Chemistry of Thienopyridines. XVII. Direct Halogenation of Thieno[2,3-*b*]pyridine (1)

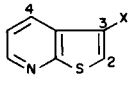
L. H. Klemm, R. E. Merrill (2), F. H. W. Lee (3), and C. E. Klopfenstein

Department of Chemistry, University of Oregon, Eugene, Oregon 97403

Received October 26, 1973

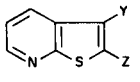
Thieno[2,3-*b*]pyridine (Ia) was converted into its 3-chloro, 3-bromo, and 3-iodo derivatives by means of elemental halogen, silver sulfate, and sulfuric acid. Bromine in a buffered chloroform solution of Ia also gave the 3-bromo compound (57% yield). Chlorine plus a refluxing mixture of Ia, chloroform, and water produced both the 3-chloro and the 2,3-dichloro derivatives. Various transformation products of these halothienopyridines (including the 2-nitro-3-halo compounds) are described and mass spectral fragmentation patterns are presented.

The prediction from quantum mechanical reactivity indices of preferential electrophilic substitution at C-3 in thieno[2,3-*b*]pyridine (Ia) (4) has been verified for two reactions which occur in strong or concentrated sulfuric acid, *viz.* deuteriodeprotonation (4) and nitration (5). Halogenation of Ia, however, has proved to be more complex due to the formation of a plethora of products from substitution, addition, and oxidation (6) processes under various conditions. Two halo compounds have already been reported. These are the 2,3-dibromo derivative (IIb) (from treatment of Ia with bromine in carbon tetrachloride-water mixture at room temperature) (4)



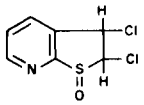
I

a: X = H
b: X = Cl
c: X = Br
d: X = I
e: X = NO_2
f: X = CN
g: X = Ac

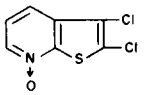


II

a: Y = Z = Cl
b: Y = Z = Br
c: Y = Cl, Z = NO_2
d: Y = Br, Z = NO_2
e: Y = I, Z = NO_2
f: Y = H, Z = Ac



III



IV

and 2,3-dichloro-2,3-dihydrothieno[2,3-*b*]pyridine 1-oxide (III) (from treatment of Ia with chlorine in chloroform-water mixture at refluxing temperature or with iodobenzene dichloride in aqueous acetonitrile at room temperature) (7-9). We report here the syntheses of monochloro, dichloro, monobromo, and monoiodo derivatives of Ia. Further studies on the formation and identification of chloro and *S*-oxide products will be presented in a subsequent paper.

Treatment of Ia with elemental chlorine, bromine, or iodine in warm concentrated sulfuric acid containing silver sulfate gave the corresponding monohalo derivatives Ib, Ic, and Id in yields of 27-40%. These reaction conditions are believed to foster electrophilic attack by positive halogen (10) on protonated Ia, in analogy to the situation proposed for halogenation of the isosteric quinoline at C-5 and C-8 (11,12). Such conditions have also been employed by Gronowitz and Sandberg in the monobrominations of thieno[2,3-*c*]- and thieno[3,2-*c*]pyridines (13). A method was then sought for monobromination of Ia under non-acidic, non-aqueous conditions. It was found that treatment of Ia with bromine in dry chloroform also gives Ic, but the product is contaminated with Ia (which partially precipitates from solution as the hydrobromide salt). This difficulty was circumvented by the addition of the chloroform-soluble buffer salt dipotassium monohydrogen orthophosphate [especially when fortified with sodium bicarbonate (to form carbon dioxide and water) and magnesium sulfate (to absorb the water)] to the reaction mixture; whereupon the yield of Ic increased to 57% (14).

It was readily apparent that the halogen atom in Ib, Ic, and Id is located in the thiophene ring since each of the pmr spectra showed a singlet for one proton (H-2 or H-3) in the range of δ 7.5-7.8 ppm (Table I). To ascertain the location of the halo substituent in the thiophene ring (15) compounds Ib-Id were nitrated to the mononitro-monohalo derivatives IIc-IIe, respectively. Absence of the aforementioned singlet in the pmr spectrum of each of these nitrohalo compounds established the fact that one had obtained either the 2-nitro-3-halothieno[2,3-*b*]pyridine (as shown in the formula) or the isomeric 2-halo-3-nitro compound. Only the former substitution pattern is consistent

TABLE I

Proton Magnetic Resonance Data for Thieno[2,3-*b*]pyridines Substituted in the 2- and/or 3-Positions

Compound No.	Solvent (a)	Substituent(s)	Chemical Shift, in δ				Coupling Constant, in Hz		
			H-2 or H-3	H-4	H-5	H-6	$J_{4,5}$	$J_{5,6}$	$J_{4,6}$
Ib	none	3-Cl	7.52	7.94	7.28	8.74	8.4	4.8	1.7
Ic	A	3-Br	7.57	8.08	7.40	8.65	7.8	4.6	1.7
Id	A	3-I	7.74	7.99	7.38	8.61	8.2	4.6	1.8
Ie (b)	B	3-NO_2	9.95	9.62	8.42	9.38	8	6	1.5
If	A	3-CN	8.32	8.35	7.56	8.80	8.3	4.8	1.6
Ig (c)	A	3-Ac	8.39	8.98	7.40	8.65	8.2	4.6	1.7
IIa	C	2,3-diCl		7.87	7.28	8.51	8	4.7	1.7
IIc	D	2-NO_2-3-Cl		8.44	7.71	8.87	8	4.5	1.5
IId	E	2-NO_2-3-Br		8.00	7.50	8.61	8.3	4.6	1.7
IIe (d)	E	2-NO_2-3-I		8.40	7.73	8.87	8.4	4.8	1.8
IIf (e)	C	2-Ac	7.84	8.17	7.36	8.79	8.2	4.5	1.8
IV	A	2,3-diCl-7-O		(f)	(f)	8.35	8	5	<2
V (g)	E	3-Cl-7-HCl	8.12	8.28	7.66	8.78	8.0	4.7	1.5

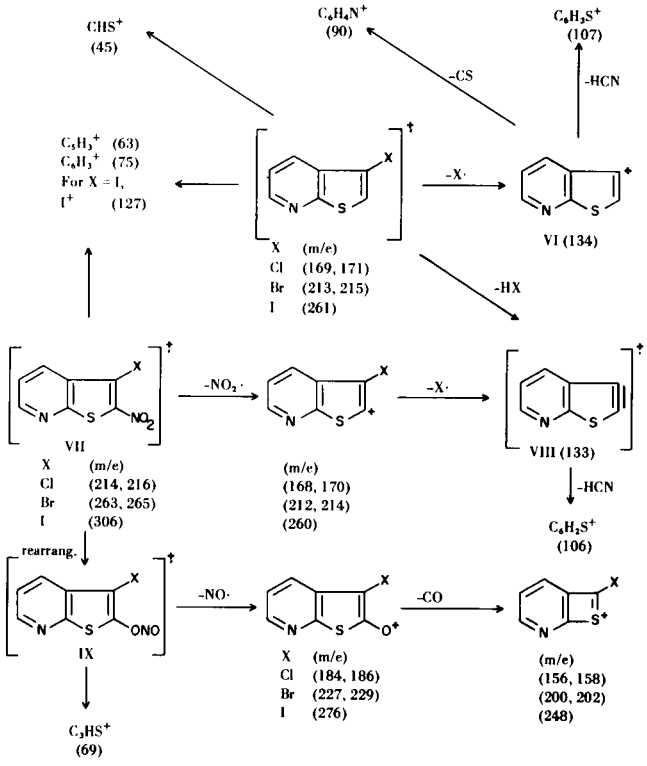
(a) Solvents used: A, deuteriochloroform; B, deuterium chloride in deuterium oxide with sodium γ-trimethylsilylpropanesulfonate as internal standard; C, carbon tetrachloride; D, hexadeuterioacetone-DMSO-d_6; E, DMSO-d_6. (b) See ref. 5. (c) Other signal: 2.62 (s, 3, methyl group). (d) Determined by means of a Varian Associates XL-100 instrument. (e) See ref. 4; other signal: 2.60 (s, 3, methyl group). (f) Multiplet, 7.3-7.9. (g) Other signal: 11.15 (s, 1, HCl).

with observed chemical shifts. On the basis of the conversion of Ia into Ie, substitution of hydrogen by a 3-nitro group is accompanied by a relatively large downfield shift ($\Delta\ \delta$ = 1.0 ppm) in the resonance of H-4, as compared to that for H-5 ($\Delta\ \delta$ = 0.45) and H-6 ($\Delta\ \delta$ = 0.23). In fact, in Ie the signal for H-4 (easily distinguished from other signals by means of *J*-values) falls downfield from that for H-6. On the other hand, a much smaller shift ($\Delta\delta < 0.5$) occurs in the resonance of H-4 on nitration of Ib-Id; this shift is closely similar to that shown by H-5 or H-6; and the signal for H-4 lies upfield of that for H-6 in the products IIc-IIe.

Confirmatory evidence for the structure of Ic was obtained by another route. Refluxing a mixture of Ic, cuprous cyanide, and DMF produced cyano derivative If, convertible to 3-acetylthieno[2,3-*b*]pyridine (Ig) on treatment with methylmagnesium iodide. Compound Ig was different from authentic 2-acetylthieno[2,3-*b*]pyridine (IIf), previously synthesized in our laboratory (4). In particular, the pmr signal for H-4 appears downfield (by 0.33 ppm) from that for H-6 in the 3-isomer and upfield (by 0.62 ppm) from that for H-6 in the 2-isomer.

Treatment of a refluxing mixture of Ia in chloroform-water with chlorine gas (in the manner used to prepare III, but with variations in processing of the crude product) gave 2,3-dichlorothieno[2,3-*b*]pyridine (IIa) (40%), plus Ib and its hydrochloride (combined yield 27%). Compounds Ib and IIa are easily separated by means of elution chromatography with silica gel, whereon III and other sulfoxides are tenaciously retained (16). As with the parent compound Ia (8), treatment of dichloro compound

SCHEME I



IIa with hydrogen peroxide and glacial acetic acid gives the N-oxide (IV), identified by its characteristic absorption at 1250 cm^{-1} (9).

Scheme 1 presents an interpretative summary of the significant mass spectral fragmentation pathways for the 3-halo compounds Ib-Id and their 2-nitro derivatives IIc-IIe. Degradations proceed very similarly to those found for 3-bromothieno[2,3-*c*]pyridine and 3-bromothieno[3,2-*c*]pyridine in cases Ib-Id and for 2-nitro-3-bromothieno-[3,2-*c*]pyridine in cases IIc-IIe (13). For Ib-Id the most abundant fragmentation ion (VI) results from loss of a halogen atom from the molecular ion. In fact, for the bromo compound fragment VI is nearly as abundant as the combined isotopic parent ions. Loss of hydrogen halide from the molecular ion, probably to form the pyridothiophyne cation radical (VIII), also occurs. For the halonitro compounds, however, peaks corresponding to simple emission of halogen from the molecular ion (VII) are not evident. Instead, one finds pertinent peaks for loss of nitric oxide and nitrogen dioxide, as well as for combined losses of nitrogen dioxide plus halogen (presumably in that order) and of nitric oxide plus carbon monoxide (probably following rearrangement of VII to the nitrite structure IX) (17,18). Both series of compounds show loss of hydrogen cyanide from the pyridine ring and the formation of various sulfur-bearing and hydrocarbon fragments. Only in the halo series (where a hydrogen atom is located at C-2) is the CHS^+ fragment significant, however. In each series an appreciably sized peak occurs at m/e 127 for the iodinium ion from the iodine-bearing substrate. Other halonium ions are not evident in the spectra.

The dichloro compound IIa shows pertinent mass spectral peaks for loss of one chlorine atom, two chlorine atoms (probably to form VIII), and two chlorine atoms plus hydrogen cyanide. This fragmentation scheme is closely analogous to the degradations of the 2,3-dibromo derivatives of thieno[2,3-*c*]- and thieno[3,2-*c*]pyridines (13). The molecular ion from the 3-cyano compound (If) emits only one molecule of hydrogen cyanide and, hence, may not produce VIII in the degradation scheme.

EXPERIMENTAL (19)

3-Bromothieno[2,3-*b*]pyridine (Ic).

To a stirred, refluxing anhydrous mixture of 40.5 g. (0.3 mole) of thieno[2,3-*b*]pyridine (Ia) (4), 78.2 g. (0.45 mole) of dipotassium monohydrogen orthophosphate, 25.2 g. (0.3 mole) of sodium bicarbonate, 45 g. of magnesium sulfate, and 750 ml. of chloroform was added (dropwise) 60 g. (0.38 mole) of bromine. Stirring and refluxing were continued for 70 hours longer. To the cooled mixture was added carbon tetrachloride, chloroform, and water. The dried (magnesium sulfate) organic layer was distilled at 3.5 mm. pressure. The fraction boiling at 77-120° was recrystallized from methylene chloride-hexane to give 36.8 g. (57%) of white platelets, m.p. 50-55°. Fractional sublimations raised the m.p. to 61-62°; uv max (absolute ethanol) 235 nm (log ϵ 4.43), 2.79 (3.72) shoulder, 288 (3.75), 298 (3.70); mass spectrum, m/e (relative abundance) (21a), 215 (61), 213 (58), 134 (100), 133 (20), 107 (32), 106 (25), 90 (30), 81 (33), 75 (36), 74 (33), 69 (30), 63 (72), 62 (41), 61 (32), 50 (44), 45 (38), 39 (28), 38 (30), 37 (34).

Anal. Calcd. for C_7H_4BrNS: C, 39.3; H, 1.9; Br, 37.3; N, 6.5; S, 15.0. Found: C, 38.9; H, 1.9; Br, 37.3; N, 6.5; S, 14.8.

The picrate of Ic crystallized from ethanol-acetone as canary yellow needles, m.p. 182.5-183.5°.

Anal. Calcd. for $C_{13}H_7BrN_4O_7S$: C, 35.2; H, 1.6; Br, 18.0; N, 12.6; S, 7.2. Found: C, 35.3; H, 1.5; Br, 18.4; N, 12.5; S, 7.2.

Halogenation of Ia in Sulfuric Acid.

To a stirred, heated mixture of 2.7 g. (20 mmoles) of Ia, 6.2 g. (20 mmoles) of silver sulfate, and 40 ml. of concentrated sulfuric acid was slowly added excess neat halogen. For chlorination, chlorine gas was bubbled into the mixture at 80-105° for 1.5 hours. For bromination, 4.8 g. (30 mmoles) of bromine was added dropwise to the mixture at 40°. For iodination, 6.3 g. (25 mmoles) of iodine was added portionwise to the mixture at 110-135°. The mixture was poured onto ice, neutralized with sodium hydroxide, and steam distilled. Extraction of the distillate (750 ml. for chloro and bromo compounds, 2 l. for iodo compound) with methylene chloride and evaporation of the organic solvent left crude halo derivative.

Evaporative distillation at *ca.* 90° (0.1 mm.) of the residue from chlorination gave 3-chlorothieno[2,3-*b*]pyridine (Ib) as a colorless liquid (1.35 g., 40%), which darkened rapidly on standing (20); uv max (absolute ethanol) 234 nm (log ϵ 4.56), 276 (3.83) shoulder, 286 (3.87), 297 (3.82); mass spectrum, m/e (relative abundance) (21c), 171 (36), 170 (11), 169 (100), 135 (11), 134 (18), 133 (16), 107 (6), 106 (5), 75 (5), 69 (6), 63 (9), 62 (6), 45 (6).

The picrate of Ib formed yellow needles from absolute ethanol m.p. 184.5-185.5°.

Anal. Calcd. for $C_{13}H_7ClN_4O_7S$: C, 39.2; H, 1.8; Cl, 8.9; N, 14.0; S, 8.0. Found: C, 39.3; H, 1.7; Cl, 9.2; N, 13.9; S, 8.3.

Crystallization from methylene chloride-hexane of the residue from bromination gave 1.15 g. (27%) of Ic, m.p. 44-53°, identical with product formed in buffer salts (as based on infrared spectrum).

Crystallization from chloroform-hexane of the residue from iodination gave 1.59 g. (30%) of 3-iodothieno[2,3-*b*]pyridine (Id), obtained as cream-colored prisms, m.p. 92-95.5°, raised to 100.5-101.5° on recrystallization from the same solvent plus evaporative distillation at 55-105° (0.2 mm.); uv max (absolute ethanol) 240 nm (log ϵ 4.31), 284 (3.72) shoulder, 289 (3.74), 298 (3.73); mass spectrum, m/e (relative abundance) (21c), 263 (6), 262 (10), 261 (100), 134 (37), 133 (5), 127 (8), 107 (8), 90 (6), 75 (6), 63 (8).

Anal. Calcd. for C_7H_4INS: C, 32.2; H, 1.5; N, 5.4; S, 12.3 Found: C, 32.2; H, 1.4; N, 5.2; S, 12.4.

Nitration of 3-Halothieno[2,3-*b*]pyridines.

To a cold (10°) solution of 0.5-1.1 g. of 3-halothieno[2,3-*b*]-pyridine (Ib-Id) in 2 ml. of concentrated sulfuric acid was added 1 ml. of 70% nitric acid. The solution was stirred at 100-115° for 15 hours and at room temperature for 12-26 hours. It was poured onto ice and neutralized with solid sodium bicarbonate. The precipitate was collected by filtration and recrystallized from a solvent.

Compound Ib gave orange needles of 2-nitro-3-chlorothieno-[2,3-*b*]pyridine (IIc) from ethanol-chloroform, m.p. 149-151° (26%), converted to yellow needles (m.p. 157.5-158.5°) on recry-

stallization from ethanol plus sublimation at 90-100° (0.7 mm.); ir (chloroform) 1530 and 1320 cm^{-1} (nitro group); mass spectrum m/e (relative abundance) (21a), 216 (34), 214 (96), 168 (30), 158 (37), 156 (100), 133 (51), 106 (22), 88 (20), 69 (22), 63 (22).

Anal. Calcd. for $C_7H_3ClN_2O_2S$: C, 39.2; H, 1.4; Cl, 16.5; N, 13.1; S, 14.9. Found: C, 39.3; H, 1.3; Cl, 16.5; N, 13.0; S, 15.1.

Compound Ic gave yellow needles of 2-nitro-3-bromothieno-[2,3-*b*]pyridine (IId) from ethanol-acetone, m.p. 156-158° (47%), raised to 163-164° on recrystallization from acetone plus sublimation at 70-130° (0.7 mm.); ir (chloroform) 1530 and 1320 cm^{-1} (nitro group); mass spectrum, m/e (relative abundance) (21a), 260 (84), 258 (81), 214 (28), 212 (24), 202 (64), 200 (60), 133 (100), 106 (34), 94 (32), 82 (21), 80 (23), 63 (23), 62 (25), 46 (20) 39 (33).

Anal. Calcd. for $C_7H_3BrN_2O_2S$: C, 32.5; H, 1.2; Br, 30.8; N, 10.8; S, 12.4. Found: C, 32.5; H, 1.1; Br, 31.0; N, 10.6; S, 12.2.

Compound Id gave bright yellow needles of 2-nitro-3-iodothieno-[2,3-*b*]pyridine (IIe) from ethanol-acetone, m.p. 230-231° (22%), raised to 243-244.5° on recrystallization from acetone plus sublimation at 120-145° (0.7 mm.); mass spectrum, m/e (relative abundance) (21a), 306 (100), 248 (33), 133 (60), 120 (21), 106 (20).

Anal. Calcd. for $C_7H_3IN_2O_2S$: C, 27.5; H, 1.0; N, 9.1; S, 10.5. Found: C, 27.3; H, 0.9; N, 8.9; S, 10.6.

3-Cyanothieno[2,3-*b*]pyridine (If).

A mixture of 1.07 g. (5 mmoles) of Ic, 1.07 g. (12 mmoles) of cuprous cyanide, and 4 ml. of dimethylformamide was refluxed for 4.5 hours and then poured into a solution of 10 g. of sodium cyanide in water. The resultant suspension was extracted with chloroform. The residue from evaporation of the dried (magnesium sulfate) extract was evaporatively distilled at 70-110° (0.4 mm) to give 361 mg. (45%) of If as needles, m.p. 95-100°, raised to 103-103.5° on recrystallization from hexane-carbon tetrachloride plus additional evaporative distillation; ir (chloroform) 2460 cm^{-1} (cyano group); uv max (absolute ethanol) 273 nm (log ϵ 3.90), 286 (3.89), 297 (3.86); mass spectrum, m/e (relative abundance) (21b), 161 (11), 160 (100, M^+), 133 (17, $[M\text{-}HCN]^+$), 111 (metastable ion, 160 → 133), 69 (21, C_3HS^+), 45 (27, CHS^+).

Anal. Calcd. for $C_8H_4N_2S$: C, 60.0; H, 2.5; N, 17.5; S, 20.0. Found: C, 60.1; H, 2.2; N, 17.1; S, 20.2.

3-Acetylthieno[2,3-*b*]pyridine (Ig).

To a cold (0°), stirred solution of 355 mg. (2.2 mmoles) of If in 15 ml. of ether and 10 ml. of benzene was added dropwise a solution of methylmagnesium iodide [prepared from 790 mg. (5.6 mmoles) of methyl iodide, 146 mg. of magnesium, and 7 ml. of ether]. The mixture was refluxed for 25 hours and then treated with aqueous ammonium chloride. Evaporation of the dried organic layer, including an extract (with methylene chloride) of the aqueous layer, gave a residue which was chromatographed on silica gel. Effluents from successive elution with hexane, benzene, methylene chloride, and chloroform were discarded. Use of ether as eluent gave a solid which was evaporatively distilled at 60-130° (0.15 mm.) to give 71 mg. (18%) of Ig, m.p. 117-121°. Recrystallization from ethanol plus sublimation (60-105°, 0.2 mm.) gave prisms, m.p. 118-119.5°; ir (chloroform) 1670 cm^{-1} (carbonyl).

Anal. Calcd. for C_9H_7NOS: C, 61.0; H, 4.0; N, 7.9; S, 18.1. Found: C, 60.8; H, 4.1; N, 8.0; S, 17.9.

Chlorination of Ia in Refluxing Chloroform-Water.

Into a vigorously stirred, refluxing mixture of 4.7 g. of Ia, 20 ml. of chloroform, and 3 ml. of water was bubbled chlorine gas for a period of 3 hours. The aqueous layer was neutralized by means of sodium bicarbonate and was extracted with more chloroform. Evaporation of the dried organic layer gave an oily solid, a portion (38%) of which was chromatographed on silica gel. Elution with carbon tetrachloride gave 1.1 g. (40%) of 2,3-dichlorothieno[2,3-*b*]pyridine (IIa), m.p. 57-64°, obtained as needles, m.p. 65-66°, on recrystallization from pentane plus evaporative distillation at 45-90° (0.4 mm.); uv max (ethanol) 234 nm (log ϵ 4.28), 277 (3.85), 287 (3.81), 298 (3.65); mass spectrum, m/e (relative abundance) (21c), 207 (13, M^+), 206 (7), 205 (72, M^+), 204 (10), 203 (100, M^+), 170 (9, $[M\text{-}Cl]^+$), 168 (24, $[M\text{-}Cl]^+$), 138-139 (metastable ion, [M-Cl]), 133 (12, $[M\text{-}2Cl]^+$), 124 (5), 106 (6, $[M\text{-}(2Cl + HCN)]^+$), 97 (5), 84 (7), 71 (5).

Anal. Calcd. for $C_7H_3Cl_2NS$: C, 41.2; H, 1.5; N, 6.9; S, 15.7. Found: C, 41.3; H, 1.1; N, 7.2; S, 15.6.

Further elution of the preceding chromatogram with chloroform gave 0.16 g. (7%) of monochloro compound Ib.

A second portion (48%) of the crude reaction product was triturated with a small amount of boiling chloroform to leave 0.7 g. (20%) of 3-chlorothieno[2,3-*b*]pyridinium chloride, m.p. 139.5-146°, obtained as needles after recrystallization from acetonitrile or isopropanol and then sublimation at 50-70° (1.5 mm.), m.p. 170-171°.

Anal. Calcd. for $C_7H_5Cl_2NS$: C, 40.8; H, 2.4; Cl, 34.4; N, 6.8 S, 15.6. Found: C, 40.8; H, 2.1; Cl, 34.9; N, 6.7; S, 15.6.

Treatment of the crystalline hydrochloride with an equivalent amount of sodium hydroxide in ethanol gave a solution. Evaporation of solvent, addition of water, and extraction with chloroform gave the free base Ib.

2,3-Dichlorothieno[2,3-*b*]pyridine 7-Oxide (IV).

A mixture of 1.9 g. of dichloro compound IIa, 3.4 ml. of 30% hydrogen peroxide, and 3 ml. of glacial acetic acid was stirred at 55-60° for 24 hours and processed further as in the preparation of thieno[2,3-*b*]pyridine 7-oxide (8). Evaporation of the chloroform extract gave 1.6 g. (78%) of crude IV, m.p. 166-177°. Recrystallization from chloroform-carbon tetrachloride gave needles m.p. 210-211°, ir (chloroform) 1250 cm^{-1} (N → O).

Anal. Calcd. for $C_7H_3Cl_2NOS$: C, 38.2; H, 1.4; Cl, 32.2; N, 6.4; S, 14.6. Found: C, 37.9; H, 1.3; Cl, 31.9; N, 6.2; S, 14.4.

Acknowledgment.

One of us (L. H. K.) wishes to thank the Office of Scientific and Scholarly Research of the University of Oregon for a grant to assist in publication of this research.

REFERENCES

(1) This investigation was supported by research grants Nos. CA-5969 from the National Cancer Institute, MH-17304 from the National Institute of Mental Health, and GM 12730 from the National Institute of General Medical Sciences, U.S. Public Health Service. For Paper XVI see ref. 18.

(2) Research and Teaching Assistant, 1969-1973.

(3) Undergraduate Research Assistant, 1969-1971.

(4) L. H. Klemm, C. E. Klopfenstein, R. Zell, D. R. McCoy, and R. A. Klemm, *J. Org. Chem.*, 34, 347 (1969).

(5) L. H. Klemm, R. Zell, I. T. Barnish, R. A. Klemm, C. E. Klopfenstein, and D. R. McCoy, *J. Heterocyclic Chem.*, 7, 373 (1970).

(6) The formation of sulfones by means of acidified hypochlorite solution was reported previously [L. H. Klemm and R. E. Merrill, *ibid.*, 9, 293 (1972)].

(7) Isomeric components of III have now been isolated in our laboratory.

(8) L. H. Klemm, I. T. Barnish, and R. Zell, *ibid.*, 7, 81 (1970).

(9) L. H. Klemm, S. B. Mathur, R. Zell, and R. E. Merrill, *ibid.*, 8, 931 (1971).

(10) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Wiley, New York, N.Y., 1968, p. 1015.

(11) Ia lacks hydrogen at a position analogous to C-8 in quinoline.

(12) P. B. D. de la Mare, M. Kiamud-din, and J. H. Ridd, *J. Chem. Soc.*, 561 (1960); *Idem., Chem. Ind.* (London), 361 (1958); M. Kiamud-din and A. K. Choudhury, *ibid.*, 1840 (1963); M. Kiamud-din and M. E. Haque, *ibid.*, 1753 (1964).

(13) S. Gronowitz and E. Sandberg, *Arkiv Kemi*, 32 249 (1970).

(14) We did not investigate bromination by means of other reagents successfully employed by Gronowitz and Sandberg (13) on their thienopyridines. We found that sodium acetate or sodium benzoate could be employed as a buffer salt in place of dipotassium monohydrogen orthophosphate, though the yield of Ic was lower when this was done.

(15) It might be noted that a definitve answer to this question is also possible by observation of the one-bond ^{13}C-^{1}H coupling constant for the unsubstituted position in the thiophene ring [unpublished results from this laboratory].

(16) Unpublished results from this laboratory. See also H. Ertel and L. Horner, *J. Chromatog.*, 7, 268 (1962); L. Fishbein and J. Fawkes, *ibid.*, 22, 323 (1966).

(17) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, Inc., San Francisco, Calif., 1967, pp. 515-521.

(18) L. H. Klemm and H. Lund, *J. Heterocyclic Chem.*, 10, 871 (1973).

(19) Elemental analyses were performed by M-H-W Laboratories, Garden City, Michigan, Micro-Tech Laboratories, Skokie, Illinois, and Dr. Susan Rottschaefer of this laboratory. Unless otherwise designated, infrared spectra were obtained by means of a Beckman IR-5 or IR-5A spectrometer; pmr spectra, by means of a Varian A-60 spectrometer (with tetramethylsilane as internal standard); ultraviolet spectra, by means of a cary model 15 spectrometer; and mass spectra, by means of a CEC model 21-110 instrument at 70 eV.

(20) Because of this instability direct elemental analysis of Ib was not obtained.

(21) Only mass spectral peaks of relative abundance (a) $\geq 20\%$ (b) $\geq 10\%$, (c) $\geq 5\%$ of the most abundant peak are reported.