product was recrystallized from water after treatment with decolorizing charcoal, care being taken to keep the temperature below 80°; yield 75%. The compound melted with decomposition at 165–166°; $[\alpha]^{30}D$ 74° in water.

Anal. Calcd. for $C_{12}H_{16}O_3N_2S$: C, 53.71; H, 6.01; N, 10.44; neut. equiv., 268. Found: C, 54.27; H, 6.08; N, 10.48; neut. equiv., 267.

L-Benzylmercaptomethyldiketopiperazine (V).—Two grams of IV was dissolved in the minimum necessary amount of boiling water, and the solution was boiled 10 minutes. On cooling, the product separated as small white plates, which melted sharply at 198°; yield 1.7 g. The compound was not soluble in dilute acid, dilute base, ether, acetone, carbon disulfide, chloroform, ethanol or cold water, but was somewhat soluble in pyridine, and very soluble in hot water; $[\alpha]^{30}D$ 65.4° in pyridine.

Anal. Calcd. for $C_{12}H_{14}O_2N_2S$: C, 57.57; H, 5.64; N, 11.19. Found: C, 57.77; H, 5.67; N, 11.14.

N-(N-Phenylacetyl-S-benzyl-L-cysteinyl)-glycine (VI).—Compound IV was treated with sodium hydroxide and phenylacetyl chloride. The product was crystallized from ethyl acetate; yield 73%, m.p. 129–131°, $[\alpha]^{24}D$ −42.5° in methanol.

Anal. Calcd. for $C_{20}H_{22}O_4N_2S$: C, 62.15; H, 5.74; N, 7.25; neut. equiv., 386. Found: C, 62.73; H, 5.89; N, 7.34; neut. equiv., 382, 386.

N-(N-Phenylacetyl-L-cysteinyl)-glycine (I).—Compound VI was reduced with sodium in liquid ammonia. The product was crystallized from water. An inert atmosphere, nitrogen, was maintained around all the operations; yield 75%, m.p. 134–135°, $[\alpha]^{27}D$ −35° in ethanol.

Anal. Calcd. for $C_{13}H_{16}O_4N_2S$: C, 52.69; H, 5.48; N, 9.46. Found: C, 52.72; H, 5.62; N, 9.62.

Determination of the mercapto group by the method of Kimball, Kramer and Reid[3] gave an equivalent weight of 300; calcd. 296.

N-(N,N'-Dicarbobenzoxy-L-cystinyl)-di-D-valine (VII).—A solution of 8.0 g. (0.068 mole) of D-valine ($[\alpha]^{27}D$ −28.4° in 20% hydrochloric acid) in 80 ml. of normal sodium hydroxide was allowed to react with the acid chloride from 15.0 g. (0.03 mole) of N,N'-(dicarbobenzoxy)-L-cystine.[10]

For purification the product was dissolved in an excess of dioxane, the solution was heated to boiling, and hot water added carefully until the solution was barely cloudy. Slow cooling of this hot solution yielded 12.5 g. (60%) of fine white needles, melting at 145–147°, $[\alpha]^{29}D$ −42.5° in methanol.

Anal. Calcd. for $C_{32}H_{42}N_4O_{10}S_2$: C, 54.41; H, 5.99; N, 7.93; neut. equiv., 353. Found: C, 53.54; H, 5.37; N, 7.89; neut. equiv., 355, 356.

N-(S-Benzyl-L-cysteinyl)-D-valine (VIII).—The procedure was similar to that used for preparation of IV. From 5.0 g. (0.007 mole) of VII, 3.0 g. (70%) of VIII, m.p. 200–202°, was obtained; $[\alpha]^{29}D$ 14.5° in 50% ethanol.

Anal. Calcd. for $C_{15}H_{22}N_2O_3S$: C, 58.04; H, 7.15; N, 9.03; neut. equiv., 310. Found: C, 58.10; H, 7.12; N, 8.96; neut. equiv., 311.

N-(N-Phenylacetyl-S-benzyl-L-cysteinyl)-D-valine.—Compound VIII was treated with phenylacetyl chloride and sodium hydroxide. The crude product was dissolved in ethyl acetate from which it separated as an oil. This product was not obtained as a solid. It was used directly for the following step.

N-(N-Phenylacetyl-L-cysteinyl)-D-valine (II).—The procedure used was similar to that used for preparation of I. Two grams of the sirup described above gave 1.0 g. (62%) of II, m.p. 178–180°, $[\alpha]^{30}D$ −46.0° in ethanol.

Anal. Calcd. for $C_{16}H_{22}N_2O_4S$: C, 56.78; H, 6.55; N, 8.28; equiv. wt., 338. Found: C, 54.05; H, 6.70; N, 7.86; equiv. wt., 344.[3]

(10) The reaction conditions were identical with those described for preparation of III.

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Thieno[3,2-b]pyridine. I. The Preparation and Properties of an S-Isosteric 8-Hydroxyquinoline[1]

BY JOHN T. SHEEHAN AND GEORGE J. LEITNER[2]

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The synthesis of 3-hydroxythieno[3,2-b]pyridine, an isoester of 8-hydroxyquinoline, from 3-(carboxymethylmercapto)-picolinic acid is described. In addition, a number of derivatives of 3-hydroxythieno[3,2-b]pyridine have been prepared.

Aside from the thianaphthene derivatives relatively little has been reported about other condensed ring systems of thiophene. For the preparation of some S-isosteric analogs[3] of Pamaquine as antimalarials the route chosen was *via* 3-hydroxythieno(3,2-b)pyridine, an isoster of 8-hydroxyquinoline.[4] The formation of this compound is intimated by Plazek and Sucharda[5] in their synthesis of δ-thiopyrindigo (Fig. 1); however, its isolation was not described nor was it characterized.

In the present work, following the method employed by Koenigs and Kantrowitz[6] in their synthesis of 3-hydroxy-4,6-dimethylthieno(3,2-c)pyridine, 3-hydroxythieno(3,2-b)pyridine was initially prepared directly by heating 3-(carboxymethylmercapto)-picolinic acid in acetic anhydride. The yields obtained by this method were only about 15%; however, it was found that by first isolating the intermediate acetate derivative and subsequently hydrolyzing it, the over-all yield of 3-hydroxythieno(3,2-b)pyridine could be raised to about 50%. An attempt to effect cyclization of 3-(carboxymethylmercapto)-picolinic acid in neutral medium like mineral oil proved unsuccessful, decarboxylation occurring to form 3-(carboxymethylmercapto)-pyridine.[7]

The 3-(thieno(3,2-b)pyridyl) acetate, unlike its isoster 8-quinolyl acetate is a stable oil which can be kept indefinitely in the absence of moisture. It is readily hydrolyzed by heating in water and the hydrolysis proceeds smoothly in an atmosphere of

(1) Presented in part before the Medicinal Section of the XIIth International Congress, New York, N. Y., Sept. 10–13, 1951.

(2) Nuodex Products Inc., Elizabeth, N. J.

(3) J. T. Sheehan, THIS JOURNAL, **74**, 5504 (1952).

(4) 4-Hydroxybenzothiazole, another isoster of 8-hydroxyquinoline has been investigated by H. Erlenmeyer, *et al.*, *Helv. Chim. Acta.*, **21**, 709, 1695 (1938).

(5) E. Plazek and E. Sucharda, *Ber.*, **59**, 2282 (1926).

(6) E. Koenigs and H. Kantrowitz, *ibid.*, **60**, 2097 (1927).

(7) The failure of 3-(carboxymethylmercapto)-pyridine to cyclize in acetic anhydride as described by A. E. Chichibabin and N. N. Vorozhtzov, Jr., *ibid.*, **66**, 364 (1933), would seem to suggest that the cyclization occurs through the carboxyl on carbon atom two of the pyridine ring.

nitrogen to form 3-hydroxythieno(3,2-b)pyridine. In the presence of air, however, varying amounts of the ether, bis-(3-thieno(3,2-b)pyridyl) oxide, are formed during hydrolysis, depending on the temperature and the period of heating. In some instances as much as 22% of this compound was formed.

Although 3-hydroxythieno(3,2-b)pyridine may be regarded as the enol form of pyridylthioindoxyl (Fig. 1) since on oxidation it forms δ-thiopyrindigo,[5]

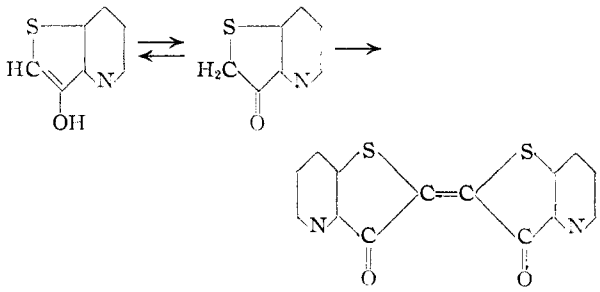

Fig. 1.

the existence of the keto form could not be established either by titration according to the method of Mitchell and Smith,[8] or by reaction with dinitrophenylhydrazine. Moreover, the ultraviolet absorption spectra[9] of the 3-hydroxythieno(3,2-b)pyridine and 8-hydroxyquinoline, as shown in Fig. 2,

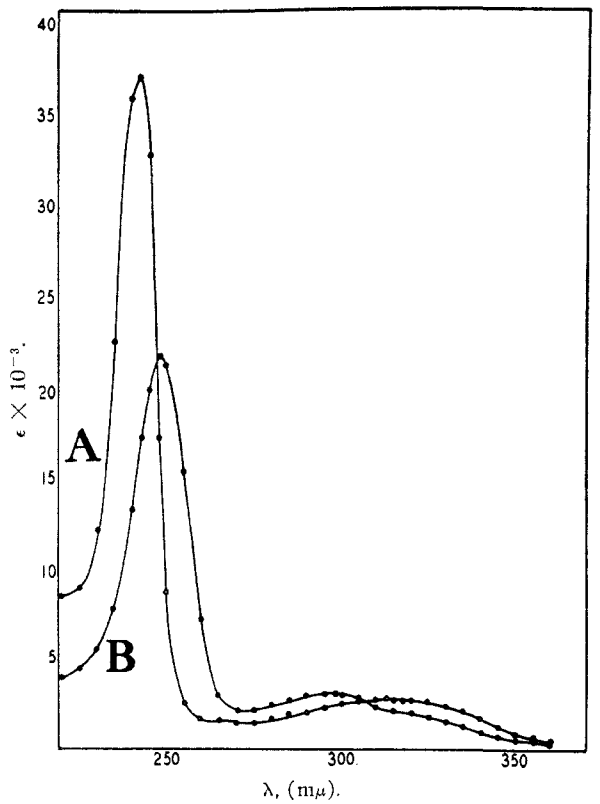

Fig. 2.—A, 8-Hydroxyquinone and B, 3-hydroxythieno-(3,2-B)pyridine; solvent, ethanol.

(8) J. Mitchell, Jr. and D. M. Smith, *Anal. Chem.*, **22**, 750 (1950).

(9) The authors are indebted to Dr. N. H. Coy of the Laboratory of Applied Physics for the determination and interpretation of the ultraviolet and infrared spectra of this compound.

are in close agreement and resemble those obtained by Ewing and Steck[10] for those quinolinols which are assigned a phenolic rather than a ketonic structure. Finally, an examination of the infrared absorption spectrum of 3-hydroxythieno(3,2-b)pyridine showed no characteristic band for either a hydroxyl or a carbonyl group, but there was a weak band at 3.78 μ which is indicative of the presence of a chelated hydroxyl group.[11,12] Unlike the free base the hydrochloride and hydroiodide salts have bands at 3.10 and 3.04 μ, respectively, indicating the presence of a hydroxyl group but bands corresponding to the presence of a carbonyl group are absent.

When 3-hydroxythieno(3,2-b)pyridine is treated with iodine monochloride, a yellow product is formed which possesses an extremely labile iodine atom. This substance when purified by reprecipitation gives a satisfactory elementary analysis for a monoiodo derivative of 3-hydroxythieno(3,2-b)-pyridine. So far, the structure of this compound has not been determined, but it is not the hydroiodide salt which is a more stable compound. The lability of the iodine suggests the possibility that an iodine complex is formed such as occurs with polyvinylpyrrolidone and iodine.[13]

Experimental[14]

3-Thieno(3,2-b)pyridyl Acetate.—The 3-(carboxymethylmercapto)-picolinic acid used in this preparation was obtained by the method of Plazek and Sucharda[5] from 3-aminopicolinic acid. The latter acid was prepared by the procedure of Sucharda.[15]

A mixture of 30 g. (0.14 mole) of 3-(carboxymethylmercapto)-picolinic acid and 150 ml. of acetic anhydride was heated with rapid stirring to an internal temperature of 135° and maintained at this temperature until the evolution of carbon dioxide ceased as indicated by barium hydroxide solution—about 45 minutes. The solution was then cooled and the excess anhydride evaporated *in vacuo*. The dark tarry residue was extracted five times with 100 ml. of acetone and the combined acetone extracts filtered and the solvent evaporated. The oily residue was dissolved in 500 ml. of ether, the insoluble material filtered and the solvent evaporated. The product, a clear oil which darkens and hydrolyzes slowly in the air, was distilled; yield 21 g. (78%), b.p. 143–145° (2.0–2.5 mm.), $n^{20}D$ 1.6104, $n^{26}D$ 1.6072, d^{25} 1.325.

Anal. Calcd. for $C_9H_7NO_2S$: C, 55.94; H, 3.65; N, 7.24; S, 16.59; CH_3CO–, 22.27. Found: C, 55.96; H, 3.87; N, 7.52; S, 16.87; CH_3CO–, 21.95.

When 3-(carboxymethylmercapto)-picolinic acid was heated to 275° in paraffin oil a product was obtained which on recrystallization from ethanol melted at 170–172°. 3-Carboxymethylmercapto)-pyridine is reported[7] to melt at 170–173°.

Anal. Calcd. for $C_7H_7NSO_2$: C, 49.70; H, 4.14; N, 8.28; S, 18.93. Found: C, 49.94; H, 4.26; N, 8.18; S, 17.46.

3-Hydroxythieno(3,2-b)pyridine.—To 500 ml. of water heated on a steam-bath in a three-necked flask fitted with a stirrer, nitrogen delivery tube and condenser set downward for distillation, a solution of 19.5 g. (0.1 mole) of 3-thieno-(3,2-b)pyridyl acetate dissolved in 100 ml. of ether was added over a period of one hour. The ether was distilled

(10) G. W. Ewing and E. A. Steck, THIS JOURNAL, **68**, 2181 (1946).

(11) R. S. Rasmussen, D. D. Tunnicliff and R. R. Brattain, *ibid.*, **71**, 1068 (1949).

(12) E. D. Amstutz, I. M. Hunsberger and J. J. Chessick, *ibid.*, **73**, 1220 (1951).

(13) *Chem. Eng. News*, **29**, 664 (1951).

(14) All melting points are uncorrected. Microanalyses were carried out by Mr. J. F. Alicino of these laboratories.

(15) K. Sucharda, *Ber.*, **58**, 1727 (1925).

off as added, in an atmosphere of nitrogen, while stirring. After the addition was complete, the mixture was heated and stirred for an additional hour, cooled and filtered. The product, 17 g., was dissolved in hexane (7 l.) and filtered hot to remove 3 g. of the insoluble **bis-(3-thieno(3,2-b)pyridyl) oxide** (see below). On cooling, 12.5 g. of product separated (80%), m.p. 146–148°. The product can be crystallized also from water or ethanol.

Anal. Calcd. for C_7H_5NOS: C, 55.61; H, 3.31; N, 9.26; S, 21.19. Found: C, 55.82; H, 3.21; N, 9.38; S, 21.25.

The hydrochloride and hydroiodide of the base were prepared by dissolving the base in ether and adding the calculated amount of acid in ethanol solution. The salts were crystallized from ethanol–ethyl acetate or acetone–hexane. The hydrochloride is bright yellow and hygroscopic. The anhydrous salt melts at 168–170°.

Anal. Calcd. for $C_7H_5NOS \cdot HCl$: N, 7.46; Cl, 18.89. Found: N, 8.00; Cl, 18.52.

The hydroiodide melts at 180–182° and is greenish-yellow in color.

Anal. Calcd. for $C_7H_5NOS \cdot HI$: N, 5.01; I, 45.47. Found: N, 4.90; I, 45.93.

Bis-(3-Thieno(3,2-b)pyridyl) Oxide.—The insoluble by-product (3 g.) obtained in the above preparation was crystallized from methanol and material melting at 198–200° obtained. Recrystallized from benzene it melted at 221–222°, yield 2.5 g.

Anal. Calcd. for $C_{14}H_8N_2OS_2$: N, 9.85; S, 22.55. Found: N, 9.49; S, 22.87.

The hydrochloride was prepared by dissolving with heating 2.5 g. of **bis-(3-thieno(3,2-b)pyridyl) oxide** in 30 ml. of 10% hydrochloric acid. The solution was filtered and cooled. On standing the salt separated; it was filtered, washed with ethanol and dried, m.p. 295–298°.

Anal. Calcd. for $C_{14}H_8N_2OS_2 \cdot HCl$: N, 8.75; Cl, 11.05; S, 19.98. Found: N, 8.81; Cl, 11.61; S, 19.71.

3-(Thieno(3,2-b)pyridyl) Benzoate.—A mixture of 2 g. of 3-hydroxythieno-(3,2-b)pyridine and 20 ml. of benzoyl chloride was heated in a sealed tube for four hours at 200°. The excess benzoyl chloride was removed by distillation; the residue was washed with 10% sodium hydroxide solution and the insoluble material filtered off. Crystallized from hexane it melted at 96°.

Anal. Calcd. for $C_{14}H_9NO_2S$: C, 65.86; H, 3.55; N, 5.48; S, 12.53. Found: C, 65.96; H, 4.02; N, 5.72; S, 12.51.

3-Hydroxythieno(3,2-b)pyridine Methiodide.—A mixture of 4 g. of 3-hydroxythieno(3,2-b)pyridine, 4 ml. of methyl iodide and 20 ml. of benzyl alcohol was placed in a sealed tube and kept for 24 hours at room temperature and for 24 hours at 60–65°. The crystalline product which formed was filtered off and washed with ether. Crystallized twice from methanol a product was obtained which melted at 190° with decomposition.

Anal. Calcd. for C_8H_8NOIS: C, 32.71; H, 2.74; N, 4.77; S, 10.93; I, 43.29. Found: C, 32.51; H, 2.87; N, 4.89; S, 10.48; I, 42.91.

Iodo-3-hydroxythieno(3,2-b)pyridine.—Three grams (0.02 mole) of 3-hydroxythieno(3,2-b)pyridine was dissolved in 100 ml. of 10% hydrochloric acid and to the solution, slowly at room temperature, with stirring, was added 3.24 g. (0.02 mole) of iodine monochloride dissolved in 50 ml. of 10% hydrochloric acid. During the addition a bright yellow crystalline material separated. When the addition was complete the mixture was stirred for an additional ten minutes while cooling. The product was then filtered off and washed immediately with about 30 ml. of 10% hydrochloric acid, sucked as dry as possible on the filter and then dried in a desiccator over sodium hydroxide. The yield of crude product was 6.0 g. (96%), m.p. 137–139°. This crude product can be purified by dissolving it in 150 ml. of methanol at room temperature and filtering. To the filtrate was added immediately 350 ml. of cold anhydrous ether and the mixture cooled in an ice–water-bath. The precipitate formed was filtered and dried *in vacuo*. The product (5.5 g., 85%) melted at 138–139°.

Anal. Calcd. for C_7H_5ONIS: N, 5.05; I, 45.80. Found: N, 5.32; I, 45.89.

3-Methoxythieno(3,2-b)pyridine.—Five grams (0.03 mole) of 3-hydroxythieno-(3,2-b)pyridine was methylated with dimethyl sulfate.[16] The alkaline reaction mixture was extracted with ether. The extract was washed, dried and the solvent evaporated. The product purified by crystallization from hexane melted at 78–79°.

Anal. Calcd. for C_8H_7NOS: C, 58.16; H, 4.26; N, 8.47; S, 19.34; CH_3O, 18.78. Found: C, 57.99; H, 4.74; N, 8.69; S, 19.42; CH_3O, 18.81.

3-Chlorothieno(3,2-b)pyridine.—A mixture of 2.5 g. of 3-hydroxythieno-(3,2-b)pyridine and 9 ml. of phosphorus oxychloride was heated for six hours at 190–195° in a sealed tube. The tube was opened, the excess phosphorus oxychloride distilled off and the residue dissolved in ice water and filtered. The filtrate was adjusted to *p*H 6 with sodium bicarbonate and extracted with ether. From this extract after evaporation was obtained a very low yield of the product which crystallized from hexane, m.p. 99°.

Anal. Calcd. for C_7H_4ClNS: N, 8.25; S, 18.90; Cl, 20.90. Found: N, 8.29; S, 18.78; Cl, 20.78.

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(16) The procedure described in "Organic Syntheses," Coll. Vol. 1, 1st Ed., p. 50, was followed.