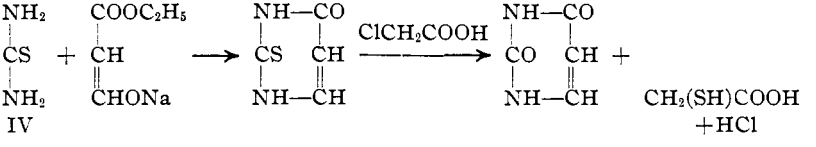
I

forward by Wheeler and Merriam,[4] which involved the following steps.



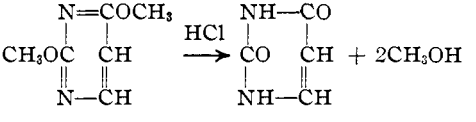
II III

The substitution of thio-urea IV for ethyl pseudo-thio-urea II in this synthesis resulted in the excellent preparative method of Wheeler and Liddle.[5]



IV

Uracil has also been prepared by other workers; thus Gabriel and Colman obtained it by the hydrolysis of 2,4-dimethoxypyrimidine;[6]



[1] Ascoli, *Z. physiol. Chem.*, **31**, 162 (1900).

[2] Osborne and Harris, *Z. physiol. Chem.*, **36**, 107 (1902). Kossel and Steudel, *ibid.*, **37**, 246 (1903). Levene, *ibid.*, **38**, 82 (1903); **39**, 6, 8 (1903). Levene and Stokey, *ibid.*, **41**, 404 (1904). Mandel and Levene, *J. Biol. Chem.*, **1**, 425 (1906). Osborne and Heyl, *Am. J. Physiol.*, **21**, 157 (1908). Levene and Jacobs, *Ber.*, **43**, 3133, 3161 (1910).

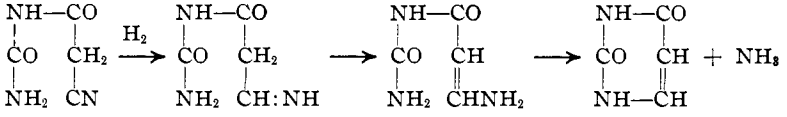
[3] Fischer and Roeder, *Ber.*, **34**, 3761 (1901).

[4] Wheeler and Merriam, *Am. Chem. J.*, **29**, 478 (1903).

[5] Wheeler and Liddle, *ibid.*, **40**, 547 (1908).

[6] Gabriel and Colman, *Ber.*, **36**, 3380 (1903).

while recently Rupe, Metzger and Vogler[7] have isolated it in the reduction of cyano-acetyl-urea.



Previous Attempts to Synthesize Uracil from Urea

Aside from the synthesis of Fischer and Roeder which is *not* a satisfactory method of preparation[8] attempts have been made to prepare uracil directly from urea by Wheeler and Merriam[4] and by Wheeler and Liddle[5] who report unsuccessful efforts to condense urea with sodium formylacetic ester III in alkaline solution. Concerning the condensation in *acid* solution analogous to that used by Behrend[9] in the preparation of 6-methyluracil, Wheeler and Merriam state: "A method similar to that of preparing methyluracil by condensing urea with aceto-acetic ester by means of hydrochloric acid, has not been applied to the preparation of uracil, probably on account of the ease with which free formylacetic ester passes into trimesic ester." This presumption is confirmed by the experience of the present authors.[10]

[7] Rupe, Metzger and Vogler, *Helvetica Chim. Acta*, **8**, 848 (1925).

[8] Fischer and Roeder, Ref. 3, p. 3761, state: "Bei dem keineswegs untergeord neten physiologischen Interesse, welches hiernach das Uracil besitzt, werden wir versuchen, die Synthese zu einer ausgiebigeren Darstellungsweise auszubilden, um eine genauere Untersuchung der Metamorphosen ausführen zu können."

[9] Behrend, *Ann.*, **229**, 5 (1885).

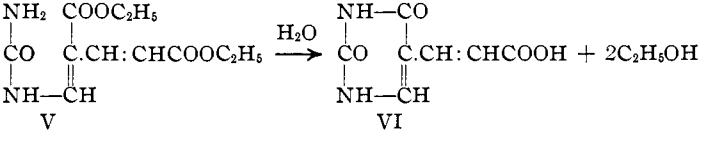
[10] When a solution of two moles of urea and the sodium formylacetic ester from 10 g. of sodium was treated with 150 cc. of concd. hydrochloric acid the solution became turbid and soon deposited a crystalline substance in fine needles. After two recrystallizations from alcohol it melted at 206–208°.

Anal. Calcd. for $C_{11}H_{16}O_5N_2$: C, 51.54; H, 6.30; N, 10.94. Found: C, 51.25; H, 6.34; N, 10.97, 10.83.

Its analysis indicates that it is a condensation product of one molecular proportion of urea with two of formylacetic ester. Its probable structure is that of ureidomethylene glutaconic ester V, and it presumably results from a reaction between urea and formylglutaconic ester which Wislicenus and others have shown to be formed by the acidification of sodium formylacetic ester. [Wislicenus and Bindemann, *Ann.*, **316**, 20, 29 (1901). Wislicenus and von Wrangell, *Ann.*, **381**, 367 (1911).] The product dissolved readily when heated with dilute alkali. Upon acidification crystals separated which decomposed at 285° and had the following composition.

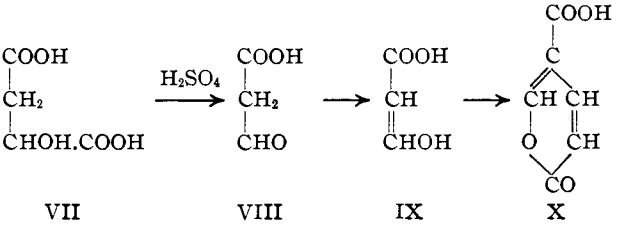
Anal. Calcd. for $C_7H_6O_4N_2$: C, 46.15; H, 3.32; N, 15.39. Found: C, 46.27; H, 3.44; N, 15.25.

These analytical results indicate that the substance is uracil-5-β-acrylic acid VI resulting from the reaction



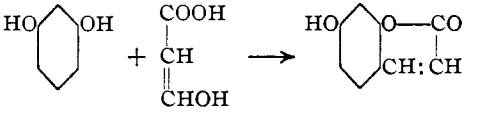
Discussion of the Synthesis

The synthesis dealt with in the present paper is based on a reaction discovered by von Pechmann.[11] Von Pechmann found that, on treatment

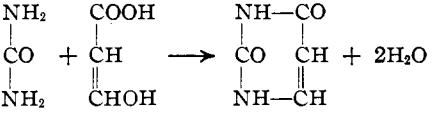


VII VIII IX X

with concd. sulfuric acid, malic acid VII split off formic acid (or CO + H_2O) yielding formylacetic acid (malonic semialdehyde) VIII. The latter product, however, immediately underwent autocondensation reacting in its enol form IX to give cumalinic acid X. Nevertheless, when a phenol was mixed with the malic acid the intermediate oxymethylene acetic acid reacted with the phenol and a coumarin resulted; thus, for example, with resorcinol[12]



It appeared to the authors that by treating a mixture of urea and malic acid with sulfuric acid a reaction might be obtained between urea and the transitory oxymethylene acetic acid.



This expectation has been realized experimentally. By utilizing this reaction excellent yields of uracil of high degree of purity are readily obtainable in the course of several hours. The method eliminates the costly use of thio-urea and avoids the presence of objectionable traces of sulfur in the final product.[13]

The synthesis presented above affords a ready approach to many interesting products. Thus, by nitrating according to Johnson and Matsuo[14]

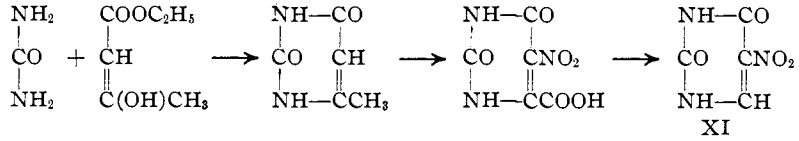
[11] (a) von Pechmann, *Ber.*, **17**, 936 (1884); (b) *Ann.*, **264**, 261 (1891).

[12] Ref. 11 a, p. 932.

[13] It is to be noted that the green color reaction of uracil with sodium aquo-pentacyano-ferroate described by Pfaltz and Baudisch [THIS JOURNAL, **45**, 2973 (1923)] is not obtained with uracil prepared by the new method. Since, however, 2-thio-uracil gives a brilliant emerald-green color reaction with the complex iron salt, the reaction previously obtained is probably ascribable to the presence of sulfur-bearing impurities. The pyrimidines isolated from natural sources also give a green color with sodium aquo-pentacyano-ferroate and likewise are probably contaminated by sulfur compounds.

[14] Johnson and Matsuo, THIS JOURNAL, **41**, 782 (1919).

5-nitro-uracil XI is obtained. This compound has previously been prepared from urea, but in three steps, utilizing aceto-acetic ester.[15]



XI

The new method in two steps, however, offers advantages in convenience and yields.

1,3-Dimethyluracil which has previously been prepared by the action of methyl iodide and potassium hydroxide or potassium uracil in alcoholic solution[16] is readily produced in excellent yield by methylating uracil in aqueous solution with sodium hydroxide and methyl sulfate.

Experimental Part

Preparation of Uracil.—Four hundred cc. of fuming sulfuric acid (15% of SO_3) is placed in a 2-liter round-bottomed flask and chilled to 0° in a freezing mixture. To it is gradually added during efficient mechanical stirring 100 g. of crystalline urea, the temperature being maintained below 10°. This step requires 15–20 minutes. One hundred g. of pulverized commercial malic acid is then added at once and the flask heated on the steam-bath for one hour. During the first 15 minutes large volumes of carbon monoxide are evolved which may be led away and burned. Carbon dioxide and sulfur dioxide are also produced during this operation, at the end of which the flask is cooled and its contents turned into 1200 cc. of water. On cooling, crude uracil separates. This is filtered off, washed with water (best by suspending in water and again filtering) and then recrystallized from 1250 cc. of boiling water with the aid of 10 g. of Darco charcoal. The product separates in snow-white needles which are dried at 100°; yield, 42–46 g., or 50–55%.

Anal. Calcd. for $C_4H_4O_2N_2$: C, 42.84; H, 3.60; N, 25.01. Found: C, 42.72; H, 3.69; N, 25.00.

Methylation of Uracil.—Twenty g. of uracil is dissolved in a solution of 17 g. of sodium hydroxide in 100 cc. of water. The solution is cooled in ice water while 40 cc. of methyl sulfate is gradually added during mechanical stirring. The mixture is then heated to boiling, cooled and extracted thrice with 100cc. portions of chloroform. The chloroform extract is filtered through a dry filter and evaporated, yielding 23.5 g. of 1,3-dimethyluracil melting at 123–124°; yield, 94%.

Anal. Calcd. for $C_6H_8O_2N_2$: N, 20.00. Found: 20.03.

The product may be recrystallized by dissolving in hot alcohol, cooling and adding an equal volume of ether.

[15] Behrend and Roosen, *Ann.*, **251**, 239 (1889). Biltz and Heyn, *Ann.*, **413**, 110 (1916).

[16] Johnson and Clapp, *J. Biol. Chem.*, **5**, 61 (1908).

Summary

An improved method for the synthesis of uracil is described.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

LECTURE EXPERIMENTS WITH THE NEW HALOGENOID, AZIDO-CARBONDISULFIDE

BY A. W. BROWNE AND R. S. VON HAZMBURG

RECEIVED JUNE 7, 1926 PUBLISHED SEPTEMBER 4, 1926

The surprising reactivity of azido-carbondisulfide toward various groups of substances, including acids, alkalies, oxidizing and reducing agents, and its susceptibility to autocatalytic decomposition even at ordinary temperatures, render available a series of instructive experiments suitable for use in lecture-table demonstration. Azido-carbondisulfide, itself a halogenoid, may be considered to contain potentially within its molecular structure three other halogenoids: $(SCN)_2$, $(CN)_2$ and $(N_3)_2$. Of these, thiocyanogen is evolved in the free state during thermal decomposition of the mother substance.

The experiments described in the present article are fairly representative of the large number that have been performed repeatedly by the authors at this University and elsewhere.

1. Demonstration of the Halogenoid Character of Azido-carbondisulfide.—(a) Like the halogens, azido-carbondisulfide reacts with aqueous solutions of potassium, sodium or ammonium hydroxide, yielding salts of the oxy-acid and hydracid corresponding, for example, to hypochlorous and hydrochloric acids. By acidification of the resulting solution, a reprecipitation of the white, crystalline halogenoid is effected.

Drop 0.5 g. of freshly prepared,[1] slightly moist azido-carbondisulfide into 100 cc. of approximately 1 *N* sodium hydroxide solution, either in a large test-tube or small cylinder, at ordinary or, better, at somewhat lower temperature. Acidify the yellow-green solution by gradual addition of 25–50 cc. of dilute (approximately 6 *N*) sulfuric acid. The precipitate may be identified by testing its behavior toward heat as outlined under Section 3.

(b) Despite its very limited solubility in water, azido-carbondisulfide is capable of discharging the iodide ion in aqueous solution to an appreciable extent, although the reaction normally proceeds in the opposite direction, as illustrated in the current method of preparing the halogenoid. In any case the equilibrium concentration of free iodine is sufficiently high to enable its detection by the usual test.

Introduce 0.5 g. of solid azido-carbondisulfide into 1 liter of a 1% aqueous

[1] Browne, Hoel, Smith and Swezey, THIS JOURNAL, **45**, 2541 (1923).