vacuum desiccator; its melting point was then 144–200° with decomposition. Crystallization from absolute alcohol gave colorless needles which on repeated recrystallization had a constant melting point of 108–113° with bubbling decomposition and slight preliminary softening about 104°. Analyses indicated either one or one and a half molecules of alcohol of crystallization:

	C, %	H, %	N, %	S, %
Found[a]	53.6	5.6	8.4	9.0
Calcd. for $C_{13}H_{12}O_4N_2S + C_2H_5OH$	53.3	5.3	8.3	9.5
Calcd. for $C_{13}H_{12}O_4N_2S + 1.5$ C_2H_5OH	53.3	5.8	7.8	8.9

[a] After drying in a vacuum pistol over boiling alcohol.

A neutral equivalent determined by alkali titration to phenolphthalein end-point was 363.7, 363.3. A potentiometric titration with a saturated calomel electrode and a hydrogen reference electrode gave a value of 354 for the molecular weight.[17] The theoretical mol. wt. for $C_{13}H_{12}O_4N_2S + C_2H_6O$ is 338; for $C_{13}H_{12}O_4N_2S + 1.5\ C_2H_6O$ it is 361. It was thus assumed that the compound crystallized with 1.5 mols of ethyl alcohol.

Compound no. 5 had a melting point of 238° with slight decomposition when precipitated from alkaline solution by neutralization. Recrystallization of this sample from cellosolve[18]–water lowered the melting point to 222–224° with decomposition. Reprecipitation from alkaline solution raised the melting point again, and both samples gave the same analytical values for carbon, hydrogen and nitrogen.

(17) The titrations were carried out by Dr. Paul H. Bell and Mr. James W. Clapp in these Laboratories.

Summary

A series of sulfones related to 4,4′-diaminodiphenylsulfone have been synthesized in endeavoring to reduce the toxicity and retain the chemotherapeutic activity of the parent compound. The preparation and properties of these sulfones is described.

Two of the new sulfones, namely, 2-sulfamyl-4,4′-diaminodiphenylsulfone and 4-aminophenyl-5′-amino-2′-pyridylsulfone, were highly active against experimental streptococcal and pneumococcal infections in mice, and were much less toxic than 4,4′-diaminodiphenylsulfone.

The relationship between molecular structure and chemotherapeutic activity in the sulfone series as compared with the corresponding sulfonamides is discussed.

(18) Ethylene glycol monoethyl ether, see ref. 15.

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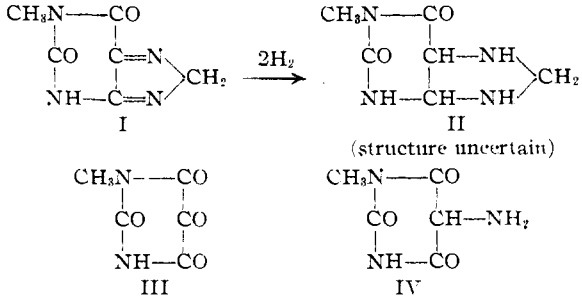
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Researches on Pyrimidines. CLXXII. The Hydrogenolysis of 4-Imidobarbituric Acid[1,2]

BY JOSEPH C. AMBELANG[3] AND TREAT B. JOHNSON

In his original investigations of the structure of *toxoflavine* I,[4] van Veen hydrogenated the natural product to an unstable tetrahydro compound II. This reduction product, on treatment with dilute hydrochloric acid was reported to yield methyl alloxan III and methyluramil IV.

With the assumption that the cyclic structure confers a degree of hydrogenolytic stability on the tetrahydro compound II, the formation of methylalloxan and methyluramil can be attributed to secondary reactions after removal of the reduction product II from the hydrogenating conditions, *viz.*, hydrolysis and atmospheric oxidation.



I II (structure uncertain) III IV

Without this assumption it is difficult in the authors' opinion to account for these products on the basis of the structure assigned to *toxoflavine* I by van Veen.[4]

Catalytic hydrogenation of cyclic compounds of this type or of purines has not, to the authors' knowledge, been reported previously. Catalytic hydrogenation of 2,6-diketopyrimidines has led to derivatives of hydrouracil.[5] Electrolytic re-

(1) The support of the Rockefeller Foundation of New York in this work is gratefully acknowledged. For Researches on Pyrimidines CLXXI, see THIS JOURNAL, **63**, 1289 (1941).

(2) Presented in part before the Organic Division of the American Chemical Society, Cincinnati, Ohio, April 10, 1940.

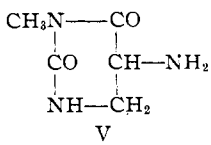
(3) Sterling Professorship of Chemistry Research Assistant, 1939–1940. Present address, D'Youville College, Buffalo, New York.

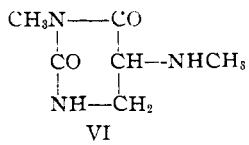
(4) Van Veen and Baars, *Rec. trav. chim.*, **57**, 248 (1938); *Proc. Koninkl. Akad. Wetenschappen Amsterdam*, **40**, 498 (1937).

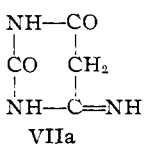
(5) Brown and Johnson, THIS JOURNAL, **45**, 2702 (1923).

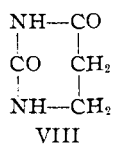
duction of uric acid results apparently in the same type of compound.[6] Assuming the structure I to be correct, the authors are inclined to predict that the hydrouracil V or possibly VI would result from the hydrogenation of *toxoflavine*.

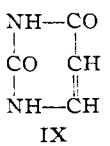
Attempted catalytic hydrogenation of xanthines having been unsuccessful,[7] investigation of related pyrimidines was next considered. The simplest 2,6-diketopyrimidine having a nitrogen atom attached at position-4 is 4-imidobarbituric acid, VIIa or VIIb. In accordance with the above prediction the authors expected hydrouracil VIII to be the product of catalytic hydrogenation of this pyrimidine.

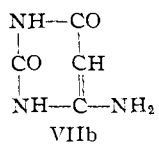

V


VI


VIIa


VIII


IX


VIIb

Hydrogenation of 4-imidobarbituric acid was attempted with Adams catalyst first in glacial acetic acid, the solvent used by van Veen in his studies on *toxoflavine*. No evidence of hydrogenation could be detected either in this solvent or in water at room temperature. In water at 75° the 4-imidobarbituric acid was slowly hydrogenated to uracil IX. Since, in the presence of acid but under otherwise similar conditions, uracil is reduced to hydrouracil,[5] the authors regard their predictions in this case to have been substantially verified. In the compound studied, the C to N bond in position 4 has been shown to undergo hydrogenolysis. Since the bond is stable in neutral and basic aqueous solutions, no other explanation of the results appears reasonable.

In so far as the authors are aware, this is the first reported direct transition from a barbituric acid derivative to a true uracil structure. It may represent one of the mechanisms involved in the preparation of uracil from cyanoacetylurea,[8] and of thymine from methyl cyanoacetylurea[9] by the action of hydrogen and platinum in water at 70°. In this connection it might be pointed out that cyanoacetylurea has been cyclized by water at 120°.[10]

(6) Tafel, *Ber.*, **34**, 1181 (1901).
(7) Johnson and Ambelang, *Science*, **90**, 68 (1939).

Experimental Part

Catalytic Hydrogenation of 4-Imidobarbituric Acid.—Two grams of 4-imidobarbituric acid was dissolved in 230 ml. of hot water, and 0.1 g. of Adams catalyst was added. At a temperature of about 80° the suspension was subjected to a pressure of 2.5 atmospheres of hydrogen and shaken for eight hours. After removal of the catalyst the solution was concentrated to 40 ml. volume, cooled, and filtered. The residue which weighed 0.8 g. did not respond to the Wheeler and Johnson color test[11] for uracil, and when dried was found to contain 32% of nitrogen. The relatively low solubility and high nitrogen content indicated it to be a mixture, largely unchanged 4-imidobarbituric acid.

The filtrate was evaporated to dryness, 0.75 g. of residue being obtained. This solid, which showed a strong Wheeler–Johnson color test,[11] was recrystallized from hot water. The material separating gave a strong Wheeler-Johnson test[11] and more of the same product was obtained from the filtrate after concentration. After drying at 117° both fractions showed the same content of nitrogen. *Anal.* Calcd. for $C_4H_4O_2N_2$: N, 25.00. Found: N, I, 25.6; II, 25.3.

Since the percentage of nitrogen was high for uracil, unchanged 4-imidobarbituric acid was assumed to be present as an impurity. Since both fractions had nearly the same composition, purification by crystallization did not seem practicable. Accordingly, the identification of uracil was checked by conversion to the following known hexahydro derivative.

2,4-Diketo-5,5-dichloro-2-ethoxyhexahydropyrimidine.—0.32 g. of the substance was chlorinated in absolute ethanol according to the directions of Johnson and Sprague.[12] Of the recrystallized product 0.2 g. was obtained, melting at 230° with effervescence and blackening. *Anal.* Calcd. for $C_6H_8O_3N_2Cl_2$: N, 12.34. Found: N, 12.5.

Summary

1. 4-Imidobarbituric acid in aqueous solution in the presence of Adams catalyst undergoes hydrogenolysis to uracil.

2. The significance of this reaction in the study of the structure of *toxoflavine* has been discussed.

NEW HAVEN, CONNECTICUT RECEIVED MARCH 17, 1941

(8) Rupe, *Helv. Chim. Acta*, **8**, 850 (1928).
(9) Bergmann and Johnson, THIS JOURNAL, **55**, 1733 (1933).
(10) Wood and Anderson, *J. Chem. Soc.*, 981 (1903).
(11) Wheeler and Johnson, *J. Biol. Chem.*, **3**, 183 (1907).
(12) Johnson and Sprague, THIS JOURNAL, **59**, 2436 (1937).