shaken at room temperature with equal volumes of 1 *N* sodium bicarbonate until solution was complete. The phthalic anhydride required fourteen hours and fifteen hours while the fluorenone anhydride required seventeen and eighteen and one-half hours. These values must be considered as only roughly qualitative but it seemed reasonable to believe that, allowing for such unknown factors as state of subdivision and solubility in water, a Mills–Nixon effect would have produced a greater difference.

2-Benzoylfluorenone-3-carboxylic acid was formed when 0.5 g. of the above anhydride in 15 cc. of thiophene-free benzene at 5° was treated with 0.90 g. of anhydrous aluminum chloride and the mixture then refluxed for two hours. The yield of yellow prisms from acetic acid (m. p. 247–250°) was 0.61 g. or 93%. *Anal.* Calcd. for $C_{21}H_{12}O_4$: C, 76.80; H, 3.69. Found: C, 77.03; H, 3.83.

Its methyl **ester** separated from methanol in tiny, yellow prisms, m. p. 185–187°.

Anal. Calcd. for $C_{22}H_{14}O_4$: C, 77.18; H, 4.12. Found: C, 76.84; H, 4.23.

Decarboxylation of the acid by quinoline and copper carbonate at 210° gave a compound which after crystallization from methanol and benzene–ligroin formed yellow needles, m. p. 173–174°. A mixed melting point of this material with some freshly prepared 2-benzoylfluorene[14] showed no depression, thus proving orientation.

Refluxing of a solution of aniline and fluorenone-2,3-dicarboxylic acid gave an anil which crystallized from aniline in fine yellow needles m. p. 310–312°. *Anal.* Calcd. for $C_{21}H_{11}O_3N$: N, 4.31. Found: N, 3.91.

Summary

Fluorenone-2,3-dicarboxylic acid, its anhydride and anil have been prepared and the anhydride has been found not to differ noticeably from phthalic anhydride in its reactions, thus indicating very little strain due to a possible Mills–Nixon effect.

It seems that with two identical substituents in positions 2 and 3 of fluorenone, that in position 2 is the more reactive.

(14) Fortner, *Monatsh.*, **23**, 921 (1902).

HARTFORD, CONNECTICUT RECEIVED JULY 9, 1941

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

The Synthesis of Some 3-(β-Hydroxyethyl)-pyrimidines and of a 3-(β-Hydroxyethyl)-uric Acid[1]

BY ALAN HART NATHAN[1a] AND MARSTON TAYLOR BOGERT

Paralleling recent investigations[2] in these laboratories on pyrimidine and purine derivatives of cystamine, we have prepared and studied some of the analogous 3-(β-hydroxyethyl) compounds, using ethanolamine (I) as initial material and, in the main, following the familiar Traube[2b,3] procedure for the synthesis of the 3-(β-hydroxyethyl)-4,5-diaminouracil (V), fusion of which with urea yielded the desired 3-(β-hydroxyethyl)-uric acid (VI). Oxazolidino-pyrimidines and -purines should be obtainable from these ethanolamine products, but we have not as yet carried out any experiments in that direction.

It is believed that it will be of interest to examine the physiological effects of the hydroxyethyl uric acid, because its solubility in water is much greater than that of uric acid itself. Further, the Farbenfabr. vorm. F. Bayer & Co., took out a patent[4] in 1906, covering 1-(β-hydroxyethyl)-theobromine, 7-(β-hydroxyethyl)-theophylline, and 3-methyl-1,7-di-(β-hydroxyethyl)-xanthine, claiming that these derivatives exhibited the diuretic activity of the parent compounds without their undesirable side effects.

Acknowledgments.—We are indebted to the Carbide & Carbon Chemicals Corp., of New York, N. Y., for the ethanolamine used in this research, and welcome this opportunity of expressing our gratitude. Our thanks are due also to Mr. Saul Gottlieb, of these laboratories, who carried out the analytical work required.

Experimental Part

All melting points are corrected unless otherwise stated.

β-Hydroxyethylurea (II) was prepared by the action of nitrourea upon ethanolamine, as described by Charlton and Day.[5]

3-(β-Hydroxyethyl)-4-iminobarbituric Acid (III).—The absolute ethanol used in this reaction was prepared as described by Lund and Bjerrum.[6] Three grams of sodium was dissolved in 80 cc. of this absolute alcohol, and to this solution there were added 7 g. of the ethanolurea (II) and 7.6 g. of ethyl cyanoacetate. The mixture was refluxed for fourteen hours protected from moisture. Approximately

(1) Presented in abstract before the Division of Organic Chemistry, April 10, 1940, at the Cincinnati Meeting of the American Chemical Society.

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(2) (a) Mills and Bogert, THIS JOURNAL, **62**, 1173 (1940); (b) Nathan and Bogert, *ibid.*, **63**, 2361 (1941).

(3) (a) Traube, *Ber.*, **33**, 1371, 3036 (1900); (b) Conrad, *Ann.*, **340**, 310 (1905).

(4) German Patent 191,106 (1906); *Chem. Zentr.*, **79**, I, 499 (1908).

(5) Charlton and Day, *J. Org. Chem.*, **1**, 552 (1936).

(6) Lund and Bjerrum, *Ber.*, **64**, 210 (1931).

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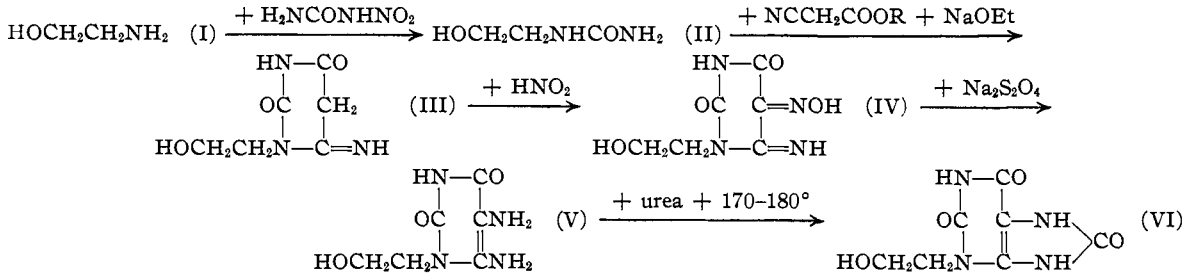


half of the solvent was removed by distillation and the residual solution taken up in an equal volume of water. This solution was made acid to congo red paper with concentrated hydrochloric acid, cooled and the gray precipitate filtered out. The filtrate, when concentrated, yielded an additional small quantity of the precipitate. The total yield of this crude iminobarbituric acid (III) was 8.1 g. or 71%. It was purified by crystallization from water, in which its solubility cold was about 0.5 g. per 100 cc., and about 2.2 g. per 100 cc. at the boiling point. When heated, it decomposed at 256° without complete melting.

Anal. Calcd. for $C_6H_9O_3N_3$: C, 42.1; H, 5.3. Found: C, 41.9; H, 5.2.

As recorded in our previous paper,[2b] a similar condensation of ethyl cyanoacetate with the analogous *bis*-(β-ureidoethyl) disulfide, could not be accomplished.

3-(β-Hydroxyethyl)-4-iminovioluric Acid (IV).—A suspension of 2 g. of the finely powdered iminobarbituric acid (III) in 60 cc. of 45% alcohol was heated on a steam-bath and 4 cc. of isoamyl nitrite was allowed to drip in slowly with stirring during a period of one hour. The suspended acid gradually dissolved and the solution turned purple. Before all the isoamyl nitrite had been added, violet crystals began to separate. Upon completion of the reaction, the flask was chilled in the refrigerator, the violet crystals removed and washed thoroughly with 95% alcohol (in which they were practically insoluble) until the odor of amyl alcohol was no longer detectable. The average yield was 90%, and the product was suitable for the next step without further purification. Recrystallized from 45% alcohol, it was obtained in beautiful violet platelets, which gradually darkened above 200°, without showing any definite melting point.

Anal. Calcd. for $C_6H_8O_4N_4$: C, 36.0; H, 4.0. Found: C, 36.3; H, 4.1.

In the above reaction, the use of sodium nitrite in place of isoamyl nitrite proved unsatisfactory, because of the difficulty of isolating and purifying the product.

Contrary to the behavior of the barbituric acids themselves, their imino derivatives would not react with sodium nitrite until the solutions were acidified, as shown by the absence of any color. Isoamyl nitrite, on the other hand, did not require the addition of any acid to bring about the reaction.

3-(β-Hydroxyethyl)-4,5-diaminouracil (V).—The iminovioluric acid (IV) was reduced by sodium hydrosulfite in ammoniacal solution, following in general the method of Hepner and Frenkenberg.[7] By mixing 7.4 g. of the iminovioluric acid with a slight excess of concentrated ammonium hydroxide solution, the orange ammonium salt was formed, and proved to be not very soluble in cold water. About 30 cc. of water was added and the mixture warmed, but it was not necessary for the success of the reduction to have all the ammonium salt in solution. To this mixture there was added all at once a solution of 14.8 g. of sodium hydrosulfite dihydrate in 45 cc. of water containing a few drops of concentrated ammonium hydroxide. Some heat was evolved by the reaction and the color of the solution changed rapidly to a clear pale yellow. Yellow crystals soon separated when the solution was chilled. They were filtered out, washed with a little cold water and dried over calcium chloride in an evacuated desiccator; yield, 6 g., or 87%. They melted at 252.5–253°, and dissolved freely in hot water, hot dilute alcohol, or cold dilute hydrochloric acid. With dilute sulfuric acid, a difficultly soluble salt was formed, which decomposed on attempted purification by recrystallization from water. Nor could the diaminouracil be purified by recrystallization. Decomposition invariably ensued, the orange color of the crystals steadily darkening, and finally only amorphous products resulted. For analysis, it was dissolved twice in dilute hydrochloric acid at room temperature, filtered, and reprecipitated by dilute ammonia. The crystals secured in this way were pale yellow and melted at 253–254°.

Anal. Calcd. for $C_6H_{10}O_3N_4$: C, 38.7; H, 5.4. Found: C, 38.4; H, 5.5.

The reduction was effected also by ammonium sulfide,[8] but the product was then apt to be contaminated with sulfur. Acid reducing agents are unsuitable, because of their tendency to hydrolyze the imino group.

3-(β-Hydroxyethyl)-uric Acid (VI).—When the diaminouracil (V) was fused for an hour at 170–180° with an equal weight of urea,[2b,9] the yield of crude ethanoluric acid (VI) was practically that calculated. It was purified by dissolving in dilute ammonium hydroxide and precipitating with hydrochloric acid, which was repeated thrice and was followed by two crystallizations from water. Dried to constant weight at 150°, it formed small white crystals, which decomposed between 315 and 325°.

Anal. Calcd. for $C_7H_8O_4N_4$: C, 39.6; H, 3.8; N, 26.4. Found: C, 39.3; H, 3.9; N, 26.4.

Its solubility in hot water was approximately 1 g. in 100 cc., whereas that of uric acid itself is in the neighborhood of 1 g. in 1800 cc. at 100°. Crystallized from water, it carried water of crystallization, which was not easily driven

(7) Hepner and Frenkenberg, *Helv. Chim. Acta*, **15**, 350, 533 (1932).

(8) Traube, *Ann.*, **351**, 64 (1904).

(9) Gabriel and Colman, *Ber.*, **34**, 1247 (1901).

off at 110°. Two samples, after standing for forty-eight hours in a desiccator over calcium chloride, lost 11.6% of their weight in an oven at 110°, and 12.9% at 150°. The calculated loss in weight for one mole of water is 7.8, and for two moles 14.5%.

Summary

1. β-Hydroxyethylurea is readily converted into the 3-(β-hydroxyethyl) derivatives of 4-iminobarbituric and 4-iminovioluric acids, of 4,5-diaminouracil, and of uric acid.

2. The new uric acid derivative may prove of some physiological interest, because its solubility in water is much greater than that of uric acid itself.

NEW YORK, N. Y. RECEIVED JULY 8, 1941

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

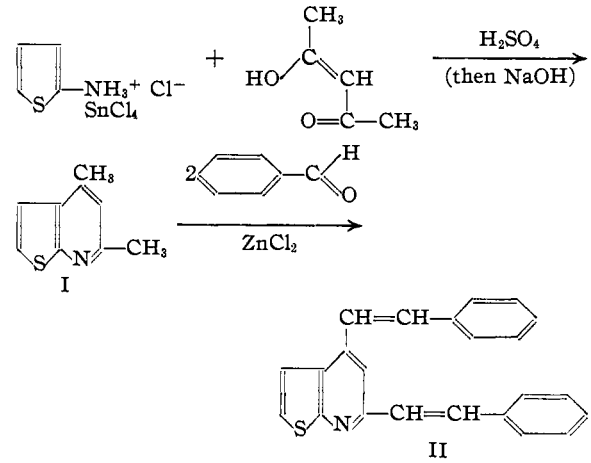
4,6-Dimethylthieno(2,3-b)pyridine, an Isoster[1] of 2,4-Dimethylquinoline

BY WILLIAM S. EMERSON,[2] F. W. HOLLY AND L. H. KLEMM

In view of the tremendous importance of such quinoline derivatives as quinine, plasmoquine and many of the cyanine dyes, and, more recently, of the related substances, sulfapyridine and sulfathiazole, the synthesis of isosters of these compounds presents a problem of especial interest.

Of the possible quinoline isosters, we selected for a start on this problem that isoster with the nitrogen and sulfur atoms attached to the same carbon atom as the most accessible because of the ready availability of 2-aminothiophene. Steinkopf and Lutzkendorf[3] prepared the only previously reported member of this series, thieno-(2,3-b)pyridine, by subjecting 2-aminothiophene to the Skraup reaction. Their yield was only about 5%. The low yield is not surprising in view of the sensitivity of 2-aminothiophene even to such mild oxidizing agents as atmospheric oxygen.[3]

We, therefore, selected a type of reaction that would not involve hydrogen removal and which we felt could be applied directly to the stable 2-aminothiophene stanni-hydrochloride. We were successful in applying it to the simplest case, acetylacetone. Using Koenigs and Mengel's procedure[4] for the preparation of 2,4-dimethylquinoline, we obtained 4,6-dimethylthieno(2,3-b)-pyridine (I) in 80% yield. It was characterized by the preparation of several salts and by the dibenzal derivative (II) which formed very readily. Experiments with similar compounds and attempts to apply the Doebner and v. Miller reaction led to tar formation.



I II

Experimental

4,6-Dimethylthieno(2,3-b)pyridine was prepared by a modification of Koenigs and Mengel's method for 2,4-dimethylquinoline.[4] A mixture of 6 g. of 2-aminothiophene stanni-hydrochloride[5] and 5 g. of acetylacetone[6] was heated on the steam-bath for thirty minutes, or until a red tar started to form. Cyclization was then effected by adding 50 cc. of concentrated sulfuric acid with cooling to keep the temperature at 25°. After the mixture had been poured on ice, made basic with sodium hydroxide and extracted with benzene, the benzene solution was dried over potassium hydroxide and distilled. In this way 2 g. (80%) of 4,6-dimethylthieno(2,3-b)pyridine was obtained. It was a nearly colorless oil which darkened quite rapidly on exposure to air, b. p. 103–108° (4 mm.); d^{20}_{20} 1.152; $n^{20}D$ 1.6230.

It was found that cyclization could be equally readily effected by boiling the initial condensation product with fused zinc chloride or phosphorus pentoxide in xylene.

The **hydrochloride** melted at 241–242° dec., after several crystallizations from an acetone–alcohol–ether mixture.

(1) For an extended discussion of this term see Tracy and Elderfield, *J. Org. Chem.*, **6**, 54 (1941); Finkelstein and Elderfield, *ibid.*, **4**, 365 (1939).

(2) Present address: Monsanto Chemical Co., Dayton, Ohio.

(3) Steinkopf and Lutzkendorf, *Ann.*, **403**, 45 (1914).

(4) Koenigs and Mengel, *Ber.*, **37**, 1322 (1904).

(5) Thiophene was nitrated by Babasinian's method ("Organic Syntheses," **14**, 76 (1934)) and the 2-nitrothiophene so produced was then reduced to 2-aminothiophene according to the procedure of Steinkopf [*Ann.*, **403**, 17 (1914)].

(6) Denoon, "Organic Syntheses," **20**, 6 (1940).