methylaniline, and increasing the temperature to about 165°, we could obtain yields of 35% of 3-amino-2,5-dimethylpyrazine.

This amine was condensed with N-acetylsulfanilyl chloride in the presence of dry pyridine to yield 3-(N^4-acetylsulfanilamido)-2,5-dimethylpyrazine. This compound was hydrolyzed and recrystallized first from ethanol and then from water, m. p. 227–228° (cor.). Its chemotherapeutic action is being investigated.

Experimental

3-Amino-2,5-dimethylpyrazine.—7.2 grams of 2,5-dimethylpyrazine was dissolved in 17 cc. of dimethylaniline, 11 g. of sodium amide was added and the reaction mixture heated to 165° in an oil-bath for two hours. The reaction mixture was poured upon 100 g. of ice, the solution saturated with potassium carbonate and extracted with ether. After the ether extract was dried with anhydrous potassium carbonate, the ether was removed by distillation. The residue was distilled under reduced pressure and 2.9 g. of 3-amino-2,5-dimethylpyrazine, b. p. 119–122° at 10 mm., was obtained (35%). The 3-amino-2,5-dimethylpyrazine was recrystallized from benzene; m. p. 111–112° (Tsch. 111°), m. p. of picrate 205° (Tsch. 205°).

3-(N^4-Acetylsulfanilamido)-2,5-dimethylpyrazine.—To 1.057 g. (1 mol) of 3-amino-2,5-dimethylpyrazine dissolved in 2.2 cc. of dry pyridine there was added gradually 2.068 g. (1.02 mol) of N-acetylsulfanilyl chloride, the temperature being kept below 50°. The reaction mixture was then heated on a steam-bath for one hour. A solution of 0.368 g. (1.1 mols) of sodium hydroxide in 1.75 cc. of water was added slowly and the heating continued for two to three minutes. The solution was cooled, 10 cc. of water added, and the pyridine was removed under reduced pressure, water being added to maintain the volume. Crude 3-(N^4-acetyl sulfanilamido)-2,5-dimethylpyrazine separated as a yellow solid; filtered and recrystallized twice from water, m. p. 238–239°, yield 1.6 g. (57%).

3-Sulfanilamido-2,5-dimethylpyrazine.—1.128 grams (1 mol) of 3-(N^4-acetyl sulfanilamido)-2,5-dimethylpyrazine and 1.75 cc. of 6*N* hydrochloric acid (3 mols) were mixed together to form a paste which was then heated slowly to 100° and held at this temp. for eight to ten minutes, during which time the paste slowly became a clear red liquid. The solution was poured upon 10 g. of cracked ice, and clarified by stirring ten minutes in the cold with activated carbon. The yellow solution was carefully neutralized to *p*H 6 with 10% sodium hydroxide solution and the yellow precipitate filtered off and recrystallized once from ethanol and twice from water, yield 0.9 g. (92%), m. p. 227–228° (cor.).

Anal. Calcd. for $C_{12}H_{14}O_2N_4S$: C, 51.76; H, 5.07; N, 20.14. Found: C, 51.93; H, 5.28; N, 20.18.

A qualitative test for the free amino group by the method of E. K. Marshall[3] was positive.

Summary

1. 3-Amino-2,5-dimethylpyrazine was prepared in yields of 35%.

2. 3-Sulfanilamido-2,5-dimethylpyrazine was prepared.

(3) E. K. Marshall, *J. Biol. Chem.*, **122**, 263 (1936).

BROOKLYN, N. Y. RECEIVED APRIL 24, 1941

[CONTRIBUTION FROM THE STAMFORD RESEARCH LABORATORIES OF THE AMERICAN CYANAMID COMPANY]

Studies in Chemotherapy. III. Sulfones[1]

BY RICHARD O. ROBLIN, JR., JAMES H. WILLIAMS AND GEORGE W. ANDERSON

In 1937 Buttle, Fourneau[2] and their co-workers reported a high degree of chemotherapeutic activity for 4,4′-diaminodiphenylsulfone and, to a lesser extent, its diacetyl derivative.[3] Since that time several other groups of investigators[4] have confirmed the original reports. From the results of all these investigations it may be concluded that 4,4′-diaminodiphenylsulfone, while it is too toxic to be of much practical value, is probably the most active of all the bacterial chemotherapeutic agents which have been studied up to the present time. In spite of this high degree of activity, relatively few attempts have been made to reduce the toxicity of this compound. Moreover, those cases in which this result was accomplished[5] involved the formation of acyl or Schiff base derivatives which were probably broken down slowly *in vivo* to liberate 4,4′-diaminodiphenylsulfone before they became therapeutically active.

This paper describes the preparation and properties of a series of sulfones many of which are

(1) Presented in part before the Division of Medicinal Chemistry, St. Louis meeting of the American Chemical Society, April 10, 1941.

(2) Buttle, Stephenson, Smith, Dewing and Foster, *Lancet*, **232I**, 1331 (1937); Fourneau, Tréfouël, Tréfouël, Nitti and Bovet, *Compt. rend.*, **204**, 1763 (1937).

(3) Fromm and Wittmann, *Ber.*, **41**, 2264 (1908).

(4) Bauer and Rosenthal, *U. S. Pub. Health Repts.*, **53**, 40 (1938); Raiziss, Severac, Moetsch and Clemence, *Proc. Soc. Expti. Biol. Med.*, **39**, 339 (1938); Feinstone, Dissertation, Johns Hopkins University, School of Hygiene and Public Health (1939); Marshall, Litchfield and White, *J. Pharmacol.*, **69** (1) 89; (2) 166 (1940).

(5) (a) Fourneau, Tréfouël, Tréfouël, Nitti and Bovet, *Compt. rend.*, **205**, 299 (1937); (b) Buttle, Dewing, Foster, Gray, Smith and Stephenson, *Biochem. J.*, **32**, 1101 (1938).

TABLE I

PROPERTIES OF SULFONES

No.	Sulfone	M. p., °C. (cor.)	Water soly.,[d] 37°C.	Max.[d] blood[e] level	Chemo-[f] therapeutic activity	Formula	Analyses, %[g] Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	4,4′-Diaminodiphenyl-[a]	175	36.9	3.6*	Active							
2	4-Acetylamino-4′-aminodiphenyl-[b]	242–3	7.1	6.8†	Active							
3	4-Octylsulfonamido-4′-aminodiphenyl-	130	0.1	0.5	Inactive	$C_{20}H_{28}O_4N_2S_2$	56.6	6.6	6.6	57.0	6.6	6.5
4	4-Sulfanilamido-4′-aminodiphenyl-	211	2.6	1.5	Active	$C_{18}H_{17}O_4N_3S_2$	53.6	4.2	10.4	53.7	4.3	10.0
5	2-Sulfamyl-4,4′-diaminodiphenyl-	238	10.4	3.0	Active	$C_{12}H_{13}O_4N_3S_2$	44.0	4.0	12.8	43.8	4.2	12.8
6	2-Carboxy-4,4′-diaminodiphenyl-(alcoholate)	108–13	422.5	0.8	Inactive	$C_{18}H_{12}O_4N_2S\cdot 3/2C_2H_6O$	53.3	5.8	7.8	53.6	5.6	8.4
7	2-Carbethoxy-4,4′-diaminodiphenyl-	182–3	6.5	1.0	Inactive	$C_{15}H_{16}O_4N_2S$	56.3	5.0	8.8	56.7	5.1	8.7
8	2,4′-Diaminodiphenyl-	117	19.5	9.9	Inactive	$C_{12}H_{12}O_2N_2S$	58.1	4.8	11.3	58.6	4.9	11.5
9	4-Sulfamyl-2-nitro-4′-aminodiphenyl-	223–5	3.1	3.5⊗	Sl. active	$C_{12}H_{11}O_6N_3S_2$	40.3	3.1	11.8	40.6	3.2	11.5
10	4-Sulfamyl-2,4′-didiaminodiphenyl-	206–7	10.7	5.8⊗	Inactive	$C_{12}H_{13}O_4N_3S_2$	44.0	4.0	12.8	44.3	4.0	12.9
11	4-Aminodiphenyl-[c]	176	8.8	5.2**	Sl. active							
12	4-Aminophenyl-2′-pyridyl-	158–60	72.8	12.7	Active	$C_{11}H_{10}O_2N_2S$	56.4	4.3	12.0	56.6	4.4	11.9
13	4-Aminophenyl-4′-pyridyl	269–71	3.0	2.1	Inactive	$C_{11}H_{10}O_2N_2S$	56.4	4.3	12.0	56.3	4.9	11.9
14	4-Aminophenyl-2′-thiazyl-	149–51	30.1	10.0	Inactive	$C_9H_8O_2N_2S_2$	45.0	3.3	11.7	45.0	3.6	11.0
15	4-Aminophenyl-5′-nitro-2′-pyridyl-	169–71	11.4	2.9	Sl. active	$C_{11}H_9O_4N_3S$			15.0			15.0
16	4-Aminophenyl-5′-amino-2′-pyridyl-	186–7	123	9.1	Active	$C_{11}H_{11}O_2N_3S$	53.0	4.5	16.9	52.9	4.5	16.8

[a] Buttle, *et al.*, and Fourneau, *et al.*, ref. 2; Fromm and Wittman, ref. 3. [b] Raiziss, Clemence, Severac and Moetsch, ref. 8. [c] Ullmann and Pasdermadjian, *Ber.*, **34**, 1150 (1901); Buttle, *et al.*, ref. 5b. [d] Mg./100 cc.; water solubilities were carried out by Mr. H. E. Faith in these Laboratories. The procedure has been described previously by Roblin and Winnek, ref. 16. [e] White mice; dosage 0.5 g./kg. body weight orally except as noted * 0.063 g./kg. body weight. † 0.125 g./kg. body weight. ** 0.25 g./kg. body weight. ⊗ Administered subcutaneously because of poor oral absorption. [f] Against experimental streptococcal or pneumococcal infections or both in white mice. [g] Microanalyses were carried out in these Laboratories under the direction of Miss Thelma Bills.

closely related to the original compound. The sulfone nomenclature has been retained for purposes of comparison, although the use of the term sulfanilyl[6] would simplify the nomenclature considerably. The synthesis of these compounds was accomplished by the condensation of 4-acetylaminobenzene sulfinic acid, usually in the form of the potassium salt, with a reactive halogen derivative in alcohol solution. The use of higher alcohols gave satisfactory results with less reactive halogens.[7] 4-Acetylamino-4′-aminodiphenylsulfone,[8] a useful intermediate in the synthesis of the sulfonamide derivatives, may be prepared in two steps by this method.

The well-known influence of sulfonamide groups on toxicity led us to prepare several of these derivatives. Furthermore, there was less likelihood that these derivatives would be broken down to 4,4′-diaminodiphenylsulfone *in vivo*. Buttle, *et al.*,[5] and Fourneau, *et al.*,[9] have described 4,4′-disulfanilamidodiphenylsulfone. The former investigators reported little activity for this substance, whereas the latter described it as being somewhat more effective. In all probability the low water solubility and poor absorption account for this discrepancy. Even the mono sulfanila-

(6) As suggested by Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2217 (1938).

(7) Roblin and Williams, U. S. Patent 2,227,400.

(8) Raiziss, Clemence, Severac and Moetsch, THIS JOURNAL, **61**, 2763 (1939).

(9) Fourneau, Tréfouël, Tréfouël, Nitti and Bovet, *Compt. rend. soc. biol.*, **127**, 393 (1938).

mido derivative was very slightly water soluble and poorly absorbed[10] (see Table I). The inactivity of 4-octylsulfonamido-4′-aminodiphenylsulfone may be due to the very low blood concentrations obtained in this case. Possibly a lower homolog such as the methyl or ethyl derivative would be more effective.

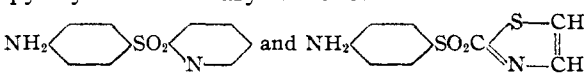
One of the most promising compounds described in this report is 2-sulfamyl-4,4′-diaminodiphenylsulfone. This substance, in spite of rather poor absorption, showed a relatively high degree of activity. The acute toxicity for white mice, even when administered subcutaneously as the sodium salt, was extremely low. In addition to its activity in experimental streptococcal and pneumococcal infections in white mice, this sulfonamide derivative gave good results against *Brucella abortus* in preliminary *in vitro* studies.[11]

The carboxy and carbethoxy derivatives were too poorly absorbed after oral administration to obtain much evidence regarding their potential effectiveness.[12] In this connection it is interesting to note that both derivatives showed *in vitro* activity. The carboxy derivative in particular might also be expected to be of low toxicity. However, because of the poor absorption, no data are available at present.

Another interesting experimental therapeutic agent in this series was the analog of 4,4′-diaminodiphenylsulfone containing one pyridine ring, *i. e.*, 4-aminophenyl-5′-amino-2′-pyridylsulfone. Its toxicity was much lower than the corresponding diphenylsulfone and it was highly effective against both streptococcal and pneumococcal infections in white mice. Similar heterocyclic and mixed heterocyclic-aryl sulfones have been prepared[13] through the corresponding sulfides. However, their poor chemotherapeutic activity, where reported, may be due to the fact that none of these compounds contained a para amino group in the benzene ring.

The relationship between structure and chemotherapeutic acitivity in this series of sulfones appears to be particularly obscure. Assuming that the high activity of 4,4′-diaminodiphenylsulfone is due to the presence of two active aromatic para amino groups, it is not too surprising to find that in some cases substitution in only one ring does not destroy the activity. But 2,4′-diaminodiphenylsulfone, still containing one para amino group, appears to have no activity. Moreover, 4-sulfamyl-2-nitro-4′-aminodiphenylsulfone is somewhat active, whereas, in spite of higher blood concentrations, the analogous diamino derivative is inactive. 4-Aminodiphenylsulfone has been reported[5b] previously to possess some activity.

Comparing the structural formulas for the 2′-pyridyl and 2′-thiazyl sulfones



with the corresponding sulfonamides, sulfapyridine and sulfathiazole, one finds that these four compounds are very closely related. Therefore, it might be predicted that if one of the heterocyclic sulfones had chemotherapeutic activity, the other would likewise be active. Both compounds were about equally bacteriostatic *in vitro*, but it was unexpected to find that the thiazylsulfone was inactive *in vivo*, while the pyridyl analog was active. Comparable blood levels were established and maintained in both cases, so that some other factor must be sought to explain this difference in chemotherapeutic action in experimental mouse infections. Among possible factors might be higher toxicity or rapid breakdown of the thiazylsulfone. In connection with the latter possibility, it is interesting that conditions (two hours of refluxing with 18% hydrochloric acid) which resulted in only 35% hydrolysis of 4-aminophenyl-2′-pyridylsulfone, led to a complete destruction of the thiazyl derivative.

Experimental

The essential experimental data are summarized in Table II. The 4-acetylaminobenzenesulfinic acid used in the synthesis of the sulfones was prepared according to the method of Smiles and Bere.[14]

Coupling reactions of the potassium sulfinate with the halogen intermediates were carried out as illustrated by the following example for the preparation of 4-aminophenyl-2′-pyridylsulfone (compound no. 12): 32.1 g. (0.20 mole) of 2-bromopyridine was added to a warm solu-

(10) The pharmacological and bateriological investigations were made in these Laboratories under the direction of Dr. W. H. Feinstone.

(11) *In vitro* studies were carried out at Lederle Laboratories, Pearl River, N. Y., under the direction of Dr. R. L. Libby.

(12) It should be noted that the method of testing for chemotherapeutic activity in mice is such that if the maximum blood level is below 5 mg./100 cc., or if the substance is very rapidly eliminated, the absence of activity may be due to these factors rather than to the inherent inactivity of the compound in question. The value of blood level determinations in connection with all chemotherapeutic studies cannot be over-emphasized.

(13) Surrey and Lindwall, THIS JOURNAL, **62**, 173 (1940); Winter and Reinhart, *ibid.*, **62**, 3508 (1940).

(14) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, New York, N. Y., 1932, p. 7.

TABLE II

PREPARATION OF SULFONES

No. (see Table I)	Intermediate	Ref.	Coupling solvent	Reflux time, hr.	Yield, %[m]	Further procedure
1	Compound no. 2					Hydrolysis
2	4-Nitrobromobenzene	*a*	Cyclohexanol[i]	3	50	Reduction[p]
3	No. 2 and *n*-octylsulfonyl chloride	*b*	Pyridine		75	Hydrolysis
4	No. 2 and acetylsulfanilyl chloride	*c*	Pyridine		35[n]	Hydrolysis
5	2-Chloro-5-nitrobenzenesulfonamide	*d*	95% Ethanol[k]	2	60	Reduction-hydrolysis
6	Compound no. 7					Hydrolysis
7	Ethyl 2-chloro-5-nitrobenzoate	*e*	Abs. ethanol[k]	2	59[n]	Reduction-hydrolysis
8	2-Nitrobromobenzene	*a*	Cellosolve[j]	5	83	Reduction-hydrolysis
9	3-Nitro-4-bromobenzenesulfonamide	*f*	Abs. ethanol[k]	2	95	Hydrolysis
10	Compound no. 9					Reduction
11	4-Nitrochlorobenzene	*a*	Carbitol[l]	6	46	Reduction
12	2-Bromopyridine	*a*	Carbitol[k]	14.5	66[o]	Hydrolysis
13	4-Chloropyridine	*g*	Water[k]	8	53	Hydrolysis
14	2-Bromothiazole	*h*	Carbitol[k]	3	63	Hydrolysis
15	2-Chloro-5-nitropyridine	*i*	Abs. ethanol[k]	1	85[o]	Hydrolysis
16	Compound no. 15					Reduction

[a] Eastman Kodak Co., Rochester, N. Y. [b] Octyl sulfonyl chloride was prepared in these Laboratories by Dr. J. T. Thurston by the general method of Johnson and Sprague, THIS JOURNAL, **61**, 2764 (1939). [c] Calco Chemical Division, American Cyanamid Co., Bound Brook, N. J. [d] Claus and Mann, *Ann.*, **265**, 88–91 (1891). [e] Rupe, *Ber.*, **30**, 1099 (1897). [f] Andrews, *ibid.*, **13**, 2127 (1880). [g] Wibaut and Broekmann, *Rec. trav. chim.*, **58**, 885–894 (1939). [h] From 2-aminothiazole, ref. *c*, Schatzmann, *Ann.*, **261**, 12 (1891). Better results were obtained by adding the 2-aminothiazole to the HBr, followed by the $NaNO_2$ solution. [i] Tschitschibabin, *J. Russ. Phys.-Chem. Soc.*, **46**, 1236 (1914). [j] Coupled with 4-acetylaminobenzenesulfinic acid and potassium acetate. [k] Coupled with potassium 4-acetylaminobenzenesulfinate. [l] Coupled with potassium benzene sulfinate, *cf.* ref. *c*, Table I. [m] Yield of crude material based on halogen intermediate. In many cases this was not purified further before the next procedure was carried out. [n] Yield of purified compound. [o] Final yield obtained by the addition of further potassium 4-acetylaminobenzenesulfinate as described under *Coupling Reactions*. [p] Reductions were carried out according to the procedure described by Witt, *Ber.*, **45**, 2382 (1912), using iron dust.

tion of 59 g. (0.25 mole) of potassium 4-acetylaminobenzenesulfinate in 125 cc. of Carbitol (diethylene glycomonoethyl ether).[15] The resulting solution was then refluxed for 14.5 hours in the presence of small amounts of iodine and copper powder. After the first hour, a white precipitate began to form. The final cooled mixture contained a considerable amount of solid which was filtered off and washed with water. Its dry weight was 33 g. Further refluxing of the Carbitol filtrate (which had the odor of 2-bromopyridine) with 15 g. more of potassium acetaminobenzenesulfinate for eleven hours gave an additional 3.7 g. of the crude product upon dilution with water. The total yield of crude material was 66% of the theoretical. After recrystallization from alcohol, the compound was deacetylated by refluxing for thirty minutes with 12% hydrochloric acid; 27 g. of the acetylamino compound refluxed with 150 cc. of the acid gave 21.3 g. of compound no. 12. Colorless crystals of pure product were obtained by recrystallization from 1.5 liters of water, using decolorizing charcoal.

A useful variation[7] of this general procedure is illustrated by the preparation of 4-acetylamino-4′-nitrodiphenylsulfone, the intermediate to compound no. 2. Refluxing of 0.10 mole of 4-nitrobromobenzene, 0.125 mole of 4-acetylaminobenzenesulfinic acid, and 0.15 mole of potassium acetate in 250 cc. of cyclohexanol for three hours, followed by steam distillation to remove the cyclohexanol and unreacted 4-nitrobromobenzene, resulted in a 50% yield of the sulfone.

When sulfonyl chlorides were coupled with the amino sulfones in pyridine solution to produce compounds no. 3 and 4, the conditions were the same as previously described.[16] These products were deacetylated by alkaline hydrolysis.

Hydrolysis of the acetylaminosulfones was generally accomplished by refluxing in 12% hydrochloric acid for five or ten minutes after the solid was completely dissolved. The amino compound was isolated by neutralizing the cooled acid solution. 4-Acetylaminophenyl-5′-nitro-2′-pyridylsulfone was particularly difficult to hydrolyze in good yields. A 35% yield was obtained by refluxing with 8–10 equivalents of 12% hydrochloric acid for fifteen minutes, filtering from some unhydrolyzed material, and further hydrolyzing the latter. Longer hydrolysis, the use of 24% hydrochloric acid, or 10% sodium hydroxide resulted in very small yields of the desired product.

Compound no. 7 was obtained from 2-carbethoxy-4-amino-4′-acetylaminodiphenyl sulfone in 88% yield by refluxing for fifteen minutes with 12% hydrochloric acid. 2-Carboxy-4,4′-diaminodiphenylsulfone alcoholate (compound no. 6) was obtained from compound 7 by hydrolysis with 5% aqueous or alcoholic sodium hydroxide solution. It was precipitated as a gum from the hydrolysis solution by adding concentrated hydrochloric acid to a maximum precipitation. This gum solidified on long drying in a

(15) Obtained from Carbide and Carbon Chemicals Corp., New York, N. Y.

(16) Roblin and Winnek, THIS JOURNAL, **62**, 2001 (1940).

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.

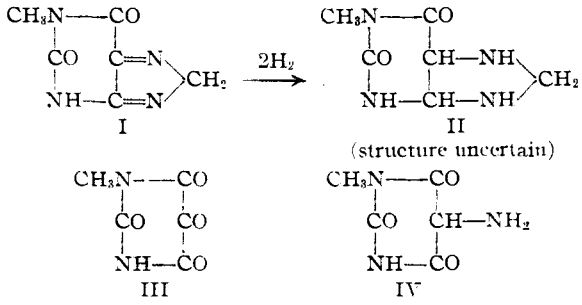
STAMFORD, CONN. RECEIVED APRIL 25, 1941

[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.

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).