

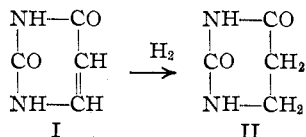
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

STUDIES ON CATALYSIS. III.¹ THE REDUCTION OF URACIL TO HYDRO-URACIL

BY ELMER B. BROWN AND TREAT B. JOHNSON

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In a preliminary paper^{1a} the writers have reported a new method of reducing the pyrimidine, uracil (I). They have applied Skita's method of catalytic reduction and have shown that this substance is reduced quantitatively with hydrogen to hydro-uracil (II) in the presence of colloidal platinum or palladium. In this paper, which is a report of their experimental work on this compound, the writers have extended their study of this catalytic reduction process, using uracil in order to establish the limiting conditions under which the reduction process in the presence of colloidal platinum or palladium can be carried out when applied to the



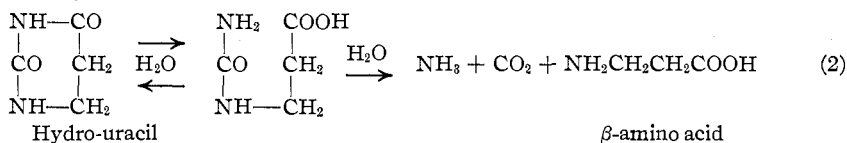
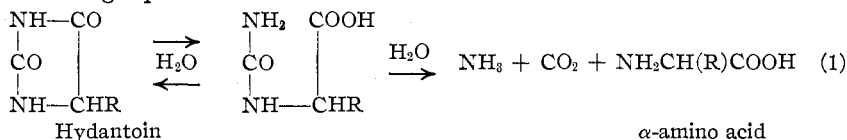
pyrimidine series. In the experimental part of the paper are recorded the results of our experiments showing the influence on the progress of the reduction of different foreign substances that are commonly met as impurities in the naturally occurring products containing the pyrimidines, thymine, cytosine and uracil. Sulfur compounds, which are of very common occurrence in nature and are often found as impurities in the solutions obtained in the isolation of the pyrimidines from that source, as well as in our synthetic methods of preparation, are shown to prevent reduction completely when present even in traces. The effect of the presence of thiopyrimidines and other sulfur combinations on the reduction process is similar to the results obtained by Willstätter and Hatt,² who found that traces of thiophene, for example, completely stopped the hydrogenation of benzene when platinum black was used as catalyst. The chlorides of sodium, potassium, calcium and magnesium exert no influence upon the reduction process in the case of uracil.

The reduction of uracil to hydro-uracil proceeds quantitatively when carried out under the conditions described in this paper and, so far as the writers are aware, no other method of bringing about this change successfully is available. Electrolytic reduction methods have been applied with success in the barbituric acid series, and hydro-uracil has been prepared, for example, by electrolytic reduction in acid solution of several

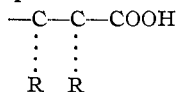
¹ Previous publications: (a) Johnson and Brown, *Proc. Nat. Acad. Sci.*, **7**, 75 (1921); (b) Gilfillan, *THIS JOURNAL*, **44**, 1323 (1922).

² Willstätter and Hatt, *Ber.*, **45**, 1471 (1912).

pyrimidines, namely, barbituric acid, dialuric acid, uramil and alloxan, but secondary products were always formed in these operations, and the yield of hydro-uracil was generally very low.³ In fact, it has been shown that hydro-uracil can be reduced still further with formation of trimethylene-urea. The reduction of uracil to this substance can probably be accomplished by our method but apparently with great difficulty only, and at present conditions have not been established whereby it has been possible to obtain this cycle in satisfactory yields for synthetic work. The fact that uracil can be reduced so easily to hydro-uracil is of special interest to us from a biochemical point of view. If the catalytic method of reduction can be shown to be one of general application in the uracil series we will have opened up a method of synthesizing β -amino acids which will prove of great practical interest. These reduced pyrimidines bear a similar relationship to β -amino acids that the hydantoins do to α -amino acids, and on hydrolysis with acids or bases are susceptible to the same hydrolytic change. This relationship is revealed by examination of the following equations.



Process 2 offers greater possibilities for amino acid synthesis than the hydantoin method which has been developed so extensively in the Yale Laboratories, because two carbon atoms are available to which substituent groups or radicals may be attached. Having available the proper uracil derivative, and an easy practical method of reduction at the double



bond in Positions 3 and 4, it will be possible to synthesize by our method several β -amino acids which are unknown, and are not easily obtained by the present methods of synthesis at our command. This investigation is being continued in the Sterling Chemistry Laboratory.

Experimental Part

Purification of Uracil.—The pyrimidine used in this research was prepared by students in the laboratory by application of the thio-urea method and was of a fair degree

³ Tafel and Weinschank, *Ber.*, **33**, 3385 (1900). Tafel and Reindl, *ibid.*, **34**, 3286 (1901).

of purity, although not of sufficient purity to permit its use in our catalytic reduction work. One hundred g. of uracil was repeatedly recrystallized from water, using Norite to remove all coloring material, when a product was easily obtained which failed to respond to the sulfur test and was apparently free from this impurity. However, in order to remove the minutest trace of sulfur impurities, 50 g. of the product described above was further purified by refluxing for 3 hours with a 2% solution of monochloro-acetic acid and then recrystallizing twice from water. In this manner we obtained a colorless sulfur-free product which caused no difficulty in our reduction operations.

The Reduction of Uracil to Hydro-uracil.—Six g. of pure uracil is placed in the reduction flask, and to this 2 g. of gum arabic dissolved in 50 cc. of hot water, 10 cc. of 10% chloroplatinic acid solution and 150 cc. of water is added. The reduction flask is then placed in position in an electric heater on a shaking machine and connected with a cylinder of hydrogen. After removal of the air from the reduction flask hydrogen is introduced until a pressure of two atmospheres is obtained, the shaking machine is then started and the electric current turned on.⁴ Within a short time the solution turns black and there is very rapid absorption of hydrogen and the formation of colloidal platinum. The temperature is soon increased to 75°, and maintained at that point by proper regulation of the electric current. The calculated amount of hydrogen is absorbed in 5 to 7 hours, and the absorption ceases under the above conditions when one molecular equivalent of hydrogen has been taken up.

The reduction solution is now poured into an equal volume of acetone and the precipitated colloid allowed to settle. Usually one hour suffices for complete separation of the colloid, leaving a clear solution which is easily filtered. The acetone is distilled and can be used for the same purpose again without further purification. The aqueous filtrate is evaporated to a small volume on the water-bath and allowed to cool. A beautiful white crystalline product quickly deposits, weighing from 5.6 to 5.8 g., depending on the volume of the solution. When recrystallized from water this separates in the form of large, transparent, 4-sided plates and melts at 272–274°, the correct melting point of hydro-uracil.

Analysis. Calc. for $C_4H_6O_2N_2$: N, 24.56. Found (Kjeldahl): 24.69.

The calculated quantity of hydro-uracil is never obtained in these reductions; this is due to the fact that the gum arabic is partially decomposed during the evaporation of the hydrochloric acid solution giving a sirup which always retains a small amount of pyrimidine that cannot be recovered. That the reduction, however, is quantitative is shown by the application of Wheeler and Johnson's color test to the reduction solution. When 3 cc. of the solution, corresponding to 0.09 g. of pyrimidine, is added to an equal volume of acetone to remove the platinum, and the color test is then applied no purple condensation product is obtained, showing the absence of unreduced product. One mg. of uracil gives a decided bluish-pink or lavender color within a short time when subjected to a similar treatment.

The Colloid Support.—In order to study the effect of various amounts of gum arabic on the progress of the reduction of uracil to hydro-uracil a series of experiments was performed using in each case 3 g. of uracil,

Gum arabic, g.....	0.2	0.5	1.0	2.0	5.0
H ₂ absorbed, cm.....	21.2	24.5	23.3	22.4	17.3
(1 cm. equals 26 cc. of hydrogen under standard conditions.)					

⁴ A special equipment was constructed for our work whereby several experiments can be run independently at the same time.

100 cc. of water, 10 cc. of 10% chloroplatinic acid and various amounts of gum arabic. The time of each run was 7 hours and 40 minutes.

In each of the above experiments the platinum remained in the colloidal state throughout the operations and the results show that the rate of absorption of hydrogen is not materially affected by the quantity of gum arabic used. Rideal⁵ states that there is an optimum amount of gum arabic for each catalyst, corresponding to about 4 mg. per 10 mg. of platinum, and that amounts in excess of this tend to retard the rate of absorption of hydrogen. He arrived at this conclusion from results obtained during the study of the reduction of the propiolic acid. Our results show that concentrations of gum arabic 25 times as great as those that retarded or stopped the reduction of propiolic acid exerted very little, if any, influence on the reduction of uracil to hydro-uracil, and that such an optimum does not exist in the case of this pyrimidine.

Several experiments were made in an effort to substitute pepsin and trypsin for gum arabic as colloid supports in the reduction of uracil to hydro-uracil. For example, 3 g. of uracil, 0.5 gm. pepsin, 100 cc. of water and 5 cc. of chloroplatinic acid were used in one experiment. During 2 hours and 15 minutes an absorption of 1 cm. (26 cc.) had taken place. The platinum had separated and fallen to the bottom of the flask, so 3 cc. more chloroplatinic acid was added and during the next 2 hours and 40 minutes an absorption of 5.3 cm. (138 cc.) was obtained, making a total of 6.3 cm. Gum arabic was then added with more chloroplatinic acid and the reduction completed. The absorption was much slower than usual, showing that pepsin probably exerts an anticatalytic effect. When this experiment was duplicated, using gum arabic as colloid support, an absorption of 23 cm. was obtained in the same length of time, using only 5 cc. of chloroplatinic acid as catalyst.

In a similar experiment using trypsin as colloid support an absorption of 9.6 cm. was obtained during a run of 7 $\frac{1}{2}$ hours, with 5 cc. of chloroplatinic acid, at the end of which time the platinum had completely separated. Gum arabic and 2 cc. more of chloroplatinic acid were then added and the reduction carried to completion. The reduction proceeded normally after the addition of the gum arabic, showing that the trypsin had no anticatalytic effect, as was observed in the case of pepsin.

Effect of Temperature and Shaking on the Rate of Absorption of Hydrogen.—Three g. of uracil, 0.5 g. of gum arabic, 100 cc. of water and 5 cc. of 10% chloroplatinic acid were placed in the reduction flask and the reduction started as in previous experiments. During one hour and 40 minutes 75 cc. of hydrogen was absorbed, which corresponds practically to the quantity necessary for the reduction of the platonic acid to colloidal platinum. No further absorption took place at ordinary temperature.

⁵ Rideal, *THIS JOURNAL*, **42**, 749 (1920).

An increase in temperature caused an immediate increase in absorption of hydrogen, and at 75° the rate was normal and continuous until 600 cc. of hydrogen gas was taken up. In other words, the rate of reduction is increased by rise in temperature. Furthermore, it is not necessary to increase the proportions of the catalyst to produce this effect.

The rate of hydrogen absorption is also influenced greatly by the intensity of agitation or shaking. In an experiment in which the motion of the reduction flask was controlled by means of lights placed in the armature circuit of the motor so as to produce a moderate or a rapid vibration of the reduction flask, it was observed that the rate of absorption could be increased 100% by intense agitation. Within 45 minutes an absorption of 175 cc. of gas was obtained when a 60-watt lamp was introduced into the armature circuit, while 405 cc. of hydrogen was absorbed in the same period of time when this light was replaced with a 100-watt lamp. Using the same proportions of reagents as above, it was found that by rapidly shaking the mixture it was possible to bring about an absorption of the calculated volume of hydrogen (600 cc.) in 1.5 hours at 75°.

Effect of Chlorides of Sodium, Potassium, Calcium and Magnesium, and of Sulfur Compounds on the Reduction of Uracil.—In a series of experiments using 3 g. of uracil, 1 g. of gum arabic, 100 cc. of water, 10 cc. of 10% chloroplatinic acid and 1 g. each of sodium, potassium, calcium and magnesium chlorides it was observed that these chlorides exerted no influence on the progress of the reduction of uracil to hydro-uracil. The reduction in each case was complete and the calculated amount of hydrogen was absorbed in the same time required for the reduction of uracil in the absence of the above salts. From 2.6 to 2.9 g. of hydro-uracil was isolated from each experiment, showing that the presence of the salts adds no difficulties in the isolation of the hydro-uracil.

In an experiment in which a sample of uracil was used containing enough thio-uracil to be detected by the nitroprusside test, an absorption of hydrogen equal to the amount required for the reduction of the chloroplatinic acid was obtained, showing that sulfur even in such small amounts completely prevents the reduction. This same sample after purification to remove sulfur (negative nitroprusside test) and repeated recrystallizations from water could then be reduced, but it required twice the platinum concentration for reduction that it did after further purification by boiling with monochloro-acetic acid which insures the complete removal of the sulfur. In an attempt to reduce pure thio-uracil a colloidal solution of the platinum was not obtained during 7 hours' treatment, using the same conditions as described above. No reduction was obtained when the platinum was first reduced to the colloidal state and the thio-uracil then added, even with much larger concentrations of platinum.

Effect of the Addition of Catalyst in Portions on the Reduction of Uracil

Containing Traces of Sulfur.—The following experiments were made on a sample of uracil containing traces of thio-uracil; in each experiment 6 g. of uracil, 2 g. of gum arabic and 200 cc. of water were used and the chloroplatinic acid was added as described below; otherwise the conditions of the experiments were the same as in the preceding reductions. With 12 cc. of chloroplatinic acid an absorption of 300 cc. of hydrogen was obtained in 2 hours, at the end of which time the absorption had practically ceased, so 10 cc. more of chloroplatinic acid was added. During the next 5 hours 900 cc. of hydrogen was absorbed, bringing the total to 1200 cc., the calculated amount required for complete reduction of the pyrimidine. In another experiment, after the addition of 22 cc. of chloroplatinic acid at first the reduction proceeded for 5 hours before coming to a standstill and 650 cc. of hydrogen was absorbed. Five cc. more of chloroplatinic acid carried the reduction to the end in 4 hours in which time 550 cc. of hydrogen was absorbed. A total of 27 cc. of chloroplatinic acid was required for the complete reduction. In another experiment in which the chloroplatinic acid was added in portions of 5, 7, 5 and 3 cc. the final absorptions were 40, 380, 500 and 320 cc. of hydrogen, respectively. Only 20 cc. of chloroplatinic acid was required for complete reduction. When this was added in portions of 12, 5 and 3 cc., the corresponding absorptions were 240, 650 and 350 cc. during $1\frac{3}{4}$, 4 and $2\frac{1}{2}$ hours, respectively. From each of the above experiments hydro-uracil was isolated in amounts varying from 5.6 g. to 5.9 g., showing that the reduction proceeded to completion in each case. These experiments show that better reduction is obtained when the catalyst is added in portions to compounds containing small amounts of "poisons" than all at the same time.

The Influence of the Solvent on the Reduction of Uracil in the Presence of Colloidal Platinum and Palladium.—The solubility of uracil in the different solvents is, as a rule, so small that only a few solvents are suitable for the reduction work. This is especially true of the organic liquids in which uracil is practically insoluble. The best solvent for uracil is water, in which the solubility is not appreciably affected by the presence of acids, but is greatly increased by alkalis; hence a study of the reduction process in alkaline solution, if successful, would add greatly to the production of hydro-uracil in quantity.

A number of experiments were carried out in alkaline solution in an effort to reduce this pyrimidine, and in none was there any evidence of the absorption of hydrogen after the amount necessary for the reduction of the chloroplatinic acid or palladium chloride used as the catalyst, in runs varying from one to three days, using the conditions employed in the preceding experiments.

In experiments carried out with glacial acetic acid, as well as dilute acetic acid of different strengths as solvents, it was shown that this medium is

equally good but no better than water for the reduction of uracil. Various strengths of hydrochloric acid when added to the reduction solution produced no effect on the reduction. Of course, in each of the experiments except those carried out in alkaline solution some hydrochloric acid was present resulting from the reduction of the chloroplatinic acid.

Experiments carried out under identical conditions showed that the reduction proceeded more rapidly with colloidal platinum than with colloidal palladium when equal weights of the two materials were used; however, the differences were never large and both are applicable for the reduction of uracil to hydro-uracil.

Summary

1. Uracil is converted quantitatively into hydro-uracil (β -lactylurea) by treatment with hydrogen in the presence of colloidal platinum or palladium.

2. Since hydro-uracil has been shown to undergo hydrolysis smoothly to β -alanine⁶ our method of reduction, therefore, offers an easy and practical method of converting uracil directly into β -alanine. From a biochemical point of view this result is one of especial interest and importance.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF WASHINGTON]

BETA-PHENOXYPROPIONIC ACID AND SOME OF ITS DERIVATIVES. CHROMANONE

BY S. G. POWELL

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In the course of an investigation of certain unsaturated phenyl ethers, which is to be reported later, a considerable quantity of β -phenoxypropionic acid was required. The only method then available for the preparation of this compound was that of Bischoff¹ which depends upon the action of sodium phenoxide on sodium β -iodopropionate. Unfortunately, the latter is difficult to obtain; moreover, the yield of β -phenoxypropionic acid under the most favorable conditions is only 20%. This paper describes a convenient method for obtaining this acid from the corresponding alcohol.

In preparing some derivatives of the acid, an attempt to purify a sample of β -phenoxypropionyl chloride by distillation resulted in the isolation of the hitherto unknown chromanone. This compound and some of its derivatives are also described.

⁶ Weidel and Roithner, *Monatsh.*, 17, 183 (1886). Lengfeld and Stieglitz, *Am. Chem. J.*, 15, 221, 517 (1893).

¹ Bischoff, *Ber.*, 33, 928 (1900).