Chemistry of Thienopyridines. III. Syntheses of the Thieno[2,3-*b*]- and Thieno[3,2-*b*]pyridine Systems. Direct Substitution into the Former System[1a,2,3]

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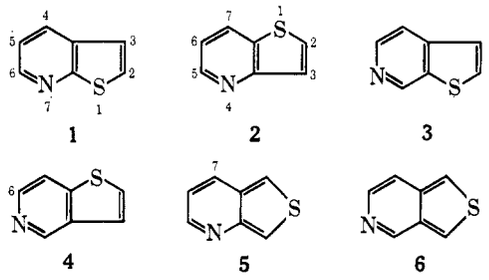
Condensation–cyclization reactions of 2- and 3-thienylammonium hexachlorostannates were used in practical syntheses of thieno[2,3-*b*]pyridine (**1**), thieno[3,2-*b*]pyridine (**2**), and their derivatives. Malondialdehyde tetraethyl acetal (MDTA) reacted with these salts to give **1** and **2** (44 and 77% yields, respectively). Acetoacetaldehyde dimethyl acetal reacted (with attendant loss of acetone) to form monoacetyl derivatives, wherein the substituent is located β to the nitrogen atom. Methyl vinyl ketone led to mixed (α and γ) monomethyl compounds. Some 1,3-diketones and 1,3-ketoaldehydes also reacted. Structures of the monomethyl derivatives were established by direct comparison with the products of reaction of vinylmethylpyridines and methylethylpyridines with hydrogen sulfide at 630°. The salts of 4- and 5-amino-2-acetylthiophene also reacted with MDTA to form 2-acetyl derivatives of **1** and **2**. Nmr data are reported and correlated with structures of the various thienopyridine compounds. Bromination of **1** gave the 2,3-dibromo derivative, while reaction of **1** with deuteriosulfuric acid gave fastest D–H exchange at C-3 and slower exchange at C-2. Reaction of **1** with methyllithium led to products expected from lithiation at C-2 and from addition to the C=N moiety. These results are consistent with calculated reactivity indices and expectations as based on data for the quinoline and benzo[*b*]thiophene systems.

Of the six theoretically possible parent thienopyridine compounds, **1**–**6**, only **1**–**4** have been previously synthesized, albeit in low yields (1–6% from available starting materials).[3–7] Chemical interest in the thienopyridine system arises from the fact that a thiophene ring (susceptible to facile electrophilic substitution, but resistant to nucleophilic substitution)[8] is fused to a pyridine ring (susceptible to facile nucleophilic substitution, but resistant to electrophilic substitution).[9,10] Pharmacological interest in these systems stems from their isosterism with quinoline and isoquinoline rings. The present paper is concerned with syntheses of systems **1** and **2** and direct substitution into the former system.



1 **2** **3** **4** **5** **6**

In the extensive studies of Steinkopf and coworkers on the reactions of thiophene[11] it was discovered that the mononitrothiophenes can be readily reduced to the corresponding aminothiophenes, but these reduction products are exceptionally easily oxidized and/or polymerized by air. Fortunately, they found that the aminothiophenes can be handled and stored as the relatively stable crystalline salts of hexachlorostannic(IV) acid.[12] As noted in an earlier paper[2] the low yield of **1** from Skraup reaction on the amine salt (under oxidizing conditions) is, thus, not surprising and leads one to investigate the possibilities of formation of the pyridinoid ring under nonoxidative conditions—in particular, under dehydrative conditions. Thus Emerson, Holly and Klemm[2] found that acetylacetone reacts with the 2-thienylammonium salt in the presence of concentrated sulfuric acid at room temperature to give **1c**. Similar condensations with other β-diketones and β-ketoaldehydes were not successful in their hands, however. More recently, Zhiryakov and Abramenko reported reactions of both aminothiophene salts with methyl vinyl ketone (MVK) in the presence of ethanolic ferric chloride–zinc chloride[13] and with acetoacetaldehyde diethyl acetal (ADEA) in the presence of ethanolic zinc chloride.[14] They assigned monomethylthienopyridine structures to their isolated products, but without experimental verification of such structures.[15] We have reinvestigated these reactions and extended and modified them so as to provide the first practical syntheses for the parent compounds **1** and **2**, as well as generally applicable syntheses for derivatives (of proven structures) of them.[15a]

(1) (a) This investigation was supported by research grant No. CA-5969 from the National Cancer Institute and by research contract No. DA-49-193-MD-2998 from the U. S. Army Medical Research and Development Command. For papers I and II in this series see ref 2 and 3, respectively. (b) Research Assistant, 1963–1965; NDEA Predoctoral Fellow, 1965–1966. (c) NATO Postdoctoral Fellow, 1966–1967; Research Associate, 1967. (d) Research Assistant, 1964–1967. (e) NSF Undergraduate Research Participant, summer 1967.

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(3) L. H. Klemm and D. Reed, *J. Org. Chem.*, **25**, 1816 (1960).

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(11) W. Steinkopf, "Die Chemie des Thiophens," Theodor Steinkopff, Leipzig, Germany, 1941.

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(13) V. G. Zhiryakov and P. I. Abramenko, *Zh. Vses. Khim. Obshchestva im. D. I. Mendeleeva*, **5**, 707 (1960); *Chem. Abstr.*, **55**, 11416 (1961).

(14) V. G. Zhiryakov and P. I. Abramenko, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR*, 334 (1965); *Chem. Abstr.*, **63**, 13231 (1965); *Chem. Heterocycl. Compounds (USSR)*, **1**, 219 (1965). The abstract and the English translation of this article are inconsistent in many details. It is presumed that the authors did not use the Pb double salt (such as is reported in the abstract).

(15) As noted later, it appears that ref 13 and 14 contain several erroneous structural assignments.

(15a) NOTE ADDED IN PROOF.—Practical syntheses of **2** and **3** from 2- and 4-vinylpyridines, respectively, have recently been achieved: L. H. Klemm, J. Shabtai, D. R. McCoy, and W. K. T. Kiang, *J. Heterocycl. Chem.*, in press.

Thiophene was nitrated directly to 2-nitrothiophene[16] (which contained 15% of the 3 isomer) and was also converted into 3-nitrothiophene (which contained 5% of the 2 isomer) by a previously reported multistep procedure.[17,18] Each nitro product was reduced with tin and hydrochloric acid to the corresponding bis(thienylammonium) hexachlorostannate(IV),[4] readily convertible into a thienopyridine mixture (44% in the former case, 77% in the latter) by treatment *in situ* with ethanol, zinc chloride, and malondialdehyde tetraethyl acetal (MDTA) at 85°. The ease of direct nitration of thiophene makes the synthesis of thieno[2,3-*b*]pyridine (**1**) by this method experimentally facile. On the other hand, despite the higher yield of thieno[3,2-*b*]pyridine (**2**) in the MDTA reaction, the arduous synthesis of 3-nitrothiophene by the reported method makes the over-all production of **2** experimentally difficult. It is better perhaps, especially if one is interested in both isomers, to separate **2** from the product mixture which results from the synthesis of **1**. Thus isomer **1** is easily freed from **2** by extraction of the mixture with a limited excess of 0.05 *M* HCl, in which **2** is considerably more soluble.[19] The **2**-enriched extract is then separable by liquid–solid chromatography with alumina onto which **2** is more strongly adsorbed.[20]

In analogous fashion the isomeric products from nitration of 2-acetylthiophene, *i.e.*, 4-nitro-2-acetylthiophene (**7**) and 5-nitro-2-acetylthiophene (**8**),[21,22] were reduced and cyclized to **2c** and **1i**, respectively, in over-all yields of *ca.* 10% each. Mixtures of **1i** and **2c** were also separable by acid extraction and chromatography on alumina, wherein the [3,2-*b*] isomer again showed a higher basicity.

The mechanism of the MDTA reaction has not been investigated. Formally it may be visualized as a combination of stepwise hydrolysis of MDTA (effectively to malondialdehyde) plus a sequence of Schiff's base formation with the amine salt (1:1) and then cyclodehydrative substitution (SE reaction) into the thiophene ring.

Treatment of the 2-amine salt with acetylacetone and zinc chloride in dioxane at 90° gave **1c** (45% yield). Similarly, **1d** (32% yield) and 5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline (**1h**, 5% yield) were obtained by reactions of 3-methylpentane-2,4-dione and 2-hydroxymethylenecyclohexanone, respectively, with the 2-amine salt. Also, reaction of acetylacetone with the salt of 2-amino-5-acetylthiophene gave **1k** (42%).

Comparison of the nmr spectra of **1** and **2** with the spectral characteristics for the heteroring protons of quinoline and benzo[*b*]thiophene shows that it is possible to ascribe, on a reasonable basis, a particular part of the total spectrum to each of the five protons present in either **1** or **2**. These assignments for the parent compounds are corroborated by spectral data for various derivatives for which structures are clearly established by their methods of synthesis. Complete data on chemical shifts and coupling constants for all thienopyridine compounds reported in this paper are given in Tables I and II. No long-range splitting effects are apparent in the spectrum of **1**, but the spectrum of **2** shows long-range coupling between H-2 and H-6 and also between H-3 and H-7.

Repetition of the studies of Zhiryakov and Abramenko gave results inconsistent with many of their reports. Thus, in our study, reaction of the 2-amine salt with MVK[13] gave two products, **1a** (as reported) in 15% yield and **1b** (not reported) in 10% yield. These isomers were readily separable by vpc on Carbowax 20M, on which **1a** (less steric hindrance to H bonding from the stationary phase) shows higher retentivity (*cf.* tlc data on alumina).[20] Tentative assignments of our structures, as based on microanalyses and chromatographic results, were corrborated by nmr spectra wherein **1a** shows signals at $\delta > 8.2$ (present also in the spectrum of **1**, but not in that of **1b**) ascribable to the presence of an aromatic proton α to the pyridinoid N atom. Confirmation of these structural assignments was provided by high-temperature (630°) reactions of hydrogen sulfide with substituted pyridines in a flow system. Thus 3-ethyl-4-methylpyridine plus H_2S gave a low yield (1%) of **1a** (only thienopyridine found) while 2-methyl-5-vinylpyridine or 2-methyl-5-ethylpyridine gave the expected isomeric pair of methylthienopyridines **1b** (2%, by preferential cyclization into the 6 position of the pyridine ring) and **4a** (0.3%, by cyclization into the 4 position of the pyridine ring).[23] Also obtained from the latter reaction were small amounts of the parent compounds (from demethylation)[24] **1** (0.5%) and **4** (0.1%).[25]

Reaction of the 3-amine salt with MVK gave **2a** (9%, not reported by Zhiryakov and Abramenko)[13] and **2b** (41%, previously reported).[13] Structures were assigned by the same methods as used in the **1** series. Thus **2b** showed greater retentivity than **2a** in vpc and tlc,[20,26] **2b** and **2** (but not **2a**) showed nmr signals at $\delta > 8.2$, and **2a** (0.9%) plus **2** (0.4%) were also obtained from reaction of 2-methyl-6-vinylpyridine with H_2S. The melting point of our **2b** picrate was 12° higher than that reported by the Russian workers. Moreover, we found no evidence for the formation of the 7-methyl derivative of **5**, reported by them.[13] It might be noted that the methylthienopyridine isomer which forms in the larger amount (from either the 2- or the 3-amine salt) results (at least in a formal sense) from initial Michael addition of the amino group to the α-vinylketo system rather than from Schiff's base formation.

(16) V. S. Babasinian, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 466.

(17) W. Steinkopf and T. Höpner, *Ann.*, **501**, 174 (1933).

(18) H. Burton and W. A. Davy, *J. Chem. Soc.*, 525 (1948).

(19) Compare 2-methylmercaptopyridine, pK_a 3.62, with 3-methylmercaptopyridine, pK_a 4.45: A. Albert, "Physical Methods in Heterocyclic Chemistry," Vol. 1, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, Chapter 1.

(20) L. H. Klemm, C. E. Klopfenstein, and H. P. Kelly, *J. Chromatog.*, **23**, 428 (1966).

(21) I. J. Rinckes, *Rec. Trav. Chim.* **52**, 538 (1933).

(22) The structure of **8** follows from its synthesis[21] from 5-nitro-2-thienoic acid, which (in turn) produces 2-nitrothiophene on decarboxylation [I. J. Rinckes, *ibid.*, **51**, 1134 (1932)]. Similar interconversions[21] show that **7** is in the 3-nitrothiophene series and, hence, must be either 3-nitro-2-acetyl- or 4-nitro-2-acetylthiophene. The small coupling constant (J = 1.6 Hz) for the aromatic AB system in **7** is consistent with the structural assignment as given (*meta* protons present).

(23) C. Hansch and W. Carpenter, *J. Org. Chem.*, **22**, 936 (1957).

(24) C. D. Hurd and J. I. Simon [*J. Amer. Chem. Soc.*, **84**, 4519 (1962)] found that picolines undergo some demethylation at 700° but do not give methyl migration at that temperature.

(25) Compound **4** is more readily obtained from H_2S and 3-vinylpyridine.[5]

(26) As expected in tlc on alumina the R_f value of **2** lies between that of **2a** and that of **2b**.[20]

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA FOR THIENO[2,3-*b*]PYRIDINES[a]

Compd	Substituent(s)	Chemical shift, δ H-2	H-3	H-4	H-5	H-6	Coupling constant, Hz $J_{2,3}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$	Other signals
1	None	7.40	7.08	7.85	7.10	8.46	5.9	8.1	1.6	4.5	
1a	4-Me	7.37	7.12		6.86[b]	8.34	6.0			4.5	2.35 (s, CH_3)[b]
1b	6-Me	7.33	7.10	7.80	7.12		6.0	8.0			2.60 (s, CH_3)
1c	4,6-DiMe	7.27	7.08		6.77		6.0				2.39, 2.51[c]
1d	4,5,6-TriMe	7.16	6.97				6.0				2.10, 2.30, 2.44[d]
1e	2-Et		6.82	7.78	7.12	8.53		8.1	1.7	4.5	1.30 (t, J = 7.6, CH_2CH_3)[e]
1f	5-Et[f]	7.41	7.10	7.79		8.38	6.0		1.8		1.22 (t, J = 7.5, CH_2CH_3)[g]
1g	6-*n*-Bu	7.27	7.03	7.76	6.98		6.0	8.2			0.92 [t, J = 6, $(CH_2)_3CH_3$][h]
1h	5,6-$(CH_2)_4$	7.23	6.92	7.43			6.0				1.5–2.1 [m, $-CH_2CH_2CH_2CH_2-$][i]
1i	2-Ac		7.84	8.17	7.36	8.79		8.2	1.8	4.5	2.60 (s, CH_3CO)
1j	5-Ac[f]	7.60	7.35	8.58		9.10	6.0		1.9		2.69 (s, CH_3CO)
1k	4,6-DiMe-2-Ac[f]		7.89		7.03						2.63 (s, CH_3CO, $2CH_3$)[j]
1l	2-D		7.11	7.90	7.12	8.45		8.0	1.7	4.6	
1m	3-D	7.41		7.92	7.14	8.46		8.0	1.7	4.6	
1n	2,3-DiD			7.90	7.14	8.45		8.0	1.7	4.6	
1o	2,3-DiBr			7.86	7.23	8.46		8.0	1.8	4.6	

[a] Unless otherwise indicated the solvent is CCl_4. Integrated areas of the signals were consistent with structural assignments. The multiplicity in the spectral pattern for each aromatic proton is 2^n, where n is the number of spin–spin couplings indicated for that proton. [b] Slightly split by coupling (J = 0.8 Hz) of H-5 with CH_3. [c] Singlets, $2CH_3$, probably at C-4 and C-6, respectively. [d] Singlets, $3CH_3$, probably at C-5, C-4, and C-6, respectively. [e] Also 2.86 (q, J = 7.6, CH_2CH_3). [f] Solvent $CDCl_3$. [g] Also 2.68 (q, J = 7.5, CH_2CH_3). [h] Also 1.1–2.0 (m, $CH_2CH_2CH_2CH_3$) and 2.83 (t, J = 7.5, $CH_2CH_2CH_2CH_3$). [i] Also 2.5–3.2 (m, $-CH_2CH_2CH_2CH_2-$). [j] Slightly split singlet.

TABLE II

NUCLEAR MAGNETIC RESONANCE DATA FOR THIENO[3,2-*b*]PYRIDINES[a]

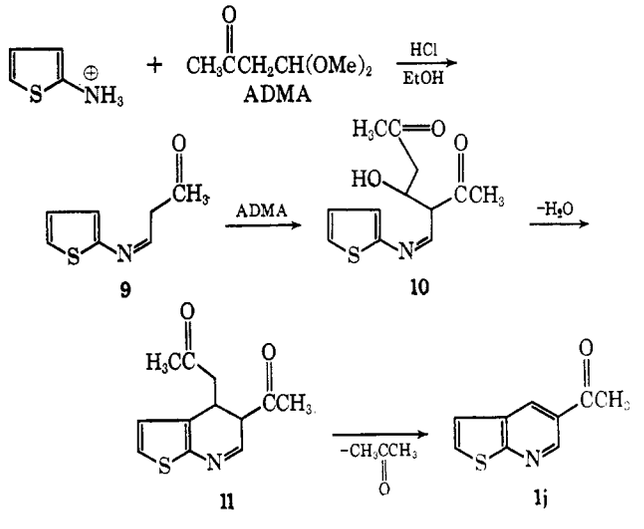
Compd	Substituent	Chemical shift, δ H-2	H-3	H-5	H-6	H-7	Coupling constant, Hz $J_{2,3}$	$J_{2,6}$	$J_{3,7}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$	Methyl signals, δ
2	None	7.68	7.51	8.64	7.12	8.08	6.1	0.4	0.8	4.8	1.6	8.8	
2a	5-Me	7.59	7.41		6.98	7.92	5.8	0.5	0.7			8.4	2.61 (s, CH_3)
2b	7-Me	7.60	7.48	8.45	6.88[b]		5.6	0.4		5.0			2.45[b]
2c	2-Ac[c]		8.22	8.88	7.45	8.33			<1	4.5	1.5	7.8	2.72 (s, CH_3CO)[d]
2d	6-Ac[c]	7.97	7.58	9.22		8.70	5.8		0.9		2.1		2.69 (s, CH_3CO)
2e	6-Et	7.59[e]	7.59[e]	8.60		7.86	*e*		<1		2		*f*

[a] See footnote *a*, Table I. [b] Slightly split by coupling (J = 0.8 Hz) of H-6 with CH_3. [c] Solvent $CDCl_3$. [d] In CCl_4 the acetyl singlet falls at δ 2.67. [e] Unresolved singlet. [f] 2.62 (q, J = 7.5 Hz, CH_3CH_2), 1.16 (t, J = 7.5 Hz, CH_3CH_2).

When the 2- or 3-amine salt was heated with excess acetoacetaldehyde dimethyl acetal (ADMA) in ethanolic hydrochloric acid, acetone was evolved and **1j** (32%) or **2d** (54%), respectively, was isolated. The structures of these products were established by ir and nmr spectra. Assignments were reinforced by comparisons with the nmr spectra of the previously described 2-acetylthienopyridines **1i**, **1k**, and **2c** (structures known from the method of synthesis). A further check was also made by comparison of spectra of the isomeric ethylthienopyridines **1e**, **1f**, and **2e** derived in fair yields from Wolff-Kishner reduction of **1i** (admixed with **2c**), **1j**, and **2d**, respectively. Scheme I shows a possible pathway for the formation of **1j**. It is assumed that ADMA is first converted effectively into free acetoacetaldehyde, which condenses with the 2-amine salt to form the Schiff's base **9**. Condensation of **9** (which contains an active methylene group) with a second molecule of acetoacetaldehyde should give ketol **10**. Acid-catalyzed dehydration–cyclization to **11** followed by a reverse Michael reaction would then lead to **1j**.[27]

In one run the mother liquors from isolation of **1j** were examined carefully for the presence of by-products. Identified were small yields (2–5%) of the monomethylthienopyridines **1a** and **1b**. In reaction of the 2-amine salt with acetoacetaldehyde tetraethyl acetal (ADEA) Zhiryakov and Abramenko[14] reported the isolation of only **1b** (20% yield). The melting point (211°) of the picrate of their product,[28] however, is more nearly like

SCHEME I



(27) In a separate experiment with ADMA and 2-naphthylamine the molar ratio of products was acetone–acetylbenzoquinoline 1:1.

(28) Zhiryakov and Abramenko[14] attempted to prove the structure of their product by an independent synthesis involving (as the first step) condensation of α-cyanothioacetamide with acetoacetaldehyde. Such process could, however, yield **1a** as well as **1b**.

that (218°) of our **1a** rather than that (171°) of our **1b**. Similarly, from the 3-amine salt the Russian workers report a 53% yield of **2a**, but again of unproved structure.[29]

In Table III are presented quantum chemical reactivity indices q_r (π-electron density) and S_r (exact superdelocalizabilities for electrophilic and nucleophilic attack) for direct substitution into **1**. Data were obtained by the use of simple Hückel molecular orbital theory and the parametric equations $\alpha_N = \alpha_C + 0.5\beta_{C-C}$, $\alpha_S = \alpha_C$, $\beta_{C-N} = 0.8\beta_{C-C}$, $\beta_{C-S} = 0.8\beta_{C-C}$. These equations neglect d-orbital interaction by the sulfur atom[30,31] and inductive effects of heteroatoms at distances beyond contiguous carbon atoms.[32] Observation of this table indicates that electrophilic substitution into **1** should occur predominantly in the thiophenoid ring with a strong preference for position C-3 over that of C-2 (analogous to observations for benzo[*b*]thiophene).[33] Nucleophilic substitution, on the other hand, should occur predominantly in the pyridinoid ring with preference shown for positions C-4 and C-6 (γ and α positions, respectively, with regard to N). Positional preference for nucleophilic substitution is thus predicted to be analogous to that which one finds in quinoline.[34,35]

TABLE III

QUANTUM CHEMICAL REACTIVITY INDICES[a] FOR THIENO[2,3-*b*]PYRIDINE (1)

Position r	q_r	S_r^{elec}	S_r^{nucl}
1 (S)	1.32	3.10	0.49
2	1.09	1.20	0.78
3	1.21	2.21	0.54
3a	1.08	1.02	0.60
4	0.94	0.96	1.19
5	1.06	1.13	0.71
6	0.93	0.92	1.15
7 (N)	1.32	1.59	0.94
7a	1.05	1.18	0.76

[a] S_r is given in units of β_C^{-1}: L. Salem, "Molecular Orbital Theory of Conjugated Systems," W. A. Benjamin, Inc., New York, N. Y., 1966, pp 326–332. Superscripts elec and nucl refer to electrophilic attack and nucleophilic attack, respectively. S_r^{rad} for free radical attack is readily calculated from the relationship $S_r^{rad} = {}^1/_2(S_r^{elec} + S_r^{nucl})$.

Limited investigations of electrophilic and nucleophilic substitutions into **1** have qualitatively confirmed the preceding predictions. Treatment of **1** with bromine in carbon tetrachloride gave 2,3-dibromothieno[2,3-*b*]pyridine in 17% yield. Reaction of **1** with deuteriosulfuric acid at 98.5° gave fastest deuteriodeprotonation at C-3 and slower exchange at C-2, as indicated by nmr studies (changes in the thiophenoid aromatic AB quartet) of samples withdrawn periodically.

Treatment of **1** with *n*-butyllithium at 25–35° gave, on addition of water, a yellow liquid (possibly containing 6-*n*-butyl-6,7-dihydrothieno[2,3-*b*]pyridine) which was converted into **1g** (47%, separated from recovered **1** by chromatography on alumina) on stirring with carbon disulfide. Assignment of the *n*-butyl group to the 6 position was made on the basis of the chromatographic elution order[20] (**1g** before **1**) and nmr analysis (absence of signal at $\delta > 8.0$). Repetition of this procedure with methyllithium (instead of *n*-butyllithium) gave a crude liquid containing *ca.* 25% of **1b** and 75% of **1**. With a reaction temperature of −25° and hydrolysis first with deuterium oxide and then with water, methyllithium gave a mixture of **1b** (11%) and deuterated **1** (containing *ca.* 50% of 2-deuteriothieno[2,3-*b*]pyridine, **1l**). Product **1l** apparently arises *via* metalation in a position *ortho* to the sulfur atom (*cf.* results for benzo[*b*]thiophene),[36] a process which competes with addition to the pyridinoid carbon–nitrogen double bond.[37]

Experimental Section[38]

2-Nitrothiophene.—Nitration of thiophene was conducted in acetic acid–acetic anhydride according to published directions.[16] Nmr analysis (CCl_4) of the product (mp 44–45°) showed that it consisted of an isomeric mixture containing 85% 2-nitrothiophene (δ 7.8–8.0, multiplet for H-3) and 15% 3-nitrothiophene (δ 8.1–8.3, multiplet for H-2).[39] Varying the reaction temperature over the range 10–30° did not alter the isomeric ratio. A reaction temperature of 25° is preferred since it gives the lightest colored product. Efforts to separate isomers by fractional crystallization and column chromatography were unsuccessful. The mixture was used directly in further reactions.

3-Nitrothiophene was prepared from thiophene in *ca.* 40% yield by the five-step procedure of previous workers.[17,18] Nmr analysis of the product (mp 74–75°) showed that it contained 5% of the isomeric 2-nitrothiophene. It was used without further purification.

Thieno[2,3-*b*]pyridine (1).—To a vigorously stirred mixture (maintained at 30°) of 13 g (0.1 mol) of the preceding 2-nitrothiophene and 195 ml of concentrated hydrochloric acid was added, in 5-g batches, a total quantity of 25 g of granular tin. After most of the tin had dissolved, 70 ml of EtOH and 6 g of anhydrous $ZnCl_2$ were added and the mixture was heated to 85°. A solution of 17.2 g (0.078 mol) of malondialdehyde tetraethyl acetal (Aldrich Chemical Co.) in 30 ml of EtOH was added all at once. The mixture was maintained at 85° for 1 hr and then poured onto 100 g of ice. The aqueous mixture was basified with concentrated aqueous NH_3 and extracted with three 75-ml portions of CCl_4. Distillation of combined extracts yielded 4.6 g (44%) of light yellow liquid, bp 61–62° (0.2 mm), found to contain about 6% of isomeric thieno[3,2-*b*]pyridine as determined by nmr analysis.

In a run conducted on five times the preceding scale the reaction mixture was basified with 40% aqueous NaOH and the resultant slurry was steam distilled. Continuous extraction for 16 hr with ether of the first 5 l. of distillate yielded 26.3 g (50%) of product.

For further purification 10.4 g (77 mmol) of mixed thienopyridine product was stirred for 1 hr with 15.3 ml of 1 *M* (15.3 mmol) hydrochloric acid and 300 ml of water. Extraction of

(29) Our picrates of **2a** and **2b** plus those reported by the Russian workers[13,14] have melting points in the range of 188–207°, but are otherwise inconsistent.

(30) R. Gerdil and E. A. C. Lucken, *J. Amer. Chem. Soc.*, **87**, 213 (1965).

(31) R. Gerdil and E. A. C. Lucken, *ibid.*, **88**, 733 (1966).

(32) The model used here is a combination of those suggested for thiophene by R. Zahradnik (*cf.* models B2 and B3) and for pyridine by R. Zahradnik and J. Koutecky, *Advan. Heterocycl. Chem.*, **5**, 2, 70 (1965).

(33) R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," 2nd ed, Interscience Publishers, New York, N. Y., 1967, pp 181–183.

(34) See ref 32, p 110.

(35) See ref 33, pp 249, 255.

(36) D. A. Shirley and M. D. Cameron, *J. Amer. Chem. Soc.*, **72**, 2788 (1950).

(37) H. Gilman and J. W. Morton, *Org. Reactions*, **8**, 272 (1954).

(38) Microanalyses were performed by Micro-Tech Laboratories, Skokie Ill. Infrared spectra were determined by means of a Beckman IR-5 instrument and nmr spectra by means of a Varian A-60 spectrometer and tetramethylsilane as an internal standard. Vapor phase chromatography was carried out with an F & M Model 202 gas chromatograph. Stationary phase A was 10% Apiezon L on Chromosorb P; B was 15% Carbowax 20M on firebrick. For many chromatograms relative retention volumes (rv) of components are reported in terms of a selected internal standard (rv = 1.0).

(39) R. A. Hoffman and S. Gronowitz, *Arkiv Kemi*, **16**, 515 (1960).

the acidic mixture with ether gave 9.4 g of pure (as adjudged by nmr) **1**. Basification of the aqueous layer and extraction thereof with ether produced 0.58 g of mixed thienopyridines—enriched in **2**.

Liquid–solid column chromatography of 3.6 g of **2**-enriched thienopyridines was conducted with 108 g of Alcoa F-20 alumina. Elution with cyclohexane–benzene (3:2 by volume) gave 1.09 g of pure **1** in the first 400 ml of effluent and 0.51 g of mixed isomers in the next 300 ml of effluent. Changing the eluent to benzene alone then yielded 1.5 g of pure **2** in 1 l. of effluent.

The methiodide of **1** formed cream-colored prisms from absolute EtOH, mp 202–203° dec.

Anal. Calcd for C_8H_8INS: C, 34.67; H, 2.91; I, 45.79; N, 5.05; S, 11.57. Found: C, 34.72; H, 3.05; I, 46.08; N, 5.06; S, 11.82.

Nmr spectral data for **1** are given in Table I. In analogy to quinoline,[40,41] a doublet of doublets at lowest field (δ 8.46) in the spectrum is assigned to H-6 (α to the heterocyclic N-atom) and a doublet of doublets at next higher field (δ 7.85) is assigned to H-4 (γ to the nitrogen)—$J_{5,6}$ = 4.5, $J_{4,6}$ = 1.6, $J_{4,5}$ = 8.1 Hz (*cf.* corresponding values for the heteroring of quinoline—$J_{2,3}$ = 4.1, $J_{2,4}$ = 1.8, $J_{3,4}$ = 8.5 Hz, respectively). The high-field portion of the spectrum consists of two overlapping sets of doublets of doublets which correspond to H-5 (β to the nitrogen, centered at δ 7.10, coupling constants as noted above) and to the thiophenoid AB proton system H-2 and H-3 (centered at δ 7.24, $J_{2,3}$ = 5.9 Hz; *cf.* $J_{2,3}$ = 5.6 as measured for benzo[*b*]thiophene in CCl_4). The lower field doublet of the latter set is ascribed to H-2, in accordance with previous observations on the methylbenzo[*b*]thiophenes[42] and with the absence of this doublet in authentic 2-ethylthieno[2,3-*b*]pyridine (**1e**, *vide infra*).

Thieno[3,2-*b*]pyridine (2).—The synthetic procedure was essentially the same as that for **1**, except that preceding 3-nitrothiophene (2.6 g) was used instead of its isomer and heating was conducted for 1.5 hr at 80°, yield 2.1 g (77%) of crude product from evaporation of combined CCl_4 extracts. The nmr spectrum of this crude product was identical with that of a sample of **2** prepared from 2-vinylpyridine and hydrogen sulfide by the vapor phase process of Klemm and Reed.[3] Also picrates of the two samples were identical, as based on melting points alone and after admixture.

An analytical sample of **2** was obtained as a faintly yellow-green liquid from vpc on A at 150°.

Anal. Calcd for C_7H_5NS: C, 62.19; H, 3.73; N, 10.36; S, 23.72. Found: C, 62.20; H, 4.08; N, 10.36; S, 23.34.

The nmr spectrum of **2** (Table II) shows more lines than that of **1** due to the presence of long-range coupling between H-2 and H-6 (J = 0.4 Hz) and between H-3 and H-7 (J = 0.8 Hz). The order of appearance in the spectrum of signals for the pyridinoid ring protons is the same as before, *i.e.*, α, γ, β (with respect to nitrogen) for increasing field strength, but signals for the thiophenoid ring protons are shifted downfield sufficiently that they fall cleanly between those for the γ and β protons (first-order spectrum). Only H-5 shows an unmodified doublet of doublets ($J_{5,6}$ = 4.8 Hz, $J_{5,7}$ = 1.6). All other spectral patterns ($J_{6,7}$ = 8.8, $J_{2,3}$ = 6.1) are again doubled by long-range spin–spin coupling constants which are consistent with observations on benzo[*b*]-thiophene ($J_{2,6}$ not observed, $J_{3,7}$ = 0.7)[42] and on 5,7-dichloroquinoline and 5,7-dimethylquinoline ($J_{4,8}$ = 0.8, analogous to $J_{3,7}$ in **2**).[43] Based on the consistency of these coupling constants one can again ascribe the lower half of the thiophenoid AB system in **2** to the proton at C-2. Although the geometry of thieno[3,2-*b*]pyrrole is considerably modified from that of **2**, it is noteworthy that long-range couplings between two sets of aromatic protons have also been observed in this thienopyrrole system.[44]

Bis(2- and 3-thienylammonium) Hexachlorostannates(IV).—These mixed salts were isolated in crystalline form from reduction of the corresponding 2- and 3-nitrothiophenes according to the procedure of Steinkopf and Lützkendorf.[4] Partial separation of mixed isomers could be achieved by fractional precipitation. Thus the initially isolated (by filtration at room temperature) salt was enriched in the 2 isomer. Cooling the filtrate to −10° caused precipitation of salt enriched in the 3 isomer. In subsequent reactions the crude salts were used without isomeric enrichment.

Reaction of 2-Thienylammonium Salt with Methyl Vinyl Ketone.—Reaction of bis(2-thienylammonium) hexachlorostannate(IV) with methyl vinyl ketone (MVK) was conducted in a manner similar to that previously described.[13] To a warm (60°) mixture of 20 g of amine salt, 22.1 g of anhydrous $FeCl_3$ and 0.5 g of anhydrous $ZnCl_2$ in 50 ml of absolute EtOH in a nitrogen atmosphere were added dropwise (over a period of 1 hr) a solution of 2.9 g of MVK in 25 ml of absolute EtOH. The mixture was then heated at 80° for 2 hr, cooled, poured onto 500 g of ice, basified with 40% aqueous NaOH and continuously extracted with ether for 1 day. The dried ($MgSO_4$) ether extract was distilled to yield 1.5 g (25%) of light yellow liquid, bp 75–85° (2 mm). Vpc of this distillate on B at 200° gave two liquid products **6-methylthieno[2,3-*b*]pyridine** (**1b**, 40%, r_V = 1.0) and **4-methylthieno[2,3-*b*]pyridine** (**1a**, 60%, r_V = 1.4).

Anal. Calcd for C_8H_7NS: N, 9.39. Found for **1a**: N, 9.80. Found for **1b**: N, 9.55.

Picrates of the chromatographically separated fractions crystallized from absolute ethanol: mp 217–218° for **1a picrate**, canary yellow needles (lit.[13] mp 213–215°), mp 169–171.5° for **1b picrate**, yellow prisms.

Anal. Calcd for $C_{14}H_{10}N_4SO_7$: C, 44.44; H, 2.66; N, 14.81; S, 8.48. Found for **1a** picrate: C, 44.29; H, 2.60; N, 14.68; S, 8.56. Found for **1b** picrate: C, 44.71; H, 2.75; N, 14.73; S, 8.42.

Reaction of 3-Thienylammonium Salt with Methyl Vinyl Ketone.—This reaction was conducted in the preceding manner to give 3 g (50%) of light yellow liquid. Vpc of this distillate gave two liquid products, **5-methylthieno[3,2-*b*]pyridine** (**2a**, 17%, r_V = 1.0) and **7-methylthieno[3,2-*b*]pyridine** (**2b**, 83%, r_V = 1.2).

The **picrate** of **2b** formed yellow needles from EtOH, mp 206–207° (lit.[13] mp 193–195°).[29]

Anal. Calcd for $C_{14}H_{10}N_4SO_7$: C, 44.44; H, 2.66; N, 14.81; S, 8.48. Found: C, 44.78; H, 2.72; N, 14.61; S, 8.50.

Reaction of 6-Methyl-2-vinylpyridine with H_2S.—In an apparatus similar to that described previously,[3] 35 g of freshly distilled 6-methyl-2-vinylpyridine (K & K Laboratories) was added at a rate of 20 drops/min to a vertical Pyrex tube (2 cm i.d.) packed to a height of 24 cm with chromia–alumina (Harshaw Chem. Co., Cr-0101T, 1/8 in. pellets) at 630° in a stream of H_2S (molar ratio 4:1 H_2S:substrate). Liquid effluent was combined with the residue from evaporation of acetone extracts of the cooled tube packing. This crude mixture was analyzed by vpc on stationary phase A at 150°. Identified by comparison of retention times with those of authentic sampes were 2-picoline, 2,6-lutidine, starting material, 2-methyl-6-ethylpyridine (all with r_V < 0.2), **2** (0.4%, r_V = 1.0), and **2a** (0.9%, r_V = 1.4).

For isolation of **2a**, low-boiling components of the crude mixture were removed by distillation up to 150° (25 mm). A benzene solution of the residue was percolated through alumina (50 g) and evaporated. The residue was triturated with acetone (20 ml) to leave undissolved sulfur. The filtrate of this mixture was evaporated and chromatographed on stationary phase A at 125°. The **2a** isolated was identical with that obtained from the 3-hexachlorostannate salt in the preceding section, as based on nmr. It formed a picrate, mp 195–196° (lit.[14] mp 188–189°).[29]

Reaction of 2-Methyl-5-vinylpyridine with H_2S.—In the preceding manner 50 g of freshly distilled 2-methyl-5-vinylpyridine (Phillips Petroleum Co.) was treated with H_2S (molar ratio 5:1 H_2S:substrate) at 630° in a flow apparatus. Identified, in the crude mixed product, by comparison of retention times (in vpc on A at 125°) with those of authentic samples (though not for **4a**) were 2-methyl-5-ethylpyridine (18%, r_V = 0.2), **1** (0.5%, r_V = 1.0), **1b** (2.2%, r_V = 1.5), and **6-methylthieno[3,2-*c*]-pyridine** (**4a**, 0.3%, r_V = 1.9). Also identified in the mixture by comparative nmr analyses were 2,5-lutidine (8%) and **thieno-[3,2-*c*]pyridine**[25] (**4**, 0.1%). A parallel run using 40 g of 2-methyl-5-ethylpyridine (Distillation Products) as substrate gave almost identical results except that there was more starting material (53% recovery) and some 2-methyl-5-vinylpyridine (6%) in the total product.

(40) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, New York, N. Y., 1966, pp 798–802.

(41) H. Suhr, "Anwendungen der Kernmagnetischen Resonanz in der Organischen Chemie," Springer-Verlag, Berlin, Germany, 1965, pp 232, 233.

(42) K. Takahashi, T. Kanda, and Y. Matsuki, *Bull. Chem. Soc. Jap.*, **37**, 768 (1964).

(43) F. A. L. Anet, *J. Chem. Phys.*, **32**, 1274 (1960).

(44) R. J. Tuite, H. R. Snyder, A. L. Porte, and H. S. Gutowsky, *J. Phys. Chem.*, **65**, 187 (1961).

For isolation of thienopyridine components the residue from distillation of the crude mixture up to 190° (0.5 mm) was chromatographed on a column of alumina (100 g). Elution with cyclohexane gave first **1b** (identified by the melting point of the picrate and its mixture melting point with product from the MVK reaction of the 2-thienylammonium salt) and then **1** (identified by comparison with preceding synthetic product). Further elution with $CHCl_3$–benzene 1:1 gave a mixture which was separated by sublimation at 60° (0.25 mm) to yield **4a**, mp 72.5–74°, picrate mp 224–226.5°, methiodide mp 241.5–242.5° (lit.[23] mp 71.5–72.5, 222–224, and 240–242°, respectively).

Reaction of 3-Ethyl-4-methylpyridine with H_2S.—In the preceding manner there was obtained from 35 g of 3-ethyl-4-methylpyridine (Aldrich) a crude product which showed two main components (identified by comparison of retention times with authentic samples) by vpc analysis on A at 125°, starting material (34% recovery, r_V = 1.0) and **1a** (1%, r_V = 3.3).

4,5,6-Trimethylthieno[2,3-*b*]pyridine (1d).—A mixture of 9 g (0.017 mol) of bis(2-thienylammonium) hexachlorostannate(IV), 3.3 g (0.029 mol) of 3-methylpentane-2,4-dione,[45] 2 g of anhydrous $ZnCl_2$, and 30 ml of dioxane was refluxed for 4 hr and then poured into absolute EtOH. To the black residue from evaporation *in vacuo* of nearly all of the solvent were added ice and 20 ml of concentrated aqueous NH_3. A CCl_4 extract of this mixture was chromatographed by means of 30 g of neutral Brinkman alumina with benzene–cyclohexane (1:3) and then $CHCl_3$ as eluents. The brown solid obtained from the $CHCl_3$ effluent was sublimed at 100° (2 mm) and combined with product from evaporation of the hydrocarbon effluent, total yield 1.65 g (32%) of white needles, mp 98–99°; uv max (95% EtOH) 234 mμ (ε 29,400), 272 (5590), 285 (4190), 291 (4190), 297 (3090), 302 (3710); uv max (95% EtOH + HCl) 242 mμ (ε 30,800), 306 (7430).

Anal. Calcd for $C_{10}H_{11}NS$: C, 67.76; H, 6.26; N, 7.90; S, 18.09. Found: C, 67.68; H, 6.42; N, 7.64; S, 17.86.

4,6-Dimethylthieno[2,3-*b*]pyridine (1c) was prepared from bis(2-thienylammonium) hexachlorostannate(IV) and acetylacetone in a manner similar to that used for **1d**, except that the product was extracted into benzene and purified by distillation (instead of chromatography) to give a light yellow liquid [45% yield, bp 100–105° (3 mm)] which slowly darkened in air [lit.[2] bp 103–108° (4 mm)].

5,6,7,8-Tetrahydrothieno[2,3-*b*]quinoline (1h).—A mixture of 0.5 g of anhydrous $ZnCl_2$, 15 ml of dioxane, 3 g (0.0057 mol) of bis(2-thienylammonium) hexachlorostannate(IV) and 1.3 g (0.01 mol) of 2-hydroxymethylenecyclohexanone[46] was stirred at 100° for 2 hr. The mixture was concentrated to a small volume and treated with 60 ml of 5% aqueous NH_3. The black product from the hydrolysate was extracted into $CHCl_3$, transferred to a benzene solution, passed through a column of Brinkman alumina, and evaporatively distilled *in vacuo* to yield 0.1 g (5%) of colorless liquid. This liquid formed a **picrate**, mp 188–189°, obtained as yellow plates from EtOH.

Anal. Calcd for $C_{17}H_{14}N_4O_7S$: C, 48.80; H, 3.37; N, 13.39; S, 7.66. Found: C, 48.95; H, 3.66; N, 13.70; S, 7.52.

Nitration of 2-Acetylthiophene.—2-Acetylthiophene (Winthrop Labs., New York, N. Y.) was nitrated in the same manner as used for thiophene itself[16] to give a mixture of solid products (37–62%), shown by nmr analysis to contain *ca.* equal parts of **4-nitro-2-acetylthiophene (7)** and **5-nitro-2-acetylthiophene (8)**. Repeated crystallization from EtOH[21] gave **7**, mp 123–125° (lit.[21] mp 125–126°), and then **8**, mp 100–110° (lit.[21] mp 106–107°); nmr ($CDCl_3$) for **7**, δ 2.62 (s, 3, CH_3CO), 8.55 (H_3), 8.61 (H_5, AB system, 2, J = 1.6 Hz); nmr ($CDCl_3$) for **8**, δ 2.62 (s, 3, CH_3CO), 7.61 (H_3), 7.91 (H_4, AB system, 2, J = 4.3 Hz). One of the authors developed a severe case of dermatitis (itching, swelling, and blistering) of the hands from handling these nitro compounds. Extreme care should be exercised in avoidance of contact with the skin.

The oxime of **8** was obtained as light yellow needles from EtOH: mp 187–188° (lit.[21] mp 189°); nmr (acetone) δ 7.25 (H_3), 7.96 (H_4, AB system, J = 4.5 Hz).

Bis[2-(5-acetylthienyl)ammonium] Hexachlorostannate(IV) (12).—To a vigorously stirred mixture of 10 g (0.058 mol) of **8**, 150 ml of concentrated hydrochloric acid, and 50 ml of EtOH was added 21 g (0.18 mol) of granular tin at such a rate as to maintain the reaction mixture at 30–34° while the reaction flask was cooled in a bath of tap water. After nearly all of the tin had dissolved the mixture was refrigerated at −10° for 10 hr and filtered to yield 6.6 g (37%) of **12**, dried *in vacuo*, used without further purification.

5-Acetylthieno[2,3-*b*]pyridine (1j).—To a stirred mixture of 9 g (0.017 mol) of bis(2-thienylammonium) hexachlorostannate(IV), 10 ml of concentrated hydrochloric acid, and 30 ml of EtOH in an atmosphere of purified nitrogen was added 12 g (0.09 mol) of acetoacetaldehyde dimethyl acetal (Aldrich Chemical Co.).[47] The mixture was heated at 75° for 8 hr (during which time acetone—detected by means of 2,4-dinitrophenylhydrazine reagent—was evolved) and then poured into sufficient excess 8% aqueous NaOH (175 ml) to basify the mixture and to dissolve most of the resultant precipitate. CCl_4 extracts of the hydrolysate were dried and evaporated to leave a residue which was sublimed at 120° (0.04 mm). Crystallization of the sublimate from cyclohexane gave needles: mp 116–117°; yield 1.9 g (32%); ir (CCl_4) 1690 cm^{-1} (C=O); uv max (95% EtOH) 247 mμ (ε 40,800), 275 (5910). The nmr spectrum showed a three-proton singlet at δ 2.69 for the acetyl group and coupling ascribed to protons at positions 2, 3, 4 and 6 but showed no evidence for coupling by a proton at C-5 (*cf.* Table I).

Anal. Calcd for C_9H_7NOS: C, 60.99; H, 3.98; N, 7.90; S, 18.09. Found: C, 61.33; H, 4.10; N, 7.89; S, 18.11.

In a larger run (0.5 mol of amine salt) evaporation of the mother liquor from crystallization of **1j** gave 11.8 g of black liquid. Chromatography of this liquid with 250 g of Alcoa F-20 alumina and successive eluents of cyclohexane–benzene (19:1), benzene, and $CHCl_3$ gave the following minor products (in order of elution):[20,48] **1b** (2.5% over-all yield), **1a** (4.6%), **2a** (?, <0.5%), additional **1j** (2%), and **2d** (1.2%, based on 3-amine salt in the starting material). No **2b** was detected.

6-Acetylthieno[3,2-*b*]pyridine (2d).—In the preceding manner 9 g of a mixture of bis(2- and -3-thienylammonium) hexachlorostannates(IV) (shown by nmr analysis to contain 40% of the 3 isomer) was allowed to react with acetoacetaldehyde dimethyl acetal (but at reflux conditions for 24 hr) and then processed further. The sublimate (3.4 g, 56%, analyzed by nmr by means of relative areas of the signals at δ 7.3 and 7.6, respectively) was found to contain equimolar amounts of **1j** and **2d**. Three recrystallizations of the sublimate from benzene–cyclohexane (1:1) gave 1.3 g (54%, based on 3 isomer only) of pure (by nmr analysis) **2d**: mp 134–135°; obtained as cream-colored crystals on sublimation at 90° (0.4 mm); ir ($CHCl_3$) 1690 cm^{-1} (C=O); uv max (95% EtOH) 246 mμ (ε 23,400), 292 (10,900); uv max (95% EtOH + HCl) 252 mμ (ε 24,900), 307 (6030), 325 (5150). The nmr spectrum showed a three-proton singlet at δ 2.69 for the acetyl group and coupling ascribed to protons at positions 2, 3, 5, and 7 but not at 6 (*cf.* Table II).

Anal. Calcd for C_9H_7NOS: C, 60.99; H, 3.98; N, 7.90; S, 18.09. Found: C, 60.76; H, 4.05; N, 8.04; S, 18.22.

2-Acetylthieno[2,3-*b*]pyridine (1i).—A mixture of 3 g (0.005 mol) of hexachlorostannate salt **12**, 2 g (0.09 mol) of MDTA, 2 g of anhydrous $ZnCl_2$, 15 ml of EtOH, and 5 ml of concentrated hydrochloric acid was refluxed for 3 hr and the mixture was processed further as for its isomer **1j**: yield 0.55 g (30%) of product from sublimation at 100° (10 mm); mp 124–126°. An additional sublimation gave light yellow needles: mp 122–123°; uv max (95% EtOH) 241 mμ (ε 14,000), 292 (17,300); uv max (95% EtOH + HCl) 248 mμ (ε 17,700), 294 (14,500).

Anal. Calcd for C_9H_7NOS: C, 60.99; H, 3.98; N, 7.90; S, 18.09. Found: C, 60.92; H, 3.86; N, 7.79; S, 18.30.

2-Acetyl-4,6-dimethylthieno[2,3-*b*]pyridine (1k).—In the manner used for preparation of **1d** (except that the reaction was

(45) Prepared by stirring 2.4 g of sodium acetylacetonate [R. G. Charles, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 869] with 5.3 g of MeI in 10 ml of CH_3CN for 13 hr, and then filtration and distillation of the reaction mixture, yield 2 g (89%), bp 80–85°.

(46) C. Ainsworth, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 536.

(47) For other syntheses with acetoacetaldehyde see W. Franke, R. Kraft, and K. Kosswig in "Newer Methods of Preparative Organic Chemistry," Vol. 2, W. Foerst, Ed., Academic Press, New York, N. Y., 1963, pp 1–30.

(48) The enhanced adsorbability of the acetyl derivatives over the methyl derivative is ascribed to strong anchoring by the carbonyl group (as well as by the pyridinoid nitrogen atom);[20] L. R. Snyder, "Chromatography," E. Heftmann, Ed., 2nd ed, Reinhold Publishing Corp., New York, N. Y., 1967, pp 63–66.

quenched with aqueous EtOH, and benzene was used as chromatographic eluent) there was obtained (from 1.9 g of amine salt **12** and 2 g of acetylacetone) 0.56 g (42%) of **1k**, mp 168–171° (after one crystallization from EtOH). Recrystallizations from EtOH and then sublimation at 120° (0.2 mm) gave light yellow needles: mp 168.5–169.5°; ir ($CHCl_3$) 1670 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82; S, 15.62. Found: C, 64.53; H, 5.45; N, 6.69; S, 15.71.

Conversion of Mixed Nitro-2-acetylthiophenes to 2-Acetylthienopyridines.—An isomeric mixture (mp 79–93°) of **7** (45% by nmr analysis) and **8** (55%) was reduced as in the preparation of **12**. The red-black solution was evaporated nearly to dryness and the crude mixture of amino-2-acetylthiophene hexachlorostannate salts (0.46 mol) was treated with 1.4 l. of EtOH, 0.45 l. of concentrated hydrochloric acid, 150 g of anhydrous $ZnCl_2$, and 150 g of MDTA. The mixture was refluxed in a nitrogen atmosphere for 5.5 hr, evaporated nearly to dryness, and extracted with 2 *N* HCl until the extract was no longer colored. Combined acid extracts were treated dropwise with 40% aqueous NaOH until a dense, dark precipitate coagulated (pH *ca.* 0.8). The filtrate of the mixture was brought to pH 1.5 and extracted with benzene. Evaporation of benzene extracts gave a dark tarry residue which was sublimed at 110–145° (1 mm) to give 27 g (17%) of yellow crystals of mixed 2-acetylthienopyridines—nearly equal parts of **1i** and of 2-acetylthieno[3,2-*b*]pyridine (**2c**) as determined by integration of the acetyl proton singlets observed in the nmr spectrum taken in CCl_4, *cf.* Table I and II.

On a 100-mg scale these isomers were separable by preparative tlc by means of a 20 × 40-cm plate coated to a thickness of 1 mm with Brinkman alumina G (activated at 110°) and elution with benzene–$CHCl_3$ (9:1 by volume) for 20 hr while the solvent overran the plate and the visually apparent yellow band approached the top closely. Spraying only the edges of the plate with Dragendorff's reagent[20] revealed the presence of an upper band (from which 32 mg of pure **1i** was obtained), an intermediate zone (mixed isomers), and a lower band (**2c**, free of **1i** but not of other impurities).

On a larger scale the isomers were separable by acid extraction. A solution of the crystalline mixed isomers in slightly more than the minimum quantity of benzene was stirred vigorously with four times the volume of 1 *N* HCl for 15–30 min. Layers were separated. Evaporation of the benzene layer gave **1i**, free of **2c** but not of other impurities.

The aqueous layer was basified with 40% aqueous NaOH and extracted with benzene until the extract remained colorless. Combined benzene extracts were evaporated nearly to saturation and the entire extraction process was repeated at least three more times, but with 0.1–0.2 *N* HCl instead of 1 *N* HCl. For the final time, combined benzene extracts were evaporated to dryness to give **2c**, free of **1i** but not of other impurities.

Extraneous impurities in preceding fractions were removed by sublimation at 80° (0.1 mm) for 3–4 hr. Two additional sublimations gave an analytically pure sample of **2c**, obtained as pale yellow prisms: mp 156–157°; ir ($CHCl_3$) 1675 cm^{-1} (C=O).

Anal. Calcd for C_9H_7NOS: C, 60.99; H, 3.98; N, 7.90; S, 18.09. Found: C, 61.30; H, 4.16; N, 7.75; S, 17.94.

2-Ethylthieno[2,3-*b*]pyridine (1e).—A mixture (1 g) of isomeric 2-acetylthienopyridines **1i** and **2c** (50% each), NaOH pellets (0.9 g), hydrazine hydrate (0.9 ml), and diethylene glycol (14 ml) was refluxed for 1.5 hr, distilled to bp 195°, and then refluxed for 3 hr longer. Addition of water to the cooled mixture, extraction with benzene, and evaporation of the extract gave 0.68 g (74%) of mixed 2-ethylthienopyridines (**1e** and its [3,2-*b*]isomer, 2:1 by vpc and nmr analysis). Vpc with 10% Bentone 34–silicone oil separated **1e** as a colorless liquid.

Anal. Calcd for C_9H_9NS: C, 66.22; H, 5.56. Found: C, 66.38; H, 5.80.

The picrate was obtained as canary yellow plates from absolute EtOH, mp 208–209°.

Anal. Calcd for $C_{15}H_{12}N_4O_7S$: C, 45.92; H, 3.08; N, 14.28; S, 8.17. Found: C, 45.77; H, 3.16; N, 14.07; S, 8.02.

5-Ethylthieno[2,3-*b*]pyridine (1f) and 6-Ethylthieno[3,2-*b*]pyridine (2e).—In the preceding manner **1j** was reduced to **1f**; and **2d** to **2e**. The respective ethyl derivatives were isolated as the picrates (65%, mp 188–190°; 83%, mp 238–239°) and recrystallized from EtOH to give bright yellow needles (mp 192–193 and 238.5–239.5°, respectively).

Anal. Calcd for $C_{15}H_{12}N_4O_7S$: C, 45.92; H, 3.08; N, 14.28; S, 8.17. Found for **1f picrate**: C, 45.94; H, 3.14; H, 14.07; S, 7.88. Found for **2e picrate**: C, 45.74; H, 3.07; N, 14.36; S, 8.13.

Dissociation of the picrates with chloroform and alumina gave the purified ethyl derivatives as light brown liquids, used for nmr characterization.

6-*n*-Butylthieno[2,3-*b*]pyridine (1g).—To a solution of 1.37 g (0.01 mol) of **1** in 20 ml of anhydrous ether in an atmosphere of nitrogen was added (over a period of 10 min) 13 ml (0.02 mol) of 1.5 *M* *n*-BuLi in ether. The mixture refluxed gently during the addition. Thereafter, it was stirred at room temperature for 30 min, while it acquired a deep red color. Water (10 ml) was added and the mixture was extracted with ether. Evaporation of the ether extract left 1.7 g of light yellow liquid (which turned dark slowly when neat, became black and gummy in CCl_4, but seemed fairly stable in ether). Addition of 20 ml of CS_2 gave a deep red solution and caused the evolution of H_2S—as evidenced by a test with lead acetate paper. The solution was stirred for 30 min and evaporated. The residual liquid was chromatographed by means of 40 g of Brinkman neutral alumina and eluents of cyclohexane (200 ml) and (then) benzene–cyclohexane (300 ml, 1:1 by volume). The first effluent yielded 0.9 g (47%) of liquid **1g**, while a later effluent gave 0.5 g of light yellow liquid—shown by nmr analysis to consist largely (*ca.* 90%) of recovered **1**. Vpc of the former liquid with a stationary phase of Apiezon L on firebrick gave an analytically pure sample.

Anal. Calcd for $C_{11}H_{13}NS$: C, 69.07; H, 6.85; N, 7.32; S, 16.76. Found: C, 69.23; H, 6.97; N, 7.14; S, 16.19.

A picrate was obtained as yellow needles from EtOH, mp 112–113°.

Anal. Calcd for $C_{17}H_{16}N_4O_7S$: C, 48.57; H, 3.84; N, 13.33; S, 7.63. Found: C, 48.87; H, 3.94; N, 13.47; S, 7.56.

Reaction of Thieno[2,3-*b*]pyridine with Methyllithium. A. At Room Temperature.—Following exactly the preceding directions, except that MeLi was used (in place of *n*-BuLi), the reaction mixture was stirred for 90 min at room temperature, and the CS_2 solution was stirred for 3 hr, there was obtained 1.2 g of crude, red liquid. Nmr analysis indicated that this liquid contained *ca.* 25% of **1b** and 75% of recovered **1**.

B. At −25°.—As before, **1** was treated with MeLi in ether solution but the reaction temperature was maintained at −25° and the time of stirring was 4 hr. To this cold ether solution was added 2 ml (excess) of D_2O (99.8 atom % D). The resultant slurry was allowed to warm (with stirring) to room temperature and treated with 10 ml of water. The ether layer, combined with ether extracts of the aqueous phase, was dried (Na_2SO_4), evaporated, and stirred with CS_2 for 2 hr. Evaporation gave 1.2 g of yellow liquid which was chromatographed as before. From the cyclohexane effluent (50 ml) was obtained 158 mg (11%) of liquid **1b**, identified by nmr. From the benzene–cyclohexane effluent (200 ml) was obtained 1.1 g (80%) of a light yellow liquid, identified as *ca.* a 1:1 mixture of **2-deuteriothieno[2,3-*b*]pyridine (1l)** and recovered **1**. The nmr parameters for **1l**, as determined on this mixture, are given in Table I.

Reaction of Thieno[2,3-*b*]pyridine with Deuteriosulfuric Acid.—A solution of **1** (0.5 g) in deuteriosulfuric acid (15 g, 85% solution in deuterium oxide) was heated at 98.5° while aliquots were removed periodically. Each aliquot portion was poured into water, basified with aqueous Na_2CO_3, extracted into CCl_4 (dried), and analyzed by nmr for deuterium incorporation. It was assumed that no deuterium exchange occurred in the pyridinoid ring. The signal at δ *ca.* 7.1 (assigned to H_3) disappeared much more rapidly than did that at δ *ca.* 7.4 (assigned to H_2). After 10 hr the former signal had decreased by >90% while the latter had decreased *ca.* 10%. The nmr parameters for **3-deuteriothieno[2,3-*b*]pyridine (1m)** and **2,3-dideuteriothieno[2,3-*b*]pyridine (1n)**, as determined on these solutions, are given in Table I.

2,3-Dibromothieno[2,3-*b*]pyridine (1o).—A mixture of 2.7 g (0.02 mol) of **1**, 9.6 g (0.06 mol) of bromine, 10 ml of CCl_4, and 50 ml of water was stirred at room temperature for 3 hr and then was evaporated. The residue was stirred with excess Na_2SO_3 and concentrated aqueous NH_3. A $CHCl_3$ extract of this mixture was evaporated and the residue therefrom was chromatographed by means of 20 g of neutral Brinkman alumina and petroleum ether. From the first liter of effluent was obtained 1 g (17%) of needles: mp 96–97°; uv max (95% EtOH) 236 mμ (ε 31,000), 282 (11,200), 288 (10,700), 299 (7860).

Anal. Calcd for $C_7H_3Br_2NS$: C, 28.70; H, 1.03; Br, 54.55; N, 4.78; S, 10.94. Found: C, 28.67; H, 1.17; Br, 54.54; N, 4.53; S, 10.83.

Registry No.—**1**, 272-23-1; **1** methiodide, 18366-61-5; **1a**, 13362-81-7; **1b**, 1759-30-4; **1b** picrate, 3395-13-9; **1c**, 18354-51-3; **1d**, 18354-52-4; **1e**, 18354-53-5; **1e** picrate, 18366-62-6; **1f**, 18354-54-6; **1f** picrate, 18366-63-7; **1g**, 18354-55-7; **1g** picrate, 18366-64-8; **1h**, 18425-96-2; **1h** picrate 18366-65-9; **1i**, 18354-56-8; **1j**, 18354-57-9; **1k**, 18354-58-0; **1l**, 18354-59-1; **1m**, 18366-53-5; **1n**, 18366-54-6; **1o**, 18366-55-7; **2**, 272-67-3; **2a**, 1759-29-1; **2b**, 13362-83-9; **2c**, 18366-58-0; **2d**, 18366-59-1; **2e**, 18366-60-4; **2e** picrate, 18425-97-3.

Determination of the Absolute Configuration of a Spiro Quaternary Ammonium Salt *via* Stevens Rearrangement[1,2]

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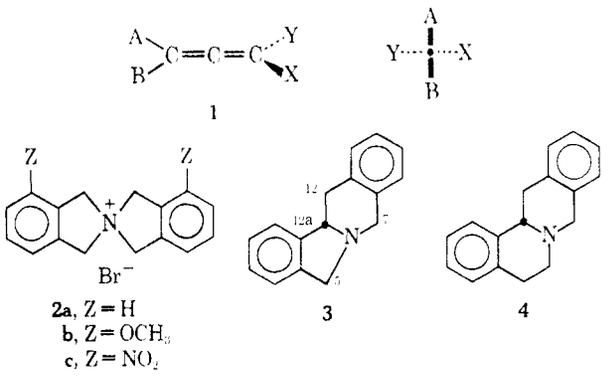
The levorotatory isomer of 4,4′-dimethoxy-1,1′,3,3′-tetrahydrospiro[isoindole-2,2′-isoindolium] bromide (**2b**) underwent Stevens rearrangement to give (−)-4,8-dimethoxy-5,7,12,12a-tetrahydroisoindolo[2,1-*b*]isoquinoline (**5a**). The absolute configuration of the latter substance was shown to be *S* by ozonolytic degradation to a derivative (**6**) of (*S*)-aspartic acid. The distribution of methoxy groups in **5a** was determined by nmr spectroscopy. These results permit an assignment of the *R* configuration to the levorotatory spiro salt, in accord with Lowe's rule, the helix conductor model and the Eyring–Jones model of optical activity. It is pointed out that a seeming failure of these rules and models in another substance might be due to swamping by other long-range effects.

Lowe[3] has pointed out that allenes having the absolute configuration **1** are dextrorotatory at the sodium D line when A is more polarizable than B and X is more polarizable than Y. This rule, like the "conformational dissymmetry rule,"[4] can be arrived at by use of a helical conductor model of optical activity.[2a] Lowe[3] suggested further that this rule may be applicable to other axially dissymmetric series of compounds, as the spirans, but doubt on this latter point has been raised by the recent work of Krow and Hill.[5] We wish to report our assignment of the *R* configuration to the levorotatory isomer of the spiro quaternary salt **2b**, consistent with Lowe's rule[3] and with the Jones–Eyring model of optical activity[6] and to suggest a reason for the *seeming* failure of Lowe's rule for the compound of Krow and Hill.



Racemic **2b** was prepared from 3-methoxyphthalic anhydride[7] *via* reduction with lithium aluminum hydride,[8] treatment of the diol with phosphorus tribromide and reaction of the crude dibromide with ammonia. Its nmr spectrum was comparable with that of a sample of the unsubstituted spiro salt **2a** prepared by reaction of *o*-xylylene dibromide with ammonia.[9] The quaternary hydroxide, formed by reaction with silver oxide, gave a salt with *d*-camphor-ω-sulfonic acid that could be resolved by crystallization from acetone–methanol mixtures. The less soluble diastereomer gave the levorotatory spiro bromide, $[M]_D$ −41°, on treatment with hydrogen bromide in methanol. The rotation varied only slightly with concentration but could be more than doubled by the addition of several equivalents of lithium bromide, indicating that the counterion also plays a role in determining the rotatory properties of this substance. The ORD curve of a dilute solution in methanol showed a relatively small negative Cotton effect, amplitude[10] [*a* = −14 (270–250 mλ)] on a strong negative background, $[M]_{235}$ −10,600.

The unsubstituted spiro quaternary salt **2a** has been shown by Wittig[11] to undergo a Stevens rearrangement[12] with strong bases to form **3** (necessarily racemic). Optically active bases of the series **3** contain an asymmetric center that might, in analogy with the work of Corrodi and Hardegger[13] with alkaloids containing the tetrahydroprotoberberine nucleus, **4**, be related to that of a derivative (**6**)[14] of aspartic acid (**7**), the configuration of which is known.[15] It is to be expected, on the basis of earlier work,[12,16,17] that the bond-break-

(1) IX. A Useful Model of Optical Acitivity.

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