Chemistry of Thienopyridines. XLII. Three Novel Compounds Derived from Thienopyridine *N*-Oxides [1]

L. H. Klemm*, Daniel R. Muchiri [2], Mark Anderson [3], William Salbador [4] and John Ford [5]

Department of Chemistry, University of Oregon
Eugene, Oregon 97403
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Extension of the Reissert-Henze reaction to treatment of thieno[2,3-*b*]pyridine 7-oxide with potassium thiocyanate and benzoyl chloride in water-methylene chloride gives a 2% yield of bis(6-thieno[2,3-*b*]pyridyl) disulfide. Peroxidation of 5-ethylthieno[2,3-*b*]pyridine (**4**) forms the 7-oxide **5** (53%), converted to a monopicrate **5a**. Picrate **5a** undergoes *N*-deoxygenation to **4**-picrate on drying at 78° *in vacuo*, but shows the expected additive mass spectrum of **5** (thermally stable) and picric acid. Nucleophilic displacement of chloride ion from 7-chlorothieno[3,2-*b*]pyridine (derived, in turn, from thieno[3,2-*b*]pyridine **4**-oxide) by the anion from ethyl cyanoacetate gives 7-(1-cyano-1-ethoxycarbonyl)methylene-4,7-dihydrothieno[3,2-*b*]pyridine (82%), stable in this iminodienic tautomeric form.

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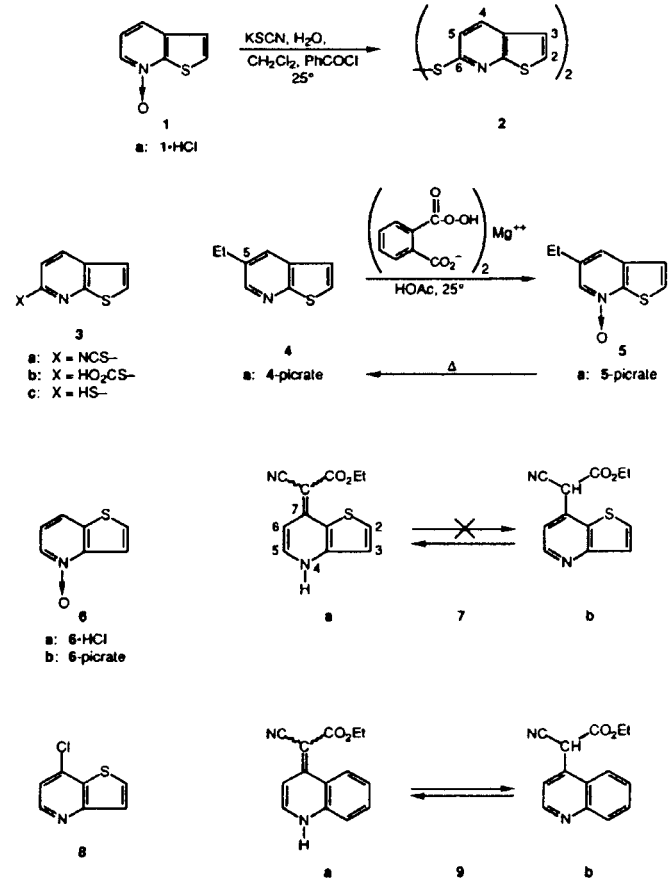
We report here the syntheses of three novel derivatives of thienopyridine *N*-oxides. First, we tried to extend the Reissert-Henze reaction by use of inorganic salts other than potassium cyanide [6]. Reaction of thieno[2,3-*b*]pyridine 7-oxide (**1**) with potassium thiocyanate and benzoyl chloride in a two-phase system of water-methylene chloride produced disulfide **2** (2% yield), plus byproducts of benzoic anhydride [7] and benzamide, instead of the expected 6-thiocyanatothieno[2,3-*b*]pyridine (**3a**). As a possible source of **2**, it is suggested that **3a** does form, but that it undergoes sequential spontaneous hydrolysis to **3b** (plus ammonia), decarboxylation to thiol **3c**, and air oxidation to **2** [8]. Benzamide could result from reaction of ammonia with benzoyl chloride [9]. Surprisingly, attempts to obtain **2** by a more direct Reissert-Henze reaction using sodium hydrosulfide or sodium disulfide instead of potassium thiocyanate were not successful. Recently Sato and coworkers reported an improved two-step route to substituted pyridinethiols and pyrazinethiols from the corresponding *N*-oxides [11]. The first step is a modified Reissert-Henze reaction in which the *N*-oxide is usually treated with diethylcarbamoyl chloride and 4-methoxytoluene-α-thiol to yield a deoxygenated 4-methoxybenzylthioheterocycle. Subsequent debenzylation produces the thiol derivative.

The molecular formula of **2** was established as $C_{14}H_8N_2S_4$ by elemental analysis, mass spectrum (molecular ion) and high resolution parent mass. The most abundant ion in the mass spectrum occurs at m/z 167 for TPSH$^+$, where TP is the thienopyridyl group. Location of the disulfide linkage at C-6 of the thienopyridine ring is apparent from the ^{1}H nmr spectrum which shows one doublet of doublets (J = 9 Hz) for H-4 and H-5 and another doublet of doublets (J = 6 Hz) for H-2 and H-3 [12].

The second study involved the synthesis of 5-ethylthieno[2,3-*b*]pyridine 7-oxide (**5**) from 5-ethylthieno[2,3-*b*]-pyridine (**4**) by means of magnesium monoperoxyphthalate hexahydrate in glacial acetic acid at room temperature. Product **5** was obtained as a yellow semisolid (53% yield), stable to evaporative distillation at 115°. Its mass spectrum was normal, *i.e.* with the molecular ion as the most intense peak and with a smaller peak (39%) for loss of oxygen [13]. For purification, **5** was converted into its



monopicrate **5a**, again with a normal mass spectrum, *i.e.* a composite of the spectra of **5** and picric acid. Surprisingly, however, **5a**, underwent thermal *N*-deoxygenation to the picrate of **4** on drying at 78° *in vacuo* for 24 hours. This transformation of a picrate may not have been observed previously.

Katritzky and Lagowski list several heterocyclic *N*-oxides which undergo thermal deoxygenation, either alone or in the presence of solid catalysts [14]. Albini and Pietra note that heterocyclic *N*-oxides are generally thermally stable though some deoxygenation may occur at elevated temperature, as during gas chromatography, mass spectrometry, or sublimation [15]. However, both *N*-oxides **1** and **6** are stable to evaporative distillation [13,16]. While the picrate of **1** has not been reported, picrate **6b** in the thieno[3,2-*b*]pyridine 4-oxide system was dried at 65° for 24 hours *in vacuo* without decomposition [17]. Moreover hydrochlorides **1a** and **6a** sublime at 60° *in vacuo* without change [17,18]. Additionally the mass spectra of **1a**, **6a**, and **6b**, obtained at elevated temperatures, were all normal. In contrast, the mass spectrum of **6**, conducted at only 50°, has a molecular ion of intensity 60% plus the *N*-deoxygenated ion as its most intense peak [18]. It is clear that there is no direct relationship between *N*-deoxygenation by heat and by electron impact.

Last of all, we extended the study of tautomerism to the system **7**. Reaction of 7-chlorothieno[3,2-*b*]pyridine (**8**), available from previous transformation of *N*-oxide **6** [18], with the sodium salt of ethyl cyanoacetate occurs in dimethylformamide at 120° to produce **7** (bright yellow needles, mp 250°) in 82% yield. These are the same conditions as used previously to convert 4-chloroquinoline into the isosteric analog **9** (mp 187°) in 53% yield [17]. Compound **7** exists exclusively in the iminodienic tautomeric form **7a** as based on its color, its ir spectrum in the solid state (NH bands at 3183 and 3155, conjugated ester carbonyl band at 1645, no absorption in the range of 1730-1750 cm^{-1}), and its ^1H NMR spectrum in hexadeuteriodimethylsulfoxide (broad singlet for NH at δ 13.4, no signal for a methinyl group). Comparatively, **9** exists largely in the iminodienic form **9a** but to a small extent in the aromatic form **9b** in the solid state. Only **9a** was noted in hexadeuteriodimethylsulfoxide solution, but equimolar amounts of **9a** and **9b** were found in deuteriochloroform solution. The ^1H nmr of **7** in deuteriochloroform was not obtained because **7** is virtually insoluble in this solvent. The thieno[2,3-*b*]pyridine analog of **7** (mp 162°), like **9**, showed clear evidence for the presence of both tautomeric forms [19].

EXPERIMENTAL [20]

Bis(6-thieno[2,3-*b*]pyridyl) Disulfide (**2**).

A vigorously stirred mixture of 1 g (6.6 mmoles) of thieno[2,3-*b*]pyridine 7-oxide [18], 2.6 g (27 mmoles) of potassium thiocyanate, 14 ml of methylene chloride, and 4 ml of water at 25° was treated dropwise with 2.8 g (20 mmoles) of benzoyl chloride. After 16 hours of additional stirring the organic layer was separated and washed successively with water, 10% hydrochloric acid, water, 2 *N* sodium hydroxide solution, and water (until neutral). The dried (sodium sulfate) organic layer was evaporated to yield a semisolid residue (0.6 g). Slow evaporation of a chloroform solution of the residue gave 47 mg (2%) of the disulfide, needles, mp 167-169°, R_f 0.56 (silica gel/ethyl acetate). Recrystallizations from the same solvent raised the melting point to 170-171°; ir (potassium bromide wafer): 3091, 1580-1530 (very strong, C=N); ^1H nmr (deuteriochloroform): δ 7.95 (d, $J_{4,5}$ = 9 Hz, 1 H, H-4), 7.66 (d, 1 H, H-5), 7.44 (d, $J_{2,3}$ = 6 Hz, 1 H, H-2), 7.18 (d, 1 H, H-3); uv (chloroform): λ max 248 nm (log ε 4.84), 311 (4.58); ms: m/z 332 (M^+, 38), 167 ($TPSH^+$, 100), 123 (37), 117 (38).

Anal. Calcd. for $C_{14}H_8N_2S_4$: C, 50.58; H, 2.42; N, 8.42; exact mass, 331.957. Found: C, 50.24; H, 2.38; N, 8.12; exact mass, 331.957.

From the chloroform recrystallization liquors were obtained benzoic anhydride and 75 mg of benzamide, mp 122-124°. The former compound was identified by direct comparison with an authentic sample [6]; while the latter was identified, by mixture melting point and mass spectrum, with a commercial sample (Aldrich).

5-Ethylthieno[2,3-*b*]pyridine 7-Oxide Picrate (**5a**).

A mixture of 1 g (6.13 mmoles) of 5-ethylthieno[2,3-*b*]pyridine (**4**) [12], 3.21 g (5.20 mmoles) of 80% magnesium monoperoxyphthalate hexahydrate (Aldrich), and 41 ml of glacial acetic acid was allowed to stand at room temperature for 60 hours, whereupon tlc (silica gel/ether) showed no evidence for unreacted **4** (R_f 0.75) and the mixture was free of peroxides (starch-iodide paper test). The mixture was concentrated, basified with solid sodium carbonate, and extracted with chloroform. The extract was dried (sodium sulfate), evaporated, and then evaporatively distilled at 115° (0.1 mm) to give 5-ethylthieno[2,3-*b*]pyridine 7-oxide (**5**) as a yellow semisolid, average yield 0.58 g (53%); positive Katritzky test [21]; ir (neat): 1237 cm^{-1} (N→O) [13].

Treatment of 1.5 g of **5** with an equimolar amount of anhydrous picric acid (1.91 g) in methanol (50 ml) gave picrate **5a** as a precipitate, recrystallized as yellow prisms from ethanol, yield 2.55 g (75%), mp 164-168°; ms: m/z 229 (TNP^+, 72), 179 (5^+, 100), 163 (5^+ -O, 18), 148 (163^+ -Me, 30), 136 (26), 123 (22).

Anal. Calcd. for $C_9H_9NOS \cdot C_6H_3N_3O_7$: Neutral equivalent 408, exact mass for **5**: 179.041. Found: Neutral equivalent [22] 408; exact mass 179.041.

Drying **5a** at 78° for 24 hours at 0.3 mm caused *N*-deoxygenation to give 5-ethylthieno[2,3-*b*]pyridine picrate (**4a**), mp 190-191°, undepressed on admixture with an authentic sample [12]; ms: m/z 229 (TNP^+, 38), 164 (11), 163 (4^+, 79), 162 (23), 149 (18), 148 (4^+ -Me, 100).

7-(1-Cyano-1-ethoxycarbonyl)methylene-4,7-dihydrothieno-[3,2-*b*]pyridine (**7a**).

Following a previous procedure [17] the sodium salt of ethyl cyanoacetate was generated in a reaction flask from 2.64 g (0.066 mole) of sodium hydride (60% dispersion in mineral oil) and 6.84 g (0.06 mole) of ethyl cyanoacetate in 10 ml of anhy-

drous dimethylformamide. The stirred mixture was cooled in an ice bath and a nitrogen atmosphere was maintained in the flask. Then 0.92 g (0.0054 mole) of 7-chlorothieno[3,2-*b*]pyridine (**8**) [18] in 5 ml of dimethylformamide was added. The cooling bath was removed and the flask was heated to 120° (oil bath), where it was maintained for 20 hours until tlc (silica gel/anhydrous ether) indicated that all **8** (R_f 0.70) had reacted to form **7** (yellow spot, R_f 0.17). The cooled mixture was treated with 20 ml of water, added dropwise, and then acidified with 2% hydrochloric acid. Gas evolution occurred and a yellow precipitate formed. The precipitate was collected by filtration and dried in air to give 1.09 g (82%) of **7a**, mp 236-247°, changed to 242-246° after washing with methanol; ir (potassium bromide wafer): 3183 and 3155 (NH), 2179 (CN), 1645 (C=O), 1583, 1479, 1212 cm^{-1}; ^1H nmr (hexadeuteriodimethyl sulfoxide): δ 13.4 (broad s, NH), 8.15 (overlapping signals, 2 aromatic H), 7.97 (d, J = 7 Hz, 1 H, H-5 or H-6), 7.33 (d, $J_{2,3}$ = 5.5 Hz, 1 H, H-2 or H-3), 4.07 (q, J_{Et} = 7 Hz, methylene group), 1.17 (t, methyl group); ms: m/z 246 (M^+, 35), 175 (19), 174 (M^+ -CH_2CH_2OC=O, 100), 173 (43), 45 (CHS^+, 35).

Recrystallization of the preceding sample from dioxane gave bright yellow, fine needles, mp 249-250° dec.

Anal. Calcd. for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37. Found: C, 58.21; H, 4.09; N, 11.07.

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