Chemistry of Thienopyridines. XXIV. Two Transformations of Thieno[2,3-*b*]pyridine 7-Oxide (1)

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Refluxing thieno[2,3-*b*]pyridine 7-oxide (**1**) with acetic anhydride plus subsequent hydrolysis produced a mixture of thieno[2,3-*b*]pyrid-6(7*H*)one (**2**) (13%) and 5-hydroxythieno[2,3-*b*]-pyridine (**4**) (4%). Refluxing **1** with phosphorus oxychloride yielded a mixture of 4- and 6-chloro-thieno[2,3-*b*]pyridines, (**5**) (54%) and (**6**) (31%), respectively. Compound **6** was also obtained directly from **2** (31%). A mechanistic rationalization for the isomerization of **1** to form **2** and **4** is presented. Marked differences in the mass spectral fragmentations of these three isomeric compounds are noted.

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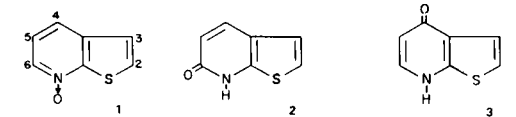
In an earlier study (3) we noted that nitration of thieno[2,3-*b*]pyridine 7-oxide (**1**) occurs at C-4 with a mixture of nitric and sulfuric acids, but at C-5 with a mixture of nitric and acetic acids. The present investigation concerns the reactions of **1** with two additional reagents, *viz.* acetic anhydride and phosphorus oxychloride.



Refluxing **1** first with excess acetic anhydride (4) and then, *in situ*, with excess water yielded both base-soluble and base-insoluble fractions. The base-soluble fraction gave crystalline **2** (10%), identified as a pyridone by means of its infrared spectrum (NH band at 3440 cm^{-1}, carbonyl absorption at 1640 cm^{-1}). Assignment of the 6-pyridone structure **2**, rather than the alternative 4-pyridone structure **3**, to this product was based on the pmr spectrum which showed, (as expected) a coupling constant of 9 Hz for H-4 and H-5, rather than the value of 4.5-6 Hz expected for H-5 and H-6 in **3** (5). Corroboration of this assignment was made by the conversion of **2** into 6-chloro-thieno[2,3-*b*]pyridine (**6**), *vide infra*.

The base-insoluble fraction was hydrolyzed by means of ethanolic sodium hydroxide and separated (by means of thick layer chromatography) into two components, additional **2** (3%) plus 5-hydroxythieno[2,3-*b*]pyridine (**4**) (4%). Compound **4** was identified by direct comparison with an authentic sample, available from an alternative synthetic pathway (6).

While none of the intermediates in the isomerization of **1** into **2** and **4** were isolated, a rationalization of these transformations is depicted in Scheme 1. 1,3-Cycloaddition of acetic anhydride to **1** forms unstable adduct **7** (7). Loss of acetic acid from **7** (pathway *a*) gives **8**, readily hydrolyzable to pyridone **2** by means of water. Alternatively, compound **7** may first undergo [1,5]sigmatropic shift to produce **9** (8) which can lose acetic acid both by pathways *c* and *b* to give **3** plus additional **2**. Reaction of the analogous quinoline 1-oxide with acetic anhydride has been reported to give higher yields of quinoline-2(1*H*)one, but the reaction is also accompanied by the formation of various unidentified byproducts (9,10).

Treatment of **1** with phosphorus oxychloride gave a mixture of 4-chloro- (**5**) (54%) and 6-chlorothieno[2,3-*b*]-pyridines (**6**) (31%), separated by preparative thick layer chromatography. Compound **5** was identified by the presence of a doublet ($J_{5,6}$ = 5 Hz) at low field (8.50 ppm) for H-6 and by its oxidation (37%) to the known 4-chloro-thieno[2,3-*b*]pyridine 7-oxide (**11**) (3). Compound **6** was identified by the presence of a doublet ($J_{4,5}$ = 8 Hz) for H-4 at 8.29 ppm and direct comparison with the product

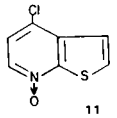


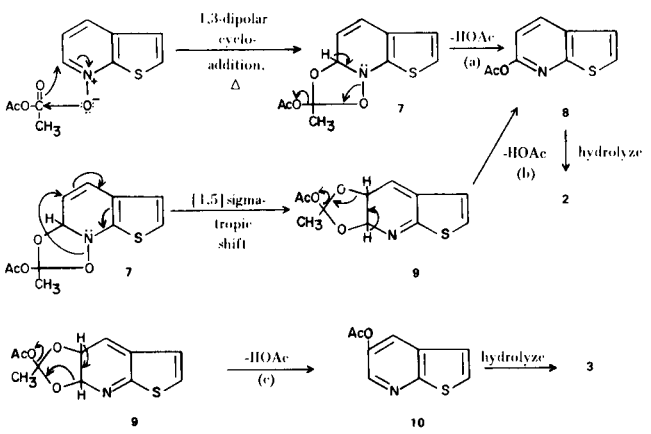
Table I

Comparative Pertinent Mass Spectral Peaks for C_7H_5NOS Isomers

m/e	Chemical Assignment	Relative Abundance of Ion, % For *N*-oxide **1**(a)	For Pyridone **2**(b)	For Hydroxy Compound **4**(c)
151	$M^{\ddagger}$	100	100	100
135	$(M\text{-}O)^{\ddagger}$	23	~0	<1
123	$(M\text{-}CO)^{\ddagger}$	12	58	3
122	$(M\text{-}\dot{C}HO)^{+}$	37	15	8
96	$(M\text{-}[CO + HCN])^{\ddagger}$	64	24	12
95	$(M\text{-}[\dot{C}HO + HCN])^{+}$	26	8	7
69	C_3HS^{+}	42	7	7
63	$C_5H_3^{+}$	28	12	3
45	CHS^{+}	41	16	6

(a) Includes all peaks of relative intensity ≥ 30%, except m/e 51 (33) and 50 (34). (b) Includes all peaks > 10%. (c) Includes all peaks ≥ 5%, except m/e 152 (9).

Scheme I



formed (31%) by treatment of pyridone **2** with phosphorus oxychloride.

It is interesting that the ratio of 1.7:1 for formation of the 4- and 6-chloro isomers in the thieno[2,3-*b*]pyridine system is the same as was reported by Bachman and Cooper (11) for the analogous 4- and 2-chloro isomers produced on treatment of quinoline 1-oxide with phosphorus oxychloride under closely similar reaction conditions. These authors noted that in the quinoline system the ratio of isomers formed varies over a range of 0.6:1 to 3.5:1 depending on the electronic nature of a substituent present in the benzenoid ring. On the basis of this criterion it appears that replacement of the benzo ring in quinoline 1-oxide by a thieno ring does not measurably alter electronic influence on the chloro-deoxygenation process.

In Table I are presented the significant mass spectral fragmentation data for the isomeric C_7H_5NOS compounds **1**, **2**, and **4**. It is apparent that these compounds are readily distinguishable on the basis of such spectra. Compound **1** is the only isomer which shows a significant loss of an oxygen atom from the parent ion (12), while **2** readily loses carbon monoxide from its molecular ion. The limited emission of carbon monoxide and the more extensive loss of formyl radical from **1** are ascribed to a partial isomerization of $\mathbf{1}^{\ddagger}$ into $\mathbf{2}^{\ddagger}$ prior to fragmentation (13). Compound **4** exhibits relatively little fragmentation, while **1** fragments extensively. The peak at m/e 45 and the loss of hydrogen cyanide typify the presence of the thienopyridine nucleus. Mass spectra of the isomeric chlorothieno[2,3-*b*]pyridines (Table II) are closely similar; with loss of a chlorine atom and of hydrogen cyanide, as well as the presence of a peak at m/e 45, noted in each case (14).

Table II

Comparative Pertinent Mass Spectral Peaks for Two Chlorothieno[2,3-*b*]pyridine Isomers

m/e	Chemical Assignment	Relative Abundance of Ion, %(a) For 4-Cl Isomer **5**	For 6-Cl Isomer **6**
171	$M^{\ddagger}$	37	37
169	$M^{\ddagger}$	100	100
134	$(M\text{-}Cl)^{+}$	45	69
107	$(M\text{-}[Cl + HCN])^{+}$	7	6
63	$C_5H_3^{+}$	16	15
45	CHS^{+}	10	14

(a) Includes all peaks of relative intensity > 10%.

EXPERIMENTAL (15)

Reaction of Thieno[2,3-*b*]pyridine 7-Oxide with Phosphorus Oxychloride.

To 2.22 g. of freshly distilled (120°/1 mm.) thieno[2,3-*b*]-pyridine 7-oxide (3) was added (dropwise and with cooling in an ice bath) 30 ml. of phosphorus oxychloride. The mixture was refluxed for 4 hours. Excess reagent was removed *in vacuo*. The residue was neutralized with 5% aqueous sodium bicarbonate and the mixture was extracted with chloroform. Removal of the solvent left a red, viscous liquid which was evaporatively distilled (60°/1 mm.) to yield 2.11 g. of colorless product. Analysis of the product by pmr (*vide infra*) showed the presence of both 4-chlorothieno[2,3-*b*]pyridine (**5**) and 6-chlorothieno[2,3-*b*]pyridine (**6**) in a ratio of 1.7:1.0. VPC analysis (0.61 m. of Carbowax, 160°) indicated the presence of 3 components (t_r 2.6 minutes, unidentified, < 3 volume %; 4 minutes, **5**; and 7.8 minutes, **6**). Tlc analysis (silica gel GF-254-chloroform; iodine vapor detection) gave R_f values of 0.30 for **5** and 0.55 for **6**.

The mixed product was separated by thick layer chromatography (6 plates, 20 x 20 cm., 2 mm. thickness), as with tlc except that development by chloroform plus drying was conducted thrice on each plate and bands (5 observed) were detected by ultraviolet light (mainly 254 nm). Compound **5** (1.34 g., 54%) was obtained as a light yellow liquid from band 2; and isomer **6** (0.76 g., 31%, m.p. 52-57°), as a yellow solid from band 4.

The 4-chloro isomer was purified further by evaporative distillation and crystallization from hexane below room temperature to form nearly colorless powder, m.p. 29.5-30°; ir (hexane): 1120, 860, 820, 760, 680 cm^{-1}; pmr (hexadeuterioacetone): δ 7.44 (2 overlapping d, 2, H-3 and H-5), 7.90 (d, 1, $J_{2,3}$ = 6 Hz, H-2), 8.50 ppm (d, 1, $J_{5,6}$ = 5 Hz, H-6).

Exact Mass Calcd. for C_7H_4ClNS: 168.975 and 170.972. Found: 168.976 and 170.973.

The 6-chloro isomer was purified further by evaporative distillation and crystallization from hexane to give needles, m.p. 56.5-58.5°; ir (potassium bromide): 1090, 870, 810, 790, 690 cm^{-1}; pmr (hexadeuterioacetone): δ 7.45 (2 overlapping d, 2, H-3 and H-5), 7.81 (d, 1, $J_{2,3}$ = 6 Hz, H-2), 8.29 (d, 1, $J_{4,5}$ = 8 Hz, H-4).

Anal. Calcd. for C_7H_4ClNS: C, 49.6; H, 2.4; N, 8.3. Found: C, 49.6; H, 2.2; N, 8.5.

4-Chlorothieno[2,3-*b*]pyridine 7-Oxide (**11**).

A mixture of 152 mg. of the aforementioned 4-chlorothieno-[2,3-*b*]pyridine (**5**), 7 ml. of glacial acetic acid, and 8 ml. of 30% hydrogen peroxide was heated at 55° for 24 hours and then processed further as in the synthesis of **1** (3). From the chloroform extract was obtained 61 mg. (37%) of light orange crystals of **11**, m.p. 168-180°; purified further by recrystallization (charcoal); identified by direct comparison (ir, pmr, tlc) with an authentic sample of **11** available from previous studies (3).

Isomerization of Thieno[2,3-*b*]pyridine 7-Oxide.

A mixture of 6.7 g. of thieno[2,3-*b*]pyridine 7-oxide dihydrate (**1**) and 57.3 g. of acetic anhydride was stirred and refluxed for 45 minutes (reaction followed by tlc), cooled, treated with 15 ml. of water, and refluxed for 10 minutes longer. Evaporation of the mixture left a red, viscous liquid which was shaken with chloroform and 5% aqueous sodium hydroxide solution. Neutralization of the aqueous layer gave a brown precipitate, purified by sublimation at 140° (0.9 mm.) and recrystallizations from cyclohexane-ethyl acetate (1:1 by volume) and carbon tetrachloride-chloroform (2:1 by volume) (plus charcoal) to give white prisms of thieno[2,3-*b*]pyrid-6(7*H*)one (**2**), yield 0.53 g., m.p. 174.5-176°; raised to 175.5-176° on recrystallization; ir (potassium bromide): 3440 (NH), 1640 cm^{-1} (carbonyl); uv (95% ethanol): max 239 nm (log ε 4.35), 247 (4.31), 264 (3.95), 323 (3.75); uv (95% ethanol plus sodium hydroxide): max 235 nm (log ε 4.34), 275 (4.04), 317 (3.80); pmr (hexadeuterioacetone): δ 6.56 (d, 1, $J_{4,5}$ = 9 Hz, H-5), 7.19 (s, 2, H-2 and H-3), 7.95 ppm (d, 1, H-4).

Anal. Calcd. for C_7H_5NOS: C, 55.6; H, 3.3; N, 9.3. Found: C, 55.5; H, 3.4; N, 9.0.

The foregoing chloroform layer (containing base insoluble products) was evaporated and the residue was refluxed with 40 ml. of 4% sodium hydroxide in aqueous ethanol (25%) for 1 hour. The hydrolysis mixture was evaporated, extracted with chloroform (to remove basic and neutral products), neutralized with hydrochloric acid, and evaporated to dryness. The residue was evaporatively distllled at 160-200° (1 mm.). The distillate was applied to a short column of alumina, through which benzene was percolated in order to elute fluorescent impurities. Crude mixed product was recovered by Soxhlet extraction of the alumina column with ethanol. Thick layer chromatography of this mixture on silica gel GF-254 (2 plates) with ethyl acetate as solvent gave 0.17 g. (13% total) of additional **2** (trailing zone) and 0.2 g. (4%) of 5-hydroxythieno[2,3-*b*]pyridine, m.p. 165-169°, identified (m.p., pmr, ir, and mass spectra) by direct comparison with an authentic sample available from earlier studies (6).

Reaction of Thienopyridone **2** with Phosphorus Oxychloride.

A mixture of 200 mg. of **2** and *ca.* 1 ml. of phosphorus oxychloride was heated under reflux for 2.2 hours. The black solid residue (16) was then refluxed with 6 ml. more of phosphorus oxychloride for 1.3 hours. Evaporation of the mixture left a residue which was treated with aqueous sodium hydroxide solution and extracted with chloroform and ether. Evaporation of the dried (sodium sulfate) combined organic extract gave a brown solid. Evaporative distillation at 66° (1 mm.) yielded 69 mg. (31%) of 6-chlorothieno[2,3-*b*]pyridine (**6**), m.p. 54-58°, identical with product obtained directly from **1** (*vide supra*).

REFERENCES AND NOTES

(1) For Paper XXIII see reference 13.

(2) NSF Undergraduate Research Participant, summer, 1975; Research Assistant, 1975-6.

(3) L. H. Klemm, I. T. Barnish, and R. Zell, *J. Heterocyclic Chem.*, 7, 81 (1970).

(4) It should be noted that **1** dihydrate was employed in this reaction. Hence, the reaction mixture may be considered to contain both acetic anhydride and acetic acid.

(5) L. H. Klemm and R. E. Merrill, *J. Heterocyclic Chem.*, 11, 355 (1974) and preceding papers.

(6) L. H. Klemm and R. Zell, *ibid.*, 5, 773 (1968).

(7) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., New York, N. Y., 1967, pp. 256-259.

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(9) E. Ochiai and T. Okamoto, *J. Pharm. Soc. Japan*, 68, 88 (1948); *Chem. Abstr.*, 47, 8073 (1953).

(10) F. Montanari and A. Risaliti, *Gazz. Chim. Ital.*, 83, 278 (1953); *Chem. Abstr.*, 47, 12388 (1953).

(11) G. B. Bachman and D. E. Cooper, *J. Org. Chem.*, 9, 302 (1944).

(12) It was noted earlier that under some conditions **1** loses oxygen so readily that it fails to exhibit a molecular ion peak in its mass spectrum [*cf.* footnote 10, reference 13].

(13) L. H. Klemm, S. Rottschaefer, and R. E. Merrill, *J. Heterocyclic Chem.*, 12, 1265 (1975).

(14) *Cf.* L. H. Klemm, R. E. Merrill, F. H. W. Lee, and C. E. Klopfenstein, *ibid.*, 11, 205 (1974).

(15) Elemental analyses were performed by M-H-W Labora-

tories, Garden City, Michigan and by Dr. R. A. Wielesek of this laboratory. Infrared spectra were obtained by means of a Beckman IR-7 or IR-10 spectrophotometer; ultraviolet absorption spectra, by means of a Cary model 15 spectrometer; pmr spectra, by means of a Varian Associates T-60 or XL-100 instrument; and mass spectra, at 70 eV by Dr. Wielesek by means of a CEC model 21-110 instrument.

(16) It is presumed that the maximum temperature attained during the initial heating period exceeds the boiling point of phosphorus oxychloride and facilitates the reaction.