

tion with charcoal, 2,4-diamino-5-(4-methyl-5- $\beta$ -hydroxyethylthiazoliumchloride)-methylpyrimidine hydrochloride was obtained in white needles; m. p. 245–247° (dec.).

*Anal.* Calcd. for  $C_{11}H_{17}ON_5SCl_2$ : C, 39.05; H, 5.02; N, 20.71; Cl, 21.00. Found: C, 39.18; H, 4.84; N, 20.60; Cl, 21.24.

The compound formed a picrate which after recrystallization from water melted at 197–199° (dec.).

**2,4-Diamino-5-(4-methyl-5- $\beta$ -hydroxyethylthiazolium bromide)-methylpyrimidine Hydrobromide (VIII).**—This compound was obtained when the reaction product of the above condensation was taken up with 10% aqueous hydrobromic acid. The red solution was extracted with methylene chloride, warmed to 40° for one hour to saponify the acetyl group and finally decolorized with charcoal. From the highly concentrated filtrate the compound was precipitated with excess ethanol. After recrystallization from dilute ethanol 2,4-diamino-5-(4-methyl-5- $\beta$ -hydroxyethylthiazolium bromide)-methylpyrimidine hydrobromide was obtained in white needles; m. p. 214–216° (dec.).

*Anal.* Calcd. for  $C_{11}H_{16}ON_5SBr_2$ : N, 16.43; Br, 37.56. Found: N, 16.29; Br, 37.64.

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### Summary

An analog of thiamin having an amino group instead of the methyl group in the C-2 position of the pyrimidine ring has been prepared. It was assayed according to the official curative method and found to be void of Vitamin B<sub>1</sub> activity at a level of 25  $\gamma$ .

RENNSELAER, N. Y.

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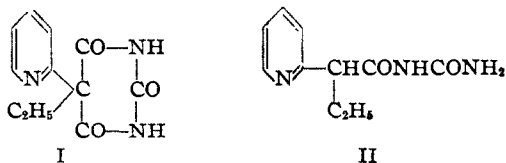
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

## 5-Ethyl-5-(2-pyridyl)-barbituric Acid

BY S. M. McELVAIN AND M. A. GOESE

In an earlier paper<sup>1</sup> from this Laboratory unsuccessful attempts to condense ethyl ethyl-2-pyridylmalonate with urea by means of sodium ethoxide, both in the dry state and in alcoholic solution, were reported. The only reaction product that could be obtained was  $\alpha$ -(2-pyridyl)-butyramide, formed through the cleavage of the malonic ester to the corresponding acetic ester followed by the ammonolysis of this latter ester.

In this work which is now reported it has been found possible to prepare 5-ethyl-5-(2-pyridyl)-barbituric acid (I) in low (10%) yields from this sensitive malonic ester by carrying out the reaction in the less efficient alcoholizing medium, *t*-butyl alcohol. It also was found advantageous to add the condensing agent, sodium *t*-butoxide, in fractional amounts as the condensation proceeded and to arrange the apparatus to permit continuous distillation of the alcohol in order to remove as much as possible of the ethyl alcohol as it is formed in the condensation



The main product of the reaction between urea and ethyl-2-pyridylmalonic ester in *t*-butyl alcohol is the  $\alpha$ -(2-pyridyl)-butyrylurea (II) which results from the condensation of the corresponding butyric ester with urea.

With sodium isopropoxide in isopropyl alcohol as the condensing agent the yield of the barbituric acid dropped to 5% of the theoretical. Under

these conditions the  $\alpha$ -(2-pyridyl)-butyramide was the principal reaction product as it was when ethyl alcohol and sodium ethoxide were used.<sup>1</sup> The yield of the barbituric acid was not improved by the use of guanidine instead of urea, a variation which Cope and Hancock<sup>2</sup> have found beneficial in the preparation of barbituric acids from certain alkali-sensitive malonic esters.

5-Ethyl-5-(2-pyridyl)-barbituric acid is being studied pharmacologically by Mr. E. E. Swanson of The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. Preliminary tests indicate that this barbituric acid has no hypnotic or anesthetic action when administered intraperitoneally or intravenously to white rats.

### Experimental

**Diethyl Ethyl-2-pyridylmalonate.**—This ester was prepared from diethyl ethylmalonate by the same procedure and in approximately the same yields (15–20%) as previously reported.<sup>1</sup> The product obtained boiled at 136–138° (2 mm.) and contained 33.6% ethoxyl (calcd. 33.9%). The use of reduced copper, as recommended by Schickh, Binz and Schultz<sup>3</sup> for the preparation of 2-methoxy-3-aminopyridine from 2-chloro-3-aminopyridine, gave no improvement in yields. In connection with the preparation of this pyridylmalonic ester it is interesting to note that Kuhn and Richter<sup>4</sup> report that they were unable to obtain any of the pyridylmalonic ester by the condensation of 2-bromopyridine with the unsubstituted malonic ester.

**5-Ethyl-5-(2-pyridyl)-barbituric Acid.**—In a 250-ml. 3-neck round-bottom flask fitted with a dropping funnel, mechanical stirrer and a condenser set for downward distillation, was placed 4.8 g. (0.08 mole) of urea, 10.6 g. (0.04 mole) of ethyl-2-pyridylmalonic ester, 1 g. of sodium *t*-butoxide and 100 ml. of dry *t*-butyl alcohol. This mixture was heated to the boiling point of the alcohol and the latter slowly distilled at the rate of about 100 ml. per hour from the reaction flask. The distilled alcohol was re-

(2) Cope and Hancock, *ibid.*, **61**, 776 (1939).

(3) Schickh, Binz and Schultz, *Ber.*, **68**, 2593 (1936).

(4) Kuhn and Richter, *This Journal*, **57**, 1927 (1935).

(1) Walter and McElvain, *This Journal*, **57**, 1891 (1935).

placed continuously by fresh *t*-butyl alcohol from the dropping funnel and each hour another 1-g. portion of sodium *t*-butoxide was added to the reaction mixture through the neck of the reaction flask that held the dropping funnel. After a total of 11.5 g. (0.12 mole) of the butoxide had been added over a period of ten hours all of the *t*-butyl alcohol was distilled off—the last traces were removed under diminished pressure—and the residue dissolved in 100 ml. of water. The exact amount of dilute hydrochloric acid to react with the sodium *t*-butoxide that was used then was added to the aqueous solution. From this neutralized solution 0.9 g. (10%) of 5-ethyl-5-(2-pyridyl)-barbituric acid,<sup>5</sup> m. p. 257–258°, crystallized on standing. This compound may be recrystallized from dilute alcohol.

(5) The preparation of this barbituric acid is reported (*Chem. Zentr.*, 108, I, 2405 (1937)) in an abstract of a French patent. However, this abstract repeats a typographical error in the text of the patent. The structure of the barbituric acid that is shown in the patent indicates it to be 5-ethyl-5-(4-pyridyl)-barbituric acid, which is the compound that would be expected from the reactants (4-pyridylpyridinium bromide hydrobromide and 5-ethylbarbituric acid) that were used. No properties of this barbituric acid are listed in the patent.

*Anal.* Calcd. for  $C_{11}H_{11}O_2N_3$ : N, 18.03. Found: N 18.07.

The aqueous solution from which the barbituric acid was filtered was evaporated to dryness and the residue extracted with hot ethyl acetate. From the ethyl acetate 4.6 g. (55%) of  $\alpha$ -(2-pyridyl)-butyrylurea (II), m. p. 122–123°, was obtained.

*Anal.* Calcd. for  $C_{10}H_{13}O_2N_3$ : N, 20.30. Found: N, 19.95.

A 0.4132-g. sample of this ureide yielded on quantitative hydrolysis<sup>6</sup> 0.0645 g. of ammonia (calcd. 0.0679).

### Summary

The preparation of 5-ethyl-5-(2-pyridyl)-barbituric acid by the condensation of ethyl-2-pyridylmalonic ester with urea in the presence of sodium *t*-butoxide in *t*-butyl alcohol is described.

This barbituric acid appears to have no hypnotic or anesthetic action.

(6) McElvain, *THIS JOURNAL*, 57, 1303 (1935).

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

## The Halogenation of Pyridine

BY S. M. McELVAIN AND M. A. GOESE

In connection with some investigations in progress in this Laboratory it became necessary to prepare the 2- and 3-bromopyridines in fairly large (300–500 g.) quantities. Work along this line started as an evaluation of the various methods that have been described in the literature and then progressed into the development of improved and, in certain respects, novel procedures for the preparation and isolation of the desired compounds. This paper reports the details of these procedures together with the results of the application of one of them to other halogens and to the three picolines.

**2-Bromopyridine.**—While this compound may be prepared from such 2-substituted pyridines as 2-aminopyridine<sup>1a</sup> or 1-methyl-2-pyridone,<sup>1b</sup> it seemed that the direct bromination procedure of Wibaut and Den Hertog<sup>2</sup> would be more suitable for its preparation in quantity. This latter procedure involves a vapor phase reaction of bromine and pyridine at 500° and is carried out by passing the vapors of the reactants through a tube that is maintained at this temperature. The yield of the 2-bromopyridine is about 48%. This procedure was found in the present work to be quite satisfactory although somewhat slow, but it was possible to improve it in this latter respect by preheating the vapors of the reactants and packing the reaction tube with short lengths of glass tubing. An apparatus and procedure in which the rate of passage of the reactants through the reaction tube may be increased five-fold over that used by

Wibaut and Den Hertog, and with which it is possible to prepare 400–500 g. of 2-bromopyridine in about five hours are described in the Experimental Part. In addition to the 2-bromopyridine, 2,6-dibromopyridine is obtained in 17% yields by this procedure.

**3-Bromopyridine.**—The preparation of this compound, together with some of the 3,5-dibromopyridine, by heating for six to eight hours at 230–250° the crystalline pyridine hydrobromide perbromides—obtained by crystallization from glacial acetic acid—has been described in an earlier paper<sup>3</sup> from this Laboratory. Yields of 36–38% of 3-bromopyridine and 30–36% of 3,5-dibromopyridine were obtained. Since this work was reported the vapor phase bromination of pyridine to 3-bromopyridine in 39% yields has been described.<sup>2</sup> This bromination was carried out in a pumice packed tube at 300°. Somewhat later, Maier-Bode<sup>4</sup> obtained 34–42% yields of 3-bromopyridine when bromine vapor was passed through fused pyridine hydrochloride at 215° in the presence of mercuric chloride.

Since the vapor phase bromination of pyridine had proved satisfactory for the preparation of 2-bromopyridine it was used at first for the preparation of 3-bromopyridine. The yields of this product were approximately those reported by Wibaut but the rate at which the reaction could be run was so low that it seemed impracticable for the preparation of the product in any considerable quantity. For example, with the apparatus shown in Fig. 1 that had proved quite efficient in

(1) (a) Craig, *THIS JOURNAL*, 56, 231 (1934); (b) Fischer, *Ber.*, 32, 1297 (1899).

(2) Wibaut and Den Hertog, *Rec. trav. chim.*, 51, 361 (1932).

(3) Englert and McElvain, *THIS JOURNAL*, 51, 863 (1929).

(4) Maier-Bode, *Ber.*, 69, 1534 (1936).