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]

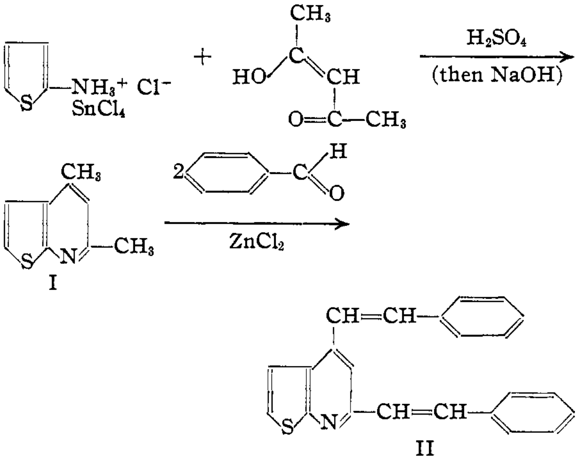
4,6-Dimethylthieno(2,3-b)pyridine, an Isoster[1] of 2,4-Dimethylquinoline

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.



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.

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(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).

Anal. Calcd. for $C_9H_{10}ClNS$: Cl, 17.8. Found: Cl, 17.9.

The **methiodide** was crystallized from a mixture of ethyl acetate and alcohol, m. p. 228–229° dec.

Anal. Calcd. for $C_{10}H_{12}INS$: I, 41.7. Found: I, 42.1.

The **picrate** melted at 190–191°, after three crystallizations from alcohol.

Anal. Calcd. for $C_{15}H_{12}N_4O_7S$: N, 14.3. Found: N, 13.8.

Attempted Preparation of Other Thieno(2,3-b)pyridines.—Similar experiments were made to form other derivatives of thieno(2,3-b)pyridine by treating either 2-aminothiophene stanni-hydrochloride or 2-aminothiophene hydrochloride[7] with (a) benzoylacetone,[8] (b) dibenzoylmethane, (c) the sodium salt of 3-formyl-2-butanone,[9] (d) the benzoate of 3-formyl-2-butanone,[10] (e) 2-formyl-3-pentanone[11] or (f) the benzoate of 2-formyl-3-pentanone[12] in the presence of such condensing agents as concentrated sulfuric acid, fused zinc chloride, hydrogen bromide in glacial acetic acid or phosphorus pentoxide. In every case a tar was obtained as the product of reaction, some of the carbonyl compound being recovered in a few instances. Procedures involving pyrolysis were equally unsuccessful. In the experiments with dibenzoylmethane, benzoic acid was always isolated in good yield.

It was also not found possible to apply the Doebner and v. Miller reaction[13] to 2-aminothiophene. Here the procedure was varied to employ either 2-aminothiophene hydrochloride or 2-aminothiophene stanni-hydrochloride with paraldehyde or crotonaldehyde. Both hydrochloric and sulfuric acids were used as condensing agents.

4,6-Distyrylthieno(2,3-b)pyridine was prepared by the methods of Wallach and Wusten,[14] and Jacobsen and Reimer[15] had employed successfully in the quinoline series. One gram of 4,6-dimethylthieno(2,3-b)pyridine and 1.3 g. of benzaldehyde were mixed with a small amount of fused zinc chloride and allowed to stand at 25° for two hours. The reaction mixture was then made basic with ammonium hydroxide and extracted with benzene. The product was isolated by precipitating it from the benzene solution as the hydrochloride and then treating the latter with alkali. After recrystallization from benzene and petroleum ether it melted at 238°.

Anal. Calcd. for $C_{23}H_{17}NS$: N, 4.13. Found: N, 4.08.

When hydrogen chloride was passed into a benzene solution of the compound, the hydrochloride precipitated as yellow crystals which turned green on standing. It was crystallized from a mixture of acetone and ether, m. p. 268°.

Anal. Calcd. for $C_{23}H_{18}ClNS$: Cl, 9.45. Found: Cl, 9.62.

Summary

4,6-Dimethylthieno(2,3-b)pyridine has been prepared and characterized. Its methyl groups are active and condense with benzaldehyde in the same manner as the quinoline analog. Attempts to prepare related compounds have so far been unsuccessful.

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[7] Stadler, *Ber.*, **18**, 2316 (1885).

[8] Claisen, *ibid.*, **38**, 693 (1905).

[9] Tracy and Elderfield, *J. Org. Chem.*, **6**, 63 (1941).

[10] Auwers and Kohlhaas, *Ann.*, **437**, 36 (1924).

[11] Claisen and Meyerowitz, *Ber.*, **22**, 3273 (1889).

[12] M. p. 68–69° after two crystallizations from alcohol. *Anal.* Calcd. for $C_{13}H_{14}O_3$: C, 71.5; H, 6.43. Found: C, 70.9; H, 6.47.

[13] Doebner and v. Miller, *ibid.*, **16**, 2464 (1883).

[14] Wallach and Wusten, *ibid.*, **16**, 2007 (1883).

[15] Jacobsen and Reimer, *ibid.*, **16** 2602 (1883).

URBANA, ILLINOIS RECEIVED JUNE 11, 1941

[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY AND THE DIVISION OF FRUIT PRODUCTS, UNIVERSITY OF CALIFORNIA]

Hypericin, the Photodynamic Pigment from St. John'swort

BY N. PACE[1] AND G. MACKINNEY

When certain domestic animals graze on St. John'swort (*Hypericum perforatum*) they sicken on exposure to sunlight owing to ingestion of a photodynamic pigment, hypericin, which has been variously described as a porphyrin, a flavone, an anthocyanin, and most recently a *meso*-dianthrone. We believe hypericin to be a partially reduced polyhydroxyhelianthrone. The chemical nature of the pigment is discussed here, but it may be noted that hypericin is a highly active photodynamic pigment, causing in concentrations as low as 10^{-7} *M*, hemolysis of red blood cells on exposure to light of suitable wave length.[2]

Location of Hypericin in the Plant.—The leaves of the St. John'swort family are covered with pellucid dots and glands. Those of *H. perforatum* exhibit numerous black dots 0.5 to 1 mm. in diameter. The pigment hypericin occurs as a semi-solid mass in these dots which are scattered over the surface of leaves, stems and petals.[3,4]

Extraction and Isolation of Hypericin.—Pigments of *Hypericum* species include chlorophyll,

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[1] A grant from the College of Agriculture is gratefully acknowledged.

[2] An observation by Dr. H. F. Blum, who attracted our attention to this problem.

[3] E. Siersch, *Planta*, **3**, 481 (1927).

[4] A. W. Sampson and K. W. Parker, *Calif. Exp. Sta. Bull.*, No. 503 (1930).