Chemistry of Thienopyridines. XV. Syntheses of Thieno[3,4-*b*]- and Thieno[3,4-*c*]pyridines (1)

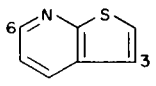
L. H. Klemm, W. O. Johnson (2), and D. V. White (3)

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

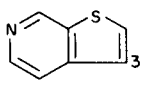
Received March 20, 1972

Thieno[3,4-*b*]pyridine (**5**) was synthesized by means of the successive steps of (a) photochlorination of 2,3-dimethylpyridine to the bis(chloromethyl) compound, (b) condensation with sodium sulfide, (c) oxidation to the sulfoxide, and (d) catalytic dehydration by means of alumina. Thieno[3,4-*c*]pyridine (**6**) was obtained in an analogous manner. Spectral properties indicate that **5** and **6** have aromatic character.

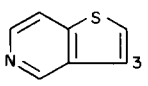
Of the six possible isomeric thienopyridines (**1-6**) syntheses on a preparative scale of **1** (4), **2** (5-7), **3** (6,7) and **4** (4,5a) have been reported in recent years. We now present details on the practical syntheses of thieno[3,4-*b*]-pyridine (**5**) and thieno[3,4-*c*]pyridine (**6**), originally reported in a brief communication (8).



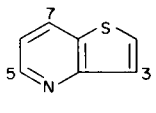
1



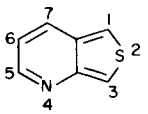
2



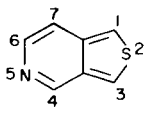
3



4

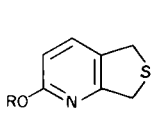


5

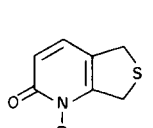


6

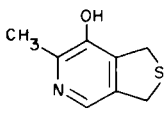
Prior to our studies parent compounds **5** and **6** were unknown. Russian workers (9) had reported the condensation of a 3-aminothiophene salt with methyl vinyl ketone to give a mixture of 7-methyl-**4** and 7-methyl-**5**. However, repetition of this reaction and structural studies on the two isolable products (4) indicated that one obtains a mixture of 5- and 7-methyl-**4**, instead. Recently, Spinner and Yeoh (10) reported syntheses of derivatives



7



8



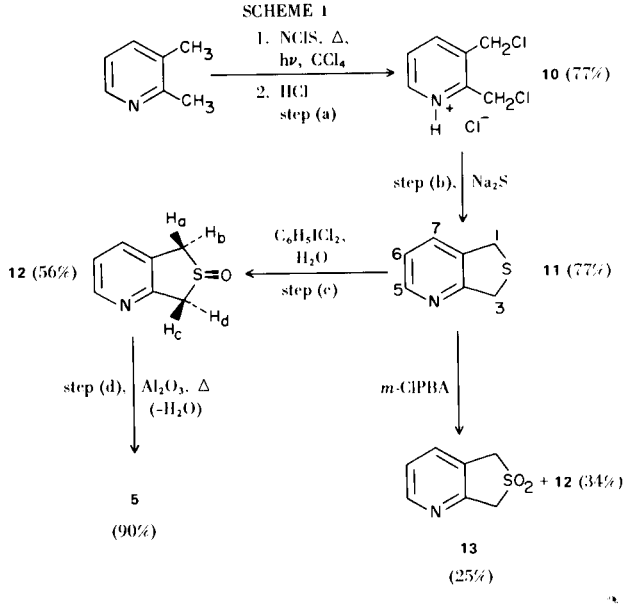
9

a, R = H; b, R = CH_3

(**7**) of the 1,3-dihydro-**5** system. Treatment of **7a** and **7b** with acetic acid-hydrogen peroxide gave the corresponding sulfones. Methylation of **7a** (with diazomethane) formed **8b**, while methylation of **7b** (with methyl iodide) gave a product to which an *S*-methyl structure was assigned. The sulfone of **8b**, plus studies on ionization constants and tautomerization of hydroxy compounds, were also described.

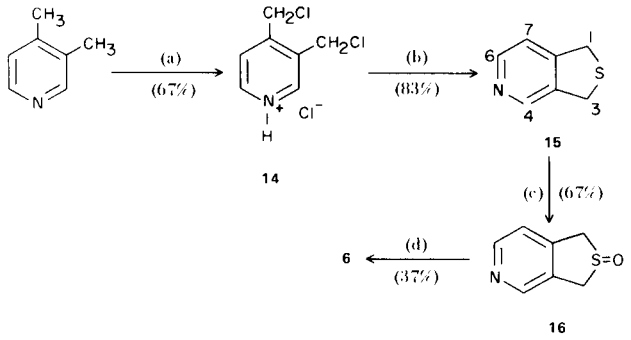
Patents (11) describe the conversion of pyridoxal into 6-methyl-7-hydroxy-**6**. The corresponding dihydro derivative **9** was synthesized from pyridoxine by Schmidt and Giesselmann (12,13), who also obtained the *O*-acetyl derivative of **9** and its sulfoxide (by oxidation with perbenzoic acid). Studies of the pharmacological properties (14) and ESR spectra (15) of **9** have been reported.

SCHEME I



In a general way, our synthetic routes to **5** and **6** followed that used for benzo[*c*]thiophene (16). Desired as the initial intermediates (Schemes I and II) were the 2,3- and 3,4-bis(chloromethyl)pyridines. A two-step conversion of diethyl quinolinate into 2,3-bis(chloromethyl)-pyridine has been reported in the literature (17). However, in our hands, the first step in this conversion, *viz.* the reduction of the ester to 2,3-bis(hydroxymethyl)pyridine, proved to be unsatisfactory due to difficulties of isolation and purification (18). Alternatively, direct photochlorinations of 2,3- and 3,4-dimethylpyridines by means of *N*-chlorosuccinimide in refluxing carbon tetrachloride gave good yields of the desired dihalo derivatives (isolated and stored as the hydrochloride salts **10** and **14**, respectively). The rationale for our procedure is based on a French

SCHEME II

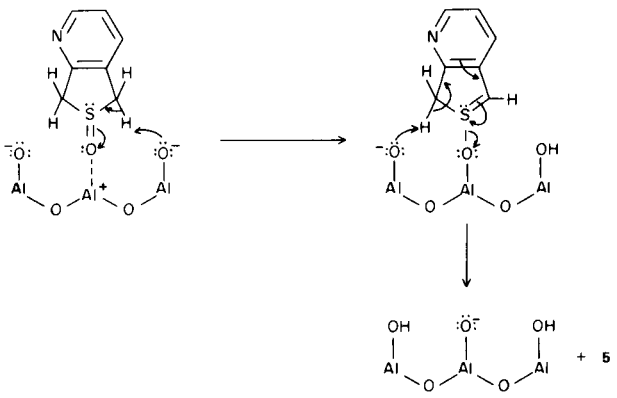


patent (19) for the conversion of 2,6-dimethylpyridine into 2,6-bis(chloromethyl)pyridine by means of chlorine gas in concentrated sulfuric acid solution at 90-110° and with either azoisobutyronitrile or ultraviolet irradiation as reaction initiator. The chlorine source and the solvent which we used (20) offer obvious simplifications in handling the reaction mixture. Refluxing (plus stirring) serves to keep the *N*-chlorosuccinimide (and its reaction product succinimide) in solution and, thus, facilitates photochlorination. The reaction is readily monitored by means of pmr spectrometry. Spectra obtained at intermediate reaction times showed relative concentrations of 4-chloromethyl-3-methylpyridine > 3-chloromethyl-4-methylpyridine (from 3,4-dimethylpyridine) and 3-chloromethyl-2-methylpyridine > 2-chloromethyl-3-methylpyridine (from 2,3-dimethylpyridine). These samples (collected largely during the latter half of the reaction) did not permit an unambiguous assignment of relative rates for the first chlorination step, but they did clearly show that the second chlorine atom which substitutes into the molecule has a strong preference for reaction at the methyl -group rather than at the chloromethyl group. Similar selectivities in competitive free radical halogenation of methylarenes have been reported by other workers (19,21).

Treatment of the bis(chloromethyl)pyridine salt with sodium sulfide gave the unstable liquid dihydro derivatives (**11** and **15**, respectively) of **5** and **6**. Compound **15** was isolated as a crystalline picrate. Treatment of **11** and **15** with iodobenzene dichloride in aqueous acetonitrile (22) gave sulfoxides **12** and **16**. Both sulfoxides were liquids which were used without further purification. However, each was characterized by means of a strong infrared band at *ca.* 1040 cm^{-1} and an appropriate pmr spectrum. In fact, the pmr spectrum of **12** allowed facile distinction amongst the four hydrogen atoms on C-1 and C-3 (23). An effort to use sodium metaperiodate for oxidation of **11** (16) failed, while use of *m*-chloroperbenzoic acid gave a mixture of **12** and the crystalline sulfone **13**. Conveniently, the sulfoxide and the sulfone were readily separable by column chromatography (24).

The final step (*d*) in each synthesis involved dehydration of the sulfoxide, by means of alumina at 100-120°, to the thienopyridine. Based on the proposals of Klemm and co-workers (25) for reductive dehydration of hydroaromatic ketones by alumina, we visualize step *d* as occurring by a mechanism such as is depicted in Scheme III (for formation of **5**). The sulfoxide is first strongly

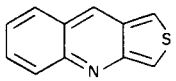
SCHEME III



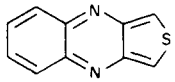
adsorbed on a Lewis acidic site of the alumina surface. The substrate molecule then loses protons from C-1 and C-3 to adjacent basic sites of the catalyst and loses an oxide ion to the site of adsorption. As suggested previously, eight-membered cyclic transition states may be involved.

Compounds **5** and **6** are yellow liquids which are unstable when subjected to laboratory conditions, whereupon they darken in a few hours and subsequently resinify. They can be stored as crystalline picrates, however. The limited shelf stabilities of **5** and **6** contrast sharply with those of isomers **1** and **2** (which darken slowly over periods of years under the same conditions) but they are reminiscent of the stability of **4** (26) (which

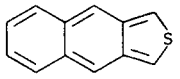
can be stored indefinitely at 0°, especially in a nitrogen atmosphere) (27). On the other hand, **5** and **6** would appear to be more stable than **17** and **18**, neither of which



17

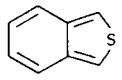


18

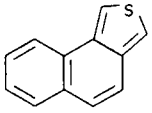


19

could be isolated from heating its dihydrosulfoxide with alumina (28,29). Compounds **17** and **18** could, however, be trapped as the Diels-Alder adducts by heating the dihydrosulfoxides with *N*-phenylmaleimide in acetic anhydride (30). As previously noted (28), the linearly annellated compound **19** behaved in the same manner as **17** (and **18**), while both the alumina dehydration and trapping methods were successful in obtaining the bicyclic **20** and the angularly annellated **21** (16).



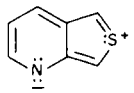
20



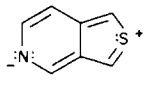
21

The pmr spectra of **5** and **6** show that only aromatic protons are present (all signals are downfield of δ 6.6 ppm in deuteriochloroform). The protons on the pyridine ring exhibit the usual splitting pattern, while those on the thiophene ring (H-1 and H-3) are coupled to one another ($J \cong 3$ Hz). Clear differentiation between the signals for H-1 and H-3 was not obtained for **6**, but it was possible for **5** by use of dual solvents. In deuteriochloroform, the signal for H-1 (resolved) falls at higher fields than that for H-3 (overlaps signal for H-7), while protonation of the nitrogen atom in trifluoroacetic acid causes a reversal in the order of these signals (both resolved) (31). In addition, long-range coupling ($J_{3,7} = 0.7$ Hz) is observed and confirms the assignment of the H-3 signal.

Protonation has a marked effect on the long wavelength ultraviolet absorption band of **5** and **6**, which shifts bathochromically by *ca.* 40 nm in each compound on changing from ethanol to ethanolic hydrogen chloride as solvent. It seems likely that the dipolar structures **5a**



5a



6a

and **6a** (fostered by protonation on the pyridinoid nitrogen atom) contribute significantly to the excited state involved in the long wavelength transition (32) of **5** and **6**, respectively. The presence of infrared absorption bands at 1590-1600 cm^{-1} (ascribed to C=C and C=N stretching) and 865 cm^{-1} (ascribed to out-of-plane lone hydrogen vibrations) in **5** and **6** are consistent with aromaticity (33,34a) in these molecules.

The radical cation which results from electron bombardment of **5** (**6** not investigated) is considerably less stable than that from **2** or **3** (35). However, the parent ion is the most abundant one in each case. Similar fragmentation processes occur in all three of these thienopyridines and exhibit characteristics ascribable to the pyridine and thiophene moieties *per se*. Loss of hydrogen cyanide - the most likely fragmentation process for pyridine, quinoline, isoquinoline, and **2** (36) - is the second most likely fragmentation process for **3** and **5**. The presence of the thiophene moiety in the thienopyridines is indicated through loss of carbon monosulfide (or of HCS) from

TABLE I

Quantum Chemical Reactivity Indices (a) for Thieno[3,4-*b*]pyridine (**5**)

Position *r*	q_r	$S_r^{elec.}$	$S_r^{nucl.}$
1	1.23	2.27	0.59
2 (S)	1.13	1.52	0.86
3	1.24	2.20	0.52
3a	1.05	1.11	0.70
4 (N)	1.33	1.60	0.94
5	0.93	0.93	1.17
6	1.06	1.13	0.71
7	0.94	0.98	1.22
7a	1.08	1.06	0.59
for Thieno[3,4-*c*]pyridine (**6**)			
1	1.22	2.25	0.57
2 (S)	1.13	1.47	0.82
3	1.21	2.31	0.63
3a	1.09	0.98	0.56
4	0.90	1.04	1.28
5 (N)	1.33	1.44	0.79
6	1.01	1.29	0.87
7	1.04	1.26	0.84
7a	1.07	1.06	0.64

(a) S_r is given in units of β_C^{-1}. For parameters used and assumptions made see similar calculations for **1** in reference 4.

the parent ion, as well as through formation of the ion HCS^+ (36,37). In fact, the combined loss of the elements of H, CS, and HCN from the parent ion results in the formation of $C_5H_3^+$, a fragment ion which ranks either first or second in relative abundance. Thiophyne$^+$ and C_3SH^+ are other sulfur-bearing ion fragments which are notable in the thienopyridine spectra.

Chemical studies on parent thienopyridines **1-4** have shown that electrophilic substitution occurs in the thiophene ring, and more readily at C-3 than at C-2 (4,35, 38,39). Nucleophilic attack by methyllithium (*i.e.* addition to the C=N group) occurs at C-6 in **1** (4). In a general way, these observations are consistent with HMO calculations for π-electron densities (q_r) and the superdelocalizabilities toward electrophilic attack ($S_r^{elec.}$) in these molecules (4,35,38). Although we have not yet investigated chemical reactions of **5** and **6**, similar calculations for these systems indicate analogous relative reactivities (Table I). Electrophilic substitution would be expected to occur at C-1 and/or C-3 in the thiophene ring, while nucleophilic substitution should take place in the pyridine ring either at C-5 or C-7 (former position is preferred on the basis of the results with **1** and quinoline) in **5** and at C-4 in **6**.

EXPERIMENTAL (40)

Thieno[3,4-*b*]pyridine (**5**) Synthesis.

2,3-Bis(chloromethyl)pyridinium Chloride (**10**) (41).

A vigorously stirred solution of 10 ml. (9.4 g., 0.088 mole) of 2,3-dimethylpyridine (Aldrich) and 24 g. (0.18 mole) of *N*-chlorosuccinimide in 900 ml. of carbon tetrachloride was refluxed under nitrogen gas in a pyrex round-bottomed flask while it was irradiated by means of a juxtaposed 200-watt Hanovia lamp (model 54A36) for 24 hours. The mixture was cooled, filtered to remove succinimide and unreacted *N*-chlorosuccinimide, treated with fresh *N*-chlorosuccinimide (24 g.), and reacted further for an additional 24 hours. Periodically, aliquot samples of the mixture were withdrawn, cooled, filtered, evaporated, dissolved in deuteriochloroform, and analyzed by pmr spectrometry in order to follow progress of the reaction. Originally singlets were observed at δ 2.13 and 2.42 ppm (3- and 2-methyl groups, respectively, of the starting material). Additional singlets at δ 2.43 and 4.73 ppm (ascribed to methyl and chloromethyl groups, respectively, in 2-chloromethyl-3-methylpyridine) and at 2.65 and 4.60 (ascribed to methyl and chloromethyl groups, respectively, in 2-methyl-3-chloromethylpyridine) appeared early in the reaction sequence, rose to maximal heights, and then decreased (along with the signals at 2.13 and 2.42) to small or negligible sizes. Meanwhile, singlets at δ 4.76 and 4.83 ppm [ascribed to 3-chloromethyl and 2-chloromethyl groups, respectively, in 2,3-bis(chloromethyl)-pyridine] appeared and attained maximal heights near the end of the reaction period.

The cooled reaction mixture was filtered and treated with excess anhydrous hydrogen chloride gas. The gummy precipitate which formed was crystallized from isopropanol to give 14.3 g. (77%) of **10**, m.p. 148.5-149.5°; pmr (hexadeuteriodimethyl sulfoxide) δ 5.07 (s, 2, CH_2Cl at C-3), 5.16 (s, 2, CH_2Cl at C-2), 7.82 (d of d, 1, $J_{4,5}$ = 8 Hz, $J_{5,6}$ = 5.2 Hz, H-5), 8.42 (d of d, 1, $J_{4,6}$ = 1.8 Hz, H-4), 8.78 (d of d, 1, H-6), 10.79 ppm (s, 1, NH^+). This product (tan to reddish) was used in the next step.

An analytical sample was obtained by recrystallization from isopropanol and repeated sublimation (once just prior to analysis) at 80° (0.1 mm.) to give a white solid, m.p. 147.5-148.5° dec.

Anal. Calcd. for $C_7H_8Cl_3N$: C, 39.6; H, 3.8; Cl, 50.1; N, 6.6. Found: C, 39.7; H, 4.1; Cl, 49.9; N, 6.7.

Treatment of **10** with aqueous sodium bicarbonate and benzene (to extract the free base) and addition of a solution of excess picric acid in ethanol to the benzene layer gave 2,3-bis(chloromethyl)pyridinium picrate, obtained as yellow prisms from benzene, m.p. 143.5-144°, lit. (17) 143-144° (for product prepared by a different method).

Anal. Calcd. for $C_{13}H_{10}Cl_2N_4O_7$: C, 38.5; H, 2.5. Found: C, 38.7; H, 2.6.

1,3-Dihydrothieno[3,4-*b*]pyridine (**11**).

To a stirred solution of 60 g. (excess) of sodium sulfide nonahydrate in 600 ml. of 80% aqueous ethanol was added, dropwise over a period of 6 hours and in an atmosphere of nitrogen, a solution of 10.1 g. of hydrochloride **10** in 150 ml. of absolute ethanol. The residue from evaporation of the solvent was treated with water and extracted with benzene. Evaporation of the dried (sodium sulfate) extract and chromatography by means of Florisil, benzene, and chloroform gave 3.8 g. (59% from 2,3-dimethylpyridine) of **11**; ir 3000 (aromatic C-H), 1580 (C=C and C=N), 1425 cm^{-1} (methylene) (34b); pmr δ 4.20 (s, 2, methylene at C-1), 4.26 (s, 2, methylene at C-3), 7.05 (d of d, 1, $J_{5,6}$ = 5 Hz, $J_{6,7}$ = 7.5 Hz, H-6), 7.50 (d of d, 1, $J_{5,7} \cong 1.5$ Hz, H-7), 8.40 ppm (d of d, 1, H-5).

Since **11** was unstable in air it was used immediately in the next step.

1,3-Dihydrothieno[3,4-*b*]pyridine 2-Oxide (**12**).

To a cold (0-5°), stirred solution of 3.05 g. (0.022 mole) of sulfide **11** in a mixture of 30 ml. of acetonitrile, 7 ml. of water, and 8 ml. of triethylamine was added, dropwise over a period of 2 hours, a solution of 12 g. (0.044 mole) of iodobenzene dichloride (42) in 275 ml. of acetonitrile. The mixture was stirred over night at room temperature and evaporated to dryness. The residue was treated with benzene, filtered to remove triethylammonium chloride, and chromatographed by means of Florisil (100 g.) and ethyl acetate containing 0-15% methanol. Sulfoxide **12**, 1.9 g. (56%), was obtained from the eluent as a colorless liquid; ir 2980 aromatic C-H), 1580 (C=C and C=N), 1425 (methylene), 1050-1030 cm^{-1} (S=O); pmr δ 3.94 (d, 1, $J_{a,b}$ = -17 Hz, H_b) (43), 3.99 (d, 1, $J_{c,d}$ = -17 Hz, H_d), 4.29 (d, 1, H_a), 4.34 (d, 1, H_c), 7.09 (d of d, 1, $J_{5,6}$ = 5 Hz, $J_{6,7}$ = 7.5 Hz, H-6), 7.57 (d of d, 1, $J_{5,7}$ = 1.2 Hz, H-7), 8.37 ppm (d of d, 1, H-5).

Reaction of Sulfide **11** with *m*-Chloroperbenzoic Acid.

To a cold (0°), stirred solution of 2.3 g. (0.017 mole) of **11** in 100 ml. of methylene chloride was added, dropwise over a period of 12 hours, a solution of 3.44 g. (0.017 mole) of *m*-chloroperbenzoic acid (85% pure, Aldrich) in 100 ml. of the same solvent. The mixture was stirred at 0° for 24 hours longer and then at -20° for 48 hours. The mixture was filtered and the filtrate was washed with aqueous sodium bicarbonate, dried, and evaporated. Chromatography of the residue by means of Florisil and a variable solvent (from chloroform, through ethyl acetate, to methanol) gave 0.73 g. (25%) of 1,3-dihydrothieno[3,4-*b*]pyridine 2,2-dioxide (**13**), eluted by pure chloroform and chloroform-ethyl

acetate (2:3). Eluted later (24), in the previous manner, was 0.87 g. (34%) of sulfoxide **12**.

Sulfone **13** formed slightly yellow prisms from ethyl acetate, m.p. 128-129°; ir 2970 (aromatic C-H), 1570 (C=C and C=N), 1425 (methylene), 1330 and 1130 cm^{-1} (sulfone); pmr δ 4.43 (s, 4, 2 methylene), 7.28 (d of d, 1, $J_{5,6}$ = 4.8 Hz, $J_{6,7}$ = 8 Hz, H-6), 7.64 (d of d, 1, $J_{5,7} \cong 1$ Hz, H-7), 8.50 ppm (d of d, 1, H-5).

Anal. Calcd. for $C_7H_7NO_2S$: C, 49.7; H, 4.2; N, 8.3; S, 19.0. Found: C, 50.0; H, 4.1; N, 8.0; S, 19.2.

Thieno[3,4-*b*]pyridine (**5**).

A solution of 0.46 g. of freshly prepared sulfoxide **12** in 5 ml. of chloroform was mixed with 1.5 g. of Woelm neutral alumina (activity I). The solvent was evaporated *in vacuo* and the residue was heated in a molecular still at 100-120° (20 mm.) for one hour. The distillate (**5**), 0.365 g. (90%), was a yellow liquid which darkened on standing in the air; uv max (ethanol) 224 nm (log ϵ = 4.27), 293 (3.81), 297 (3.78) shoulder, 306 (3.88), 343 (3.45); uv max (ethanolic hydrogen chloride) 232 nm (log ϵ = 4.16), 303 (4.07) shoulder, 308 (4.14), 388 (3.41); ir (neat) 1590 (C=C and C=N), 865 (lone aromatic H), 800 and 775 cm^{-1} (3 vicinal aromatic H); pmr δ 6.90 (d of d, 1, $J_{5,6}$ = 3.7 Hz, $J_{6,7}$ = 8.5 Hz, H-6), 7.66 (d, 1, $J_{1,3}$ = 3.2 Hz, H-1), 7.78-8.02 (m, 2, H-3 and H-7), 8.57 (d of d, 1, $J_{5,7}$ = 1.8 Hz, H-5); pmr (trifluoroacetic acid, HA-100) δ 7.67 (d of d, 1, $J_{5,6}$ = 5.5 Hz, $J_{6,7}$ = 8.5 Hz, H-6), 8.37 (d of d, 1, $J_{1,3}$ = 3.2 Hz, $J_{3,7}$ = 0.7 Hz, H-3), 8.63 (d, 1, H-1), 8.4-9.1 (m, 2, H-5 and H-7); mass spectrum, m/e (relative abundance), 137 (16), 136 (33), 135 (100, M^+), 134 (34), 108 (53) $[M\text{-}HCN]^+$, 91 (35) $[M\text{-}CS]^+$, 82 (21), 81 (19), 70 (16), 69 (28), 64 (21), 63 (66), 62 (30), 61 (17), 45 (37, HCS^+).

The picrate formed yellow prisms from ethanol, m.p. (sealed tube) 207.5-209°, with darkening.

Anal. Calcd. for $C_{13}H_8N_4O_7S$: C, 42.9; H, 2.2; N, 15.4; S, 8.8. Found: C, 43.2; H, 2.3; N, 15.1; S, 8.6.

Thieno[3,4-*c*]pyridine (**6**) Synthesis.

3,4-Bis(chloromethyl)pyridinium Chloride (**14**) (41).

In the same manner as used to photochlorinate 2,3-dimethylpyridine, a stirred, refluxing solution of 3,4-dimethylpyridine (Aldrich) (4 g., 0.037 mole) and *N*-chlorosuccinimide (14 g., 0.1 mole) in 1.5 l. of carbon tetrachloride was irradiated for 7.5 hours in a nitrogen atmosphere. During this time a pmr singlet at δ 2.28 ppm (methyl groups in starting material) decreased in relative intensity, while one at 4.75 [ascribed to chloromethyl groups in 3,4-bis(chloromethyl)pyridine] attained a maximum relative intensity. Other singlets due to the intermediate formation of 3-methyl-4-chloromethylpyridine (at 2.46 and 4.65) and of 3-chloromethyl-4-methylpyridine (at 2.54 and 4.56) were also observed. Near the end of the reaction period a singlet at 6.90 (ascribed to the dichloromethyl group) appeared and increased in intensity with reaction time. Filtration of the cooled reaction mixture and treatment of the filtrate with anhydrous hydrogen chloride gave **14** as a gum which crystallized on standing at 3°. This product was recrystallized from acetone and sublimed slowly at 100-120° (0.3 mm.) to give 5.2 g. (67%) of white solid, m.p. 157-159° dec.; pmr (hexadeuteriodimethyl sulfoxide) δ 5.15 (s, 2, CH_2Cl at C-3), 5.18 (s, 2, CH_2Cl at C-4), 8.13 (d of d, 1, $J_{5,6}$ = 6 Hz, $J_{2,5} \cong 0.7$ Hz, H-5), 8.98 (broadened d, 2, H-6), 9.10 ppm (broadened s, 1, H-2).

Anal. Calcd. for $C_7H_8Cl_3N$: C, 39.6; H, 3.8; Cl, 50.1; N, 6.6. Found: C, 39.6; H, 3.8; Cl, 50.3; N, 6.6.

When the photochlorination was conducted at room temperature (instead of in refluxing solvent) some of the *N*-chlorosuccinimide remained undissolved and the reaction progressed very slowly. During 50 hours of illumination the maximum yield of 3,4-bis(chloromethyl)pyridine was < 5%, while the production of dichloromethyl groups was already apparent. Repetition of the procedure at reflux temperature, but without ultraviolet irradiation, gave no formation of chloromethyl products.

1,3-Dihydrothieno[3,4-*c*]pyridine (**15**).

This compound was prepared from hydrochloride **14** in a manner closely similar to that used for its isomer **11**. However, to limit decomposition of the product, the reaction mixture was treated directly (without preceding evaporation) with an equal volume of benzene. This mixture was then washed with water, dried, and evaporated to give **14** as a slightly yellow liquid (83%) which was not purified further; ir 3000 (aromatic C-H), 1590 cm^{-1} (C=C and C=N); uv max (absolute ethanol) 262 nm (log ϵ = 3.33), 267 (3.33), 345 (2.28); uv max (ethanolic hydrogen chloride) 258 nm (log ϵ = 3.58), 263 (3.58) shoulder, *ca.* 380 (2.20); pmr δ 4.27 (s, 4, two methylenes), 7.23 (broadened d, 1, $J_{6,7}$ = 5 Hz, H-7), 8.45 (d, 1, H-6), 8.57 ppm (broadened s, 1, H-4).

The picrate, formed in absolute ethanol, was obtained as canary yellow crystals from hexane-methylene chloride, m.p. > 180° dec.

Anal. Calcd. for $C_{13}H_{10}N_4O_7S$: C, 42.6; H, 2.8; N, 15.3. Found: C, 42.5; H, 2.7; N, 15.3.

1,3-Dihydrothieno[3,4-*c*]pyridine 2-Oxide (**16**).

This compound was prepared by oxidation of **15** with iodobenzene dichloride plus water in the manner used to convert **11** to **12**. Chromatography by means of Florisil plus benzene (to remove iodobenzene formed) and then plus methanol (0-15%) in ethyl acetate gave **16** (67%) as a red-brown liquid; ir 3000 (aromatic C-H), 1590 (C=C and C=N), 1055-1040 cm^{-1} (S=O); pmr δ 4.24 (broadened s, 4, two methylenes) 7.49 (broadened d, 1, H-7), 8.61 (d, 1, $J_{6,7}$ = 5 Hz, H-6), 8.69 ppm (broadened s, 1, H-4).

Thieno[3,4-*c*]pyridine (**6**).

In the manner used to obtain **5**, a deposit of fresh sulfoxide **16** on alumina was heated at 100-120° (but at 0.3 mm.) to give **6** as a slightly yellow liquid (37%); ir (neat) 1600 (C=C and C=N), 865 cm^{-1} (lone aromatic H); uv max (absolute ethanol) 224 nm (log ϵ = 4.32), 270 (3.35) shoulder, 280 (3.46), 291 (3.31), 342 (3.47); uv max (ethanolic hydrogen chloride) 236 nm (log ϵ = 4.38), 281 (3.69), 290 (3.54), 380 (3.44); pmr δ 7.38 (slightly split d, 1, $J_{6,7}$ = 6.5 Hz, H-7), 7.64 (d, 1, $J_{1,3}$ = 3 Hz, H-3 or H-1), 8.02 (d, 1, H-1 or H-3), 8.04 (d overlapping 8.02 signal, 1, H-6), 9.12 ppm (broadened s, 1, H-4); pmr (trifluoroacetic acid) δ 7.86 and 8.63 ppm (2d, 2, $J_{1,3}$ = 3 Hz, H-1 and H-3), remainder of spectrum complex (reaction products?).

The picrate, formed in absolute ethanol, was obtained as yellow needles from benzene-hexane, m.p. 234-235° dec.

Anal. Calcd. for $C_{13}H_8N_4O_7S$: C, 42.9; H, 2.2; N, 15.4; S, 8.8. Found: C, 42.8; H, 2.1; N, 15.2; S, 8.6.

REFERENCES

(1) This investigation was supported by research grants Nos. CA-5969 from the National Cancer Institute and MH-17304 from the National Institute of Mental Health. For paper XIV (on basicities of thienopyridines) in this series, see L. H. Klemm and R. D. Jacquot, *J. Electroanal. Chem.*, in press (1972).

(2) Texaco Predoctoral Fellow, 1968-1969.

(3) Research Associate, 1969-1970.

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

(5a) L. H. Klemm, J. Shabtai, D. R. McCoy, and W. K. T. Kiang, *J. Heterocyclic Chem.*, 5, 883 (1969); (b) *ibid.*, 6, 813 (1969).

(6) S. Gronowitz and E. Sandberg, *Arkiv Kemi*, 32, 217 (1970).

(7) F. Eloy and A. Deryckere, *Bull. Soc. Chim. Belges*, 79, 301 (1970).

(8) L. H. Klemm, W. O. Johnson, and D. V. White, *J. Heterocyclic Chem.*, 7, 463 (1970).

(9) V. G. Zhiryakov and P. I. Abramenko, *Zhur. Vsesoyuz. Khim. Obshchestva im. D. I. Mendeleeva*, 5, 707 (1960); [*Chem. Abstr.*, 55, 11416 (1961)].

(10) E. Spinner and G. B. Yeoh, *J. Chem. Soc. (B)*, 289 (1971).

(11) G. Schorre, German Patent, 1,193,049, issued May 20, 1965 to E. Merck A. G., [*Chem. Abstr.*, 63, 2961 (1965)]; French Patent, M 3091, issued Feb. 26, 1965, [*Chem. Abstr.*, 62, 16209 (1965)].

(12) U. Schmidt and G. Giesselmann, *Ann. Chem.*, 657, 162 (1962).

(13) An earlier report of the synthesis of **9** by S. Kreisky [*Monatsh. Chem.*, 89, 685 (1958)] was questioned by Schmidt and Giesselmann (12). Kreisky obtained a different m.p. for the product and reported elemental analysis for sulfur only.

(14) R. Koch, D. Klemm, and I. Seiter, *Arzneim. Forsch.*, 10, 683 (1960), [*Chem. Abstr.*, 55, 807 (1961)]; H. G. Kraft, L. Fiebig, and R. Hotovy, *Arzneim. Forsch.*, 11, 922 (1961), [*Chem. Abstr.*, 56, 9353 (1962)].

(15) R. Koch, H. Lagendorff, and H. Moenig, *Atomkernenergie*, 11, 209 (1966), [*Chem. Abstr.*, 65, 9302 (1966)]; H. Mönig and R. Koch, *Biophysik*, 3, 11 (1966).

(16) M. P. Cava and N. M. Pollack, *J. Am. Chem. Soc.*, 88, 4112 (1966), and references cited therein.

(17) K. Tsuda, N. Ikekawa, R. Takasaki, and Y. Yamakawa, *Pharm. Bull., Japan*, 1, 142 (1953) [*Chem. Abstr.*, 50, 13895 (1956)].

(18) These same difficulties were encountered in the reduction of the isomeric diethyl pyridine-3,4-dicarboxylate, although limited success was attained in this case [*cf.* H. S. Mosher and J. E. Tessieri, *J. Am. Chem. Soc.*, 73, 4925 (1951)].

(19) J. Kollonitsch, French Patent, 1,394,362, issued April 2, 1965 to Merck and Co., Inc., [*Chem. Abstr.*, 63, 8326 (1965)].

(20) We are indebted to Dr. John Lawson, formerly of this laboratory, for preliminary studies which incorporated some of the modifications used here.

(21) P. Beltrame and S. Carra, *Tetrahedron Letters*, 3909 (1965); P. R. Taussig, G. B. Miller, and P. W. Storms, *J. Org. Chem.*, 30, 3122 (1965); P. W. Storms and G. B. Miller, *ibid.*, 31, 2705 (1966); S. S. Friedrich, E. C. Friedrich, L. J. Andrews, and R. M. Keefer, *ibid.*, 34, 900 (1969).

(22) See L. H. Klemm, S. B. Mathur, R. Zell, and R. E. Merrill, *J. Heterocyclic Chem.*, 8, 931 (1971).

(23) *Cf.* pmr spectrum of 2-thiaindan 2-oxide [R. F. Watson and J. F. Eastham, *J. Am. Chem. Soc.*, 87, 664 (1965)].

(24) H. Ertel and L. Horner, *J. Chromatog.*, 7, 268 (1962); L. Fishbein and J. Fawkes, *ibid.*, 22, 323 (1966); unpublished results by Mr. Francis H. W. Lee in this laboratory.

(25) L. H. Klemm, C. E. Klopfenstein, and J. Shabtai, *J. Org. Chem.*, 35, 1069 (1970); J. Shabtai, L. H. Klemm, and D. R. Taylor, *ibid.*, 35, 1075 (1970).

(26) L. H. Klemm and D. Reed, *ibid.*, 25, 1816 (1960).

(27) Our limited experience with isomer **3** indicates that it should be classified with **1** and **2** in shelf stability [L. H. Klemm and D. R. McCoy, *J. Heterocyclic Chem.*, 6, 73 (1969)].

(28) D. W. H. MacDowell, A. T. Jeffries, and M. B. Meyers, *J. Org. Chem.*, 36, 1416 (1971).

(29) R. C. Anderson and M. M. Roland, Abstract No. 129, Northwest Regional Meeting, Am. Chem. Soc., Bozeman, Mont., June, 1971.

(30) Preliminary investigations on the reactivities of **5** and **6** with dienophiles have been inconclusive.

(31) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed., Pergamon Press, Inc., New York, N. Y., 1969, p. 82.

(32) *Cf.* the effect of acid on the spectrum of an indolophenanthridine [L. H. Klemm, W. O. Johnson, and D. R. Olson, *J. Heterocyclic Chem.*, **9**, 927 (1972)].

(33) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., Methuen and Co., Ltd., London, England, 1958, pp. 263, 277.

(34) N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964, (a) pp. 212-213, 226-227, (b) p. 306.

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

(36) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, California, 1967, chaps. 20 and 24.

(37) American Petroleum Institute, *Catalog of Mass Spectral Data*, spectrum No. 158; Q. N. Porter, *Aust. J. Chem.*, 20, 103 (1967); J. Heiss, K. P. Zeller, and B. Zeeh, *Tetrahedron*, 24, 3255 (1968); L. H. Klemm, D. R. McCoy, and D. R. Olson, *J. Heterocyclic Chem.*, 7, 1347 (1970).

(38) L. H. Klemm, R. Zell, I. T. Barnish, R. A. Klemm, C. E. Klopfenstein, and D. R. McCoy, *ibid.*, 7, 373 (1970); M. L. Dressler and M. M. Joullié, *ibid.*, 7, 1257 (1970).

(39) L. H. Klemm, R. E. Merrill, F. H. W. Lee, and C. E. Klopfenstein, Abstract No. 131, Northwest Regional Meeting, Am. Chem. Soc., Bozeman, Montana, June, 1971.

(40) Elemental analyses were performed by M-H-W Laboratories, Garden City, Michigan. Unless otherwise designated, infrared spectra were obtained by means of a Beckman IR-7 or IR-5A spectrometer with chloroform as solvent; pmr spectra, by means of a Varian A-60 spectrometer with deuteriochloroform as solvent and 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. Only mass spectral peaks of relative abundance $\geqslant 15\%$ of the most abundant peak are reported.

(41) The bis(chloromethyl)pyridines and their hydrochloride salts are skin irritants. Gloves should be worn when one is handling them.

(42) H. J. Lucas and E. R. Kennedy, *Org. Syn.*, Coll. Vol. 3, 482 (1955).

(43) The algebraic sign of the geminal coupling constant is assumed to be negative [*cf.* ref. 31, pp. 270-276].