

2. The 2-ethylmercapto-4-methyl-6-oxypyrimidine is converted quantitatively into its characteristic hydrochloride without any evidence of the introduction of the grouping ( $\cdot\text{CH}_2\text{Cl}$ ) into the pyrimidine ring.

3. 2,6-Dichloro-4-methylpyrimidine interacts with the chloromethyl ether to form 2-chloro-4-methyl-6-oxypyrimidine and a polymeric modification of 5-oxymethyl-4-methyluracil. Reduction of this "polymer" with hydriodic acid leads to the formation of (a) 4,5-dimethyluracil and (b) bis-(4-methyl-2,6-dioxypyrimidyl-5)-methane.

4. 4-Methyluracil and the chloromethyl ether interact to form bis-(4-methyl-2,6-dioxypyrimidyl-

5)-methane and 5-acetoxymethyl-4-methyluracil.

5. Vavon and Bolle<sup>7</sup> have interpreted the interaction of chloromethyl ether with aromatic hydrocarbons in acetic acid solution as a simple double decomposition with elimination of methanol and substitution of the grouping ( $\cdot\text{CH}_2\text{Cl}$ ). The evidence produced in the authors experimentation indicates that the active reagent under these conditions is  $\text{CH}_3\text{COOCH}_2\text{OCH}_3$  rather than  $\text{CH}_3\text{OCH}_2\text{Cl}$ , and that the mechanism of reaction in these changes is more complex than Vavon and Bolle postulated.

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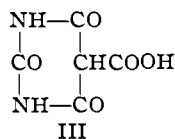
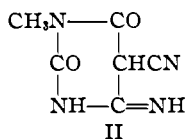
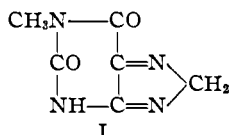
RECEIVED DECEMBER 5, 1941

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

## Researches on Pyrimidines. Derivatives of Pyrimidine-5-carboxylic Acid<sup>1,2</sup>

BY JOSEPH C. AMBELANG<sup>3</sup> AND TREAT B. JOHNSON

Following the failure of the authors<sup>4</sup> to synthesize a compound resembling in structure that proposed for *toxoflavine*<sup>5</sup> (I) the possibility of the isomeric structure (II) was next considered. The latter compound may be regarded as a methylated imidonitrile of 2,4,6-triketo-hexahydropyrimidine-5-carboxylic acid (III).



Although this acid (III) appears not to be recorded in the literature, its acid amide (IV) was prepared by Baeyer<sup>6</sup> in 1865; later by two other workers<sup>7</sup> and was named *malobiursäure* because it was formed by heating barbituric acid with fused urea.

(1) The support of the Rockefeller Foundation of New York in this work is gratefully acknowledged by the authors.

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

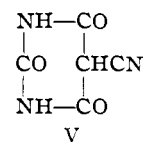
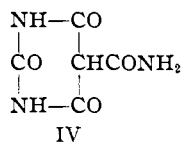
(3) Sterling Professorship of Chemistry Research Assistant, 1939-40. Present address, D'Youville College, Buffalo, New York.

(4) Johnson and Ambelang, *THIS JOURNAL*, **61**, 2483 (1939).

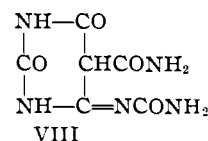
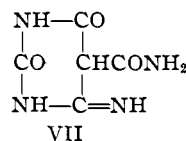
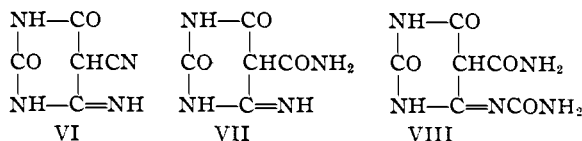
(5) van Veen and Baars, *Proc. Koninkl. Akad. Wetenschappen*, **40**, 498 (1937).

(6) Baeyer, *Ann.*, **135**, 312 (1865).

(7) Nencki, *Ber.*, **5**, 888 (1872); Curtius, *ibid.*, **56**, 1579 (1923).



Since the 5-cyanobarbituric acids are unknown, the authors sought to prepare a member of this series to find out whether its reactions resembled the unusual behavior of *toxoflavine*.<sup>5</sup> The synthesis of 5-cyanobarbituric acid (V) and its 4-imido derivative (VI) was attempted according to the usual technique namely, by condensation of urea or thiourea with esters of cyanomalonic acid and dicyanoacetic acid, respectively.



No product suggestive of a barbiturate was isolated. When thiourea was heated with methyl dicyanoacetate in the presence of sodium ethylate there was formed a very small quantity of an unidentified product, acidic in nature, containing sulfur and nitrogen, but much too low a percentage of the latter element to be the expected pyrimidine.

The failure of these esters to condense under the experimental conditions employed for the preparation of barbiturates is not inconsistent

with the behavior of cyanocarboethoxyacetamide as reported by Frerichs and Hartwig.<sup>8</sup> This compound, likewise a derivative of methanetricarboxylic acid, was profoundly broken down by alcoholic potash, by dilute aqueous ammonia and also by hydrochloric acid. It, therefore, seems reasonable to assume that ethyl cyanomalonate and the dicyanoacetic esters are similarly disintegrated by the condensing agent used, *viz.*, sodium ethylate. Furthermore, the condensation of malonitrile with urea was found to yield only 5% of the expected pyrimidine—**barbituric acid-4,6-diimide**. No yield is mentioned in the literature.<sup>9</sup> This pyrimidine has been prepared by acid hydrolysis of 2-methylmercapto-4,6-diaminopyrimidine.<sup>10</sup>

Paralleling Baeyer's reaction a synthesis of the imido homolog (VII) was undertaken from imido-barbituric acid and urea. This pyrimidine (VII) would be a demethylated isomer of **toxoflavine hydrate**.<sup>5</sup> However, the product formed appeared to contain two molecules of cyanic acid. It formed a mono-sodium salt and was attacked by bromine water giving 5,5-dibromobarbituric acid. The similarities of the compound to **malobiursäure** described by Baeyer lead to the probable structure expressed by formula (VIII). Attempts to hydrolyze it to the desired pyrimidine (VII) were unsuccessful. Since the imido-group of 4-imidobarbituric acid derivatives is easily removed by acid hydrolysis, the linkage of the second  $-\text{CONH}_2$  group to the imido-nitrogen in position-4 of the pyrimidine ring (VIII) seems not unreasonable.

### Experimental Part

**Unsuccessful Attempts to Prepare 5-Cyanobarbituric Acid (V) and its 4-Imino Derivative (VI).**—A. **Ethyl cyanomalonate** was prepared according to the directions of Haller<sup>11</sup> and obtained in a yield of about 20%, boiling at 136–137° at 13 mm. To a solution of sodium (0.25 g.) dissolved in absolute alcohol were added 0.65 g. of urea and 2.0 g. of ethyl cyanomalonate and the resulting solution heated at 100° in a sealed tube for seven hours. This reaction mixture was then acidified with acetic acid and evaporated to dryness *in vacuo*. No evidence was obtained of the formation of a pyrimidine, and the only solid product identified was unaltered urea.

b. **Ethyl dicyanoacetate** was prepared according to the

(8) Frerichs and Hartwig, *J. prakt. Chem.*, **180**, 489 (1905).

(9) Merck, German Patent 166,448, *Chem. Zentr.*, **77**, 1, 620 (1906).

(10) Wheeler and Jamieson, *Am. Chem. J.*, **32**, 349 (1904).

(11) Haller, *Compt. rend.*, **95**, 142 (1882); *Ann. Chim.*, [6] **16**, 419, 428 (1889); Mignonac and Rambeck, *Compt. rend.*, **188**, 1298 (1929).

method of Hesse<sup>12</sup> and was used in the form of its sodium salt.

*Anal.* Calcd. for  $\text{C}_6\text{H}_5\text{O}_2\text{N}_2\text{Na}$ : N, 17.50. Found: N, 17.51.

Digestion of this salt or the corresponding methyl dicyanoacetate<sup>13</sup> with urea or thiourea in alcohol solutions did not lead to the production of the desired acid derivatives. Urea and thiourea were always recovered. In the condensation with thiourea there was isolated a very small amount of unknown material melting at 198.5–199.5° with decomposition. This gave a test for sulfur and contained 23.2% of nitrogen.

**2,6-Diketo-4-ureido-1,2,3,4-tetrahydropyrimidine-5-carboxylamide (VIII).**—20.7 g. of powdered urea was thoroughly mixed with 6.9 g. of 4-imidobarbituric acid and the mixture heated at 150–160° in a sand-bath. The turbid melt evolved ammonia on heating, became a thick paste after twenty minutes and at the end of two and one-half hours was nearly solid. The melt was extracted with 140 ml. of hot water, and the undissolved residue then recrystallized from a large volume of boiling water (1000 ml.). After two recrystallizations from hot water there was recovered 5 g. of the above pyrimidine. It showed no definite melting point below 300° and was dried for analysis at 117°.

*Anal.* Calcd. for  $\text{C}_6\text{H}_7\text{O}_4\text{N}_5$ : C, 33.80; H, 3.31; N, 32.86. Found: C, 34.1; H, 3.78; N, 32.76, 32.81.

This pyrimidine is very resistant to acid hydrolysis. One gram was refluxed for two hours with boiling hydrochloric acid without alteration.

*Anal.* Calcd. for  $\text{C}_6\text{H}_7\text{O}_4\text{N}_5$ : N, 32.86. Found: N, 32.54, 32.56.

**Formation of the Monosodium Salt; Attempted Basic Hydrolysis.**—One gram of the product in 20 ml. of 8% sodium hydroxide solution was refluxed for five hours at 110–120°. Distillation into standard acid and titration indicated that less than 0.2 millimole of ammonia had been evolved from 5 millimoles of sample. The residue was cooled and filtered; the solid recrystallized from water and dried to constant weight.

*Anal.* Calcd. for  $\text{C}_6\text{H}_6\text{O}_4\text{N}_5\text{Na}$ : N, 29.79; Na, 9.78. Found: N, 29.50; Na, 9.99.

The mother liquor from the hydrolase was acidified with hydrochloric acid, whereupon the unaltered pyrimidine deposited.

*Anal.* Calcd. for  $\text{C}_6\text{H}_7\text{O}_4\text{N}_5$ : N, 32.86. Found: N, 32.61.

**Action of Bromine Water on the Acid Amide (VIII).**—To a suspension of 0.65 g. of the pyrimidine acid amide in 4 ml. of water was added 1 g. of bromine in 3 ml. of water. Effervescence and immediate decolorization of the bromine occurred. The insoluble material was filtered off and the filtrate evaporated to dryness. Ammonium bromide was separated from the residue obtained by precipitation from methanol by benzene. After repeating this reprecipitation several times there was finally obtained a residue of 0.6 g. of dibromobarbituric acid which melted at 239° with effervescence.

(12) Hesse, *Am. Chem. J.*, **18**, 738 (1896); see also Haller, *Compt. rend.*, **111**, 54 (1890).

(13) Arndt, Scholz and Frobel, *Ann.*, **521**, 118 (1935).

*Anal.* Calcd. for  $C_4H_2O_3N_2Br_2$ : N, 9.83. Found: N, 9.93.

### Summary

1. Ethyl cyanomalonate, ethyl dicyanoacetate and methyl dicyanoacetate failed to condense with urea (or thiourea) in the presence of sodium ethylate to give the nitrile and 4-imidonitrile, respectively, of 2,4,6-triketohexahydropyrimidine-5-carboxylic acid.

2. 4-Imidobarbituric acid reacted with fused urea to give 2,6-diketo-4-ureidohexahydropyrimidine-5-carboxylamide, which could not be converted by hydrolysis to the corresponding 2,6-diketo-4-imidohexahydropyrimidine-5-carboxylamide. Interaction with bromine water led to the formation of 5,5-dibromobarbituric acid.

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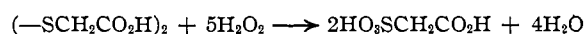
RECEIVED FEBRUARY 24, 1941

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

## Rate Characteristics of the Oxidation of Disulfide-Acids by Hydrogen Peroxide

BY GEORGE G. STONER AND GREGG DOUGHERTY

As a means of studying the oxidation of disulfides, the action of hydrogen peroxide on four aliphatic disulfide-acids was followed by determinations of peroxide and acidity. The reactions were conducted at 30 and 40° for dithiodiacetic acid and  $\beta,\beta'$ -dithiodipropionic acid, and at 30° for  $\alpha,\alpha'$ -dithiodipropionic acid and  $\gamma,\gamma'$ -dithiodibutyric acid. Disulfide and hydrogen peroxide were allowed to react in proportions to satisfy the over-all equation to sulfonic acid, illustrated as follows with dithiodiacetic acid.



The solutions were initially 0.1 *M* with respect to disulfide-acid and 0.5 *M* with respect to hydrogen peroxide, 0.005 mole of acid and 0.025 mole of peroxide having been diluted to 50 g. with water or dioxane-water as solvent. Table I is a list of experiments and conditions. The resulting curves are in Fig. 1.

### Experimental Part

**Materials.**—Disulfide-acids were prepared from corresponding Bunte salts as described previously.<sup>1</sup> Data for m. p. and equivalent weight, calculated and found, were, respectively, as follows: dithiodiacetic acid, 102–103°, 91.1, 91.1;  $\beta,\beta'$ -dithiodipropionic acid, 154°, 105.1, 106;  $\alpha,\alpha'$ -dithiodipropionic acid, 127–135°, 105.1, 106; and  $\gamma,\gamma'$ -dithiodibutyric acid, 103–105°, 119.2, 120. The Superoxol analyzed 29.2% hydrogen peroxide. Purified<sup>2</sup> *p*-dioxane was distilled from sodium as it was needed. The sulfoacetic acid<sup>3</sup> melted at 86–89°. Bath temperatures were constant to 0.05°, and were calibrated against a platinum resistance thermometer.

**Procedure.**—The weights of substances which were used in each experiment are in Table I. Distilled water was weighed into a tared flask, followed by Superoxol, dioxane,

TABLE I

EXPERIMENTAL CONDITIONS AND COMPOSITIONS OF SOLUTIONS

Expt. <sup>a</sup>	Disulfide <sup>b</sup>	Water added, <sup>c</sup> g.	Dioxane, g.	Solvent <sup>d</sup>	
				Dioxane, %	<i>D</i> <sub>30</sub> <sup>e</sup>
1a, 1b	Blank	0	47.16	94	3.8
2a, 2b	Blank	47.16	0	0	76.7
3a, 3b	A	46.25	0	0	76.7
4 <sup>f</sup>	A	45.74	0	0	76.7
5 <sup>g</sup>	A	44.85	0	0	76.7
6a, 6b	A	6.98	39.27	80	10.4
7a, 7b	A	2.07	44.18	90	5.5
8a, 8b	A	0	46.25	94	3.8
9a, 9b	B	6.95	39.16	80	10.4
10a, 10b	B	2.05	44.06	90	5.5
11a, 11b	B	0	46.11	94	3.8
12	C	6.95	39.16	80	10.4
13	D	6.92	39.05	80	10.4

<sup>a</sup> Reaction temperature was 30° except for the "b" series of experiments, in which cases it was 40°. <sup>b</sup> Weights of disulfide-acids were as follows: A, dithiodiacetic acid, 0.91 g.; B,  $\beta,\beta'$ -dithiodipropionic acid, 1.05 g.; C,  $\alpha,\alpha'$ -dithiodipropionic acid, 1.05 g.; and D,  $\gamma,\gamma'$ -dithiodibutyric acid, 1.19 g. <sup>c</sup> This weight did not include water in the Superoxol. In each run 2.84 g. of Superoxol was used. <sup>d</sup> In calculating composition of solvent, hydrogen peroxide was regarded as water because of its large and similar dielectric constant. <sup>e</sup> Dielectric constants for 30°. The corresponding values for 40° are less by ca. 5%. Åkerlöf and Short, *THIS JOURNAL*, 58, 1241 (1936). <sup>f</sup> Concd. sulfuric acid (0.51 g., 0.005 mole) was added as a catalyst. <sup>g</sup> Sulfoacetic acid (1.4 g., 0.01 mole) was added as a catalyst.

and disulfide-acid, the latter being dissolved immediately. After mixing, solutions were transferred at once to 10-inch test-tubes which were placed in a well-stirred water-bath, the temperature of which was either 30 or 40°. Tubes were kept stoppered except during the withdrawal of samples for titration. In sampling, a 2.00-cc. portion was pipetted into a freshly mixed solution of 50 cc. of 2% potassium iodide and 15 cc. of cold 1:1 sulfuric acid. After being stoppered for five minutes in the dark it was

(1) Stoner and Dougherty, *THIS JOURNAL*, 63, 987 (1941).

(2) Eigenberger, *J. prakt. Chem.*, 130, 75 (1931).

(3) Stillech, *ibid.*, 73, 541 (1906), reported a m. p. of 84–86°.