The Synthesis and Chemical Reactivity of Thieno[2,3-*c*]- and Thieno[3,2-*c*]pyridines.

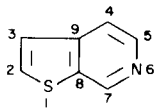
Mitchell L. Dressler (1) and Madeleine M. Joullié

Department of Chemistry, University of Pennsylvania

The syntheses and reactions of various thieno[2,3-*c*]- and thieno[3,2-*c*]pyridines are described. Molecular orbital calculations were performed on thieno[2,3-*c*]pyridine (I) in order to determine the most susceptible sites to electrophilic and nucleophilic attack. Superdelocalizability values, S_r, are reported for each position in this molecule to give relative orders of reactivity towards the two types of reactions. Electrophilic attack was found to occur experimentally at C-3 in all the thienopyridines studied. Peracid oxidation of thieno[2,3-*c*]- and thieno[3,2-*c*]pyridines produced only the *N*-oxide. The lack of reactivity of certain thienopyridines under Vilsmeier formylation and Friedel-Crafts acetylation conditions was related to their basicities. The dissociation constants of various thienopyridinium salts are reported.

Thienopyridines are of chemical interest because of their similarity to benzo[*b*]thiophene whose derivatives are plant growth regulators (2) and to isoquinoline, an important nucleus in certain alkaloids (3).

Thieno[2,3-*c*]pyridine (I) consists of an electron rich 5-membered heterocycle fused to an electron poor pyridine ring. These systems should retain certain chemical properties of the isolated rings. However, the chemical reactivity of the fused system should be lower than that of the individual rings. Molecular orbital calculations



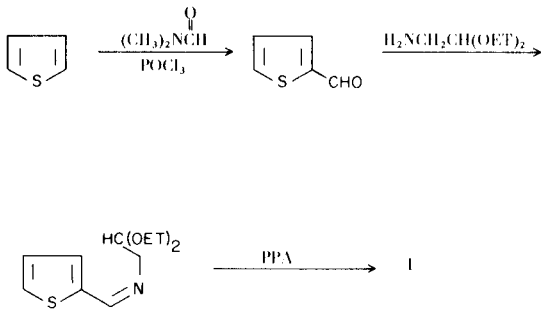
I

were performed on I, and these showed that electrophilic attack should occur at C-3. Benzo[*b*]thiophene, thieno[2,3-*b*]pyridine (4), and thieno[3,2-*b*]pyridine (5) exhibit similar chemical behavior.

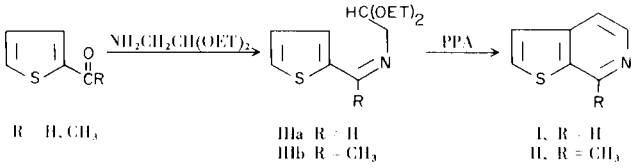
Thieno[2,3-*c*]pyridine (I) has been previously prepared by Herz and Tsai (6) and by Klemm, *et al.* (7), but their yields were less than 6%. After this present study was completed, Klemm, *et al.* (8) prepared I by a convenient two-step synthesis involving the reaction of 4-vinylpyridine with benzyl mercaptan, followed by the pyrolysis of the resulting product.

Synthetic Schemes.

The route used to prepare I in this study was developed by Herz and Tsai (6).



7-Methylthieno[2,3-*c*]pyridine (II) was prepared in a similar manner from the amino acetal of 2-acetylthiophene (III) to determine the directive influence of a methyl group in the pyridine ring.



R = H, CH_3 IIIa R = H; IIIb R = CH_3 I, R = H; II, R = CH_3

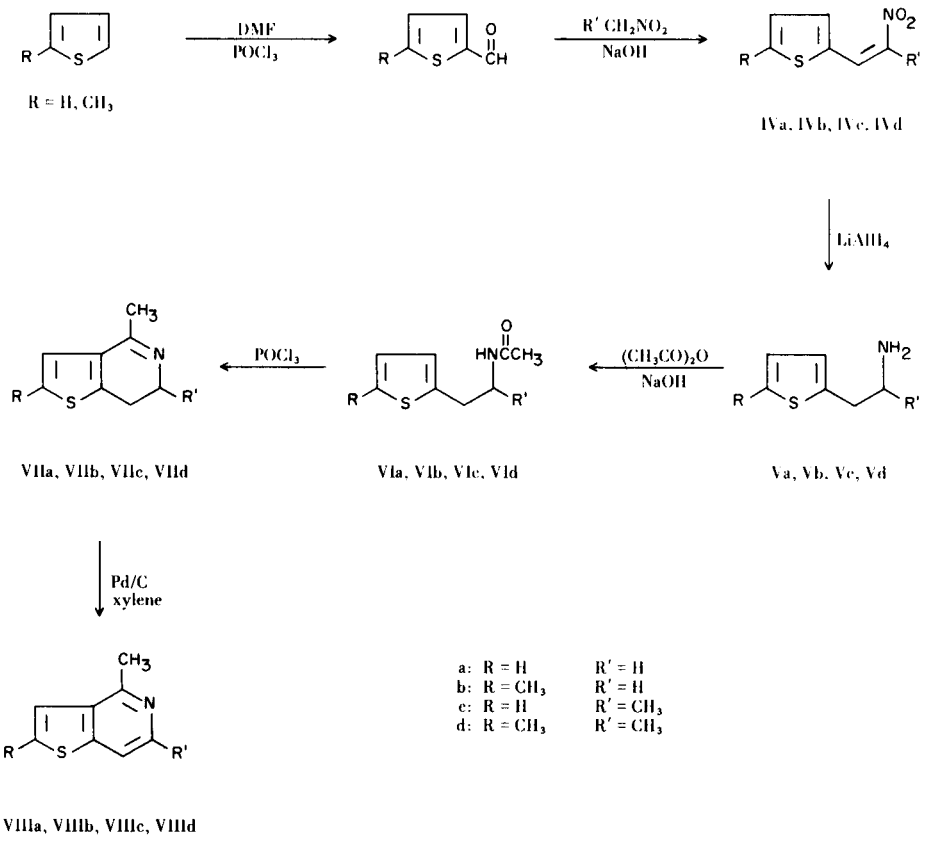
Various substituted thieno[3,2-*c*]pyridines were prepared as shown in Scheme I.

Simple Hückel molecular orbital calculations (9) which neglect the inductive effects of atoms at distances beyond adjoining atoms were performed on I. These calculations were designed to determine which sites would undergo electrophilic and nucleophilic attack most readily.

The parametric equations (10,11) used in these calculations are

$\alpha_S = \alpha_C$, $\alpha_{\dot{N}} = \alpha_C + 0.3\beta$, $\beta_{C\text{-}S} = 0.8\beta$, and $\beta_{C\text{-}\dot{N}} = 0.8\beta$

SCHEME I



The superdelocalizability values for the various positions in I are shown in Table I. S_r is a measure of the relative rates of substitution in conjugated molecules, *i.e.*, the greater the value, the more reactive the r^{th} position in the molecule.

TABLE I

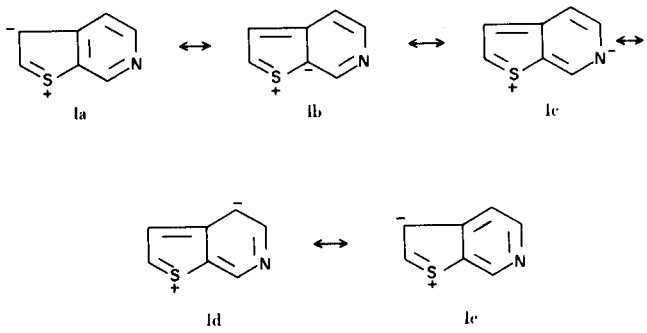
Quantum Chemical Reactivity Indices (a) for I

Position$_r$	S_r^{elec}	S_r^{nucl}
1 (S)	3.36	0.56
2	1.19	0.75
3	2.31	0.52
4	1.28	0.83
5	1.29	0.84
6 (N)	1.54	0.84
7	1.14	1.11
8	1.04	0.59
9	1.08	0.63

(a) S_r is superdelocalizability in units of β. Superscripts elec and nucl refer to electrophilic and nucleophilic attack, respectively.

The S_r^{elec} values indicate that C-3 is the most favorable position for electrophilic attack. Further support to substantiate electrophilic attack at C-3 rather than C-2 may be obtained by a consideration of the transition states involved in the reaction of I with an electrophile.

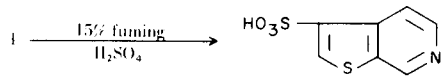
The increased electron density at the 3-position is in agreement with the valence-bond point of view. From the variety of contributing structures which may be written



for I, the more important ones are clearly those which preserve the aromatic integrity of the pyridine ring (Ia, Ie) rather than those where resonance in this ring has been destroyed and where charge separation is larger (Ic, Id).

Reactions.

The sulfonation of I gave thieno[2,3-c]pyridine-3-sulfonic acid (IX). The structure assigned to IX was

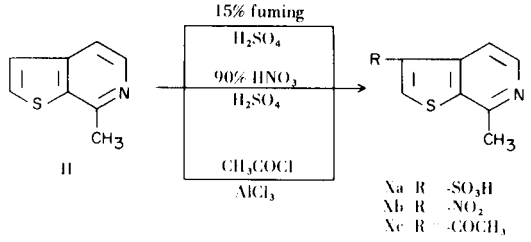


IX

supported by nmr decoupling experiments on I which showed that H-3, H-4, and H-5 are all coupled to H-7. The H-2 proton exists as a pure doublet coupled only to H-3. Similar results have been observed in studies on benzofuran (12), indene (12), indole (13), and 2-methyl benzo[*b*]thiophene. In these systems H-3 interacts with H-7 (J = 0.7-1.0 Hz). The nmr spectrum of IX (Table II) exhibited two slightly split doublets (H-4 and H-5) and two singlets (H-2 and H-7), one of which was also slightly split. The peak assigned to H-2 was a pure singlet and therefore not coupled to H-7. The infrared spectrum of IX exhibited a band characteristic of two consecutive protons and another band characteristic of one isolated proton on the pyridine moiety (827 and 890 cm^{-1}, respectively). These absorptions support the assumption that electrophilic attack has occurred in the thiophene moiety.

Sulfonation, nitration, and Friedel-Crafts acetylation of II yielded products which resulted from attack at C-3. (Scheme II).

SCHEME II

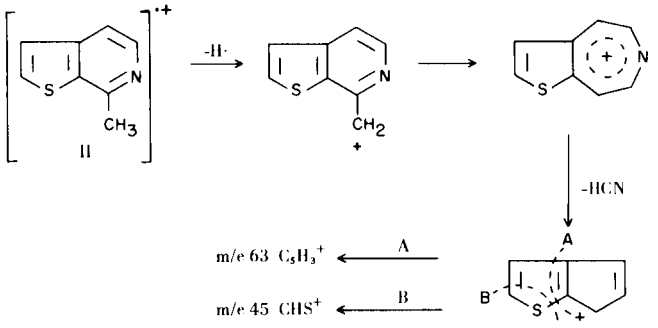


The nmr spectrum of Xa similarly supports attack at the 3-position. The absorption at 820 cm^{-1}, characteristic of two adjacent hydrogen atoms in the pyridine ring, in the infrared spectrum of Xa, substantiates attack in the thiophene moiety.

Additional support for substitution at the 3-position may be derived from the mass spectrum of Xb. Scheme III illustrates the fragmentation pattern for II, similar to the one postulated for 1-methylisoquinoline (14).

After the expulsion of HCN from the azatropilium ion, the most important fragments are $C_5H_3^+$ (m/e 63) and CHS^+ (m/e 45). The fragment at m/e 63 is often observed in fused ring systems where it arises from the cleavage

SCHEME III



along path A (15). The mass spectrum of Xb exhibits a large peak at m/e 63 (64.73%) which indicates that substitution has not occurred in the pyridine moiety. The fragment at m/e 45 (26.33%) supports substitution at C-3 rather than at C-2. The nmr and infrared spectra of Xc similarly support attack at the 3-position.

A methyl group α or γ to a nitrogen atom in a heteroaromatic system is activated and able to condense with carbonyl groups (16). The methyl group of II condensed with benzaldehyde, as expected, to give 7-styrylthieno[2,3-c]pyridine (XI) which was oxidized with osmium tetroxide to thieno[2,3-c]pyridine-7-carboxaldehyde (XII), as shown in Scheme IV.

SCHEME IV

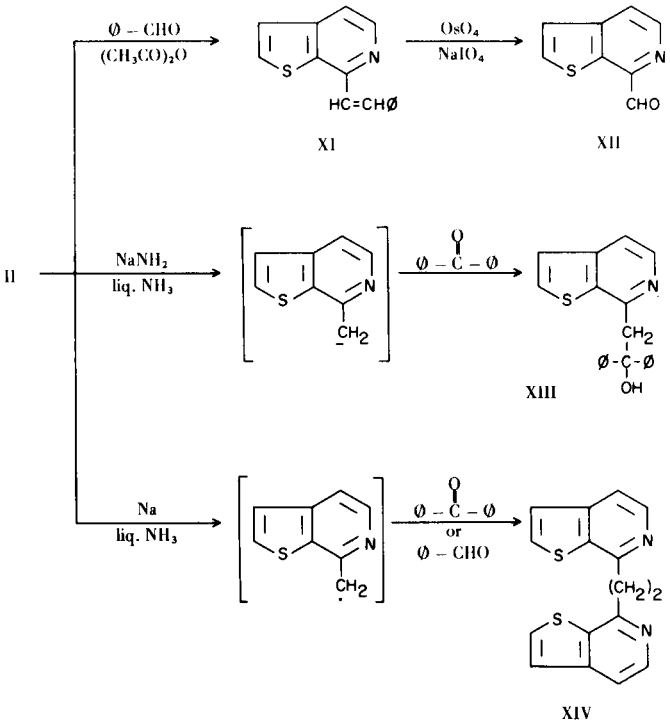


TABLE II

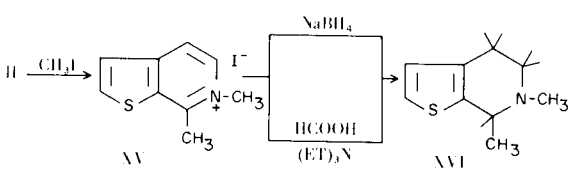
NMR Values for Thienopyridines.

Compound	Solvent	H-2	H-3	H-4	H-5	H-6	H-7
I	CCl_4	7.60	7.26	7.56	8.42	----	9.06
	HCl/D_2O	8.68	7.80	8.60	8.36	----	9.54
IX	HCl/D_2O	9.18	----	8.86	8.64	----	9.80
II	$CDCl_3$	7.50	7.18	7.36	8.38	----	(CH_3) 2.72
	CF_3CO_2D	8.64	7.94	8.62	8.34	----	(CH_3) 3.28
Xa	CF_3CO_2D	9.24	----	8.84	8.60	----	(CH_3) 3.24
Xb	$CDCl_3$	8.84	----	8.28	8.64	----	(CH_3) 2.84
Xc	$CDCl_3$	8.36	----	8.32	8.48	----	(CH_3) 2.76
VIIIa	$CDCl_3$	7.42	7.42	(CH_3) 2.83	----	8.33	7.61
	DMSO (d_6)	7.86	7.86	(CH_3) 2.80	----	7.86	7.63
	CF_3CO_2D	8.19	7.95	(CH_3) 3.25	----	8.38	8.38
XVIIIa	CF_3CO_2D	9.00	---	(CH_3) 3.66	----	8.48	8.48
XIXa	DMSO (d_6)	8.98	----	(CH_3) 2.74	----	8.52	8.08
VIIIb	$CDCl_3$	(CH_3) 2.52	6.97	(CH_3) 2.74	----	8.25	7.44
	CF_3CO_2D	(CH_3) 2.81	7.58	(CH_3) 3.16	----	8.24	8.35
XVIIIb	CF_3CO_2D	(CH_3) 3.62	----	(CH_3) 3.09	----	8.25	8.40
VIIIc	$CDCl_3$	7.27	7.27	(CH_3) 2.76	----	(CH_3) 2.59	7.36
	CF_3CO_2D	7.98	7.30	(CH_3) 3.17	----	(CH_3) 2.88	8.11
XVIIIc	CF_3CO_2D	8.80	----	(CH_3) 3.56	----	(CH_3) 2.90	8.12
XIXc	$CDCl_3$	8.12	----	(CH_3) 2.77	----	(CH_3) 2.63	7.44
VIIId	$CDCl_3$	(CH_3) 2.43	6.85	(CH_3) 2.68	----	(CH_3) 2.53	7.19
	CF_3CO_2D	(CH_3) 2.79	7.50	(CH_3) 3.16	----	(CH_3) 2.87	8.05
XVIIId	CF_3CO_2D	(CH_3) 3.56	----	(CH_3) 3.04	----	(CH_3) 2.88	8.01

When sodamide in liquid ammonia was treated with II, the reaction proceeded through the anion intermediate to produce α,α-diphenylthieno[2,3-*c*]pyridine-7-ethanol (XIII). However, when sodium in liquid ammonia was treated with II, a hydrogen atom instead of a proton was abstracted from the methyl group and a dimer (XIV) was formed. (Scheme IV). Dimerization therefore occurred before reaction of the presumed free radical intermediate with the carbonyl compound could take place.

Quaternization of II with methyl iodide gave the expected 6,7-dimethylthieno[2,3-*c*]pyridinium iodide (XV) which was reduced by two methods: sodium borohydride, and formic acid and triethylamine, to give 4,5,6,7-tetrahydro-6,7-dimethylthieno[2,3-*c*]pyridine (XVI) (isolated as the picrate due to its instability in the free state), as shown in Scheme V.

SCHEME V



Compound VIIIa behaved in the same manner as II (Scheme IV) with sodamide in liquid ammonia to form α,α-diphenylthieno[3,2-*c*]pyridine-4-ethanol (XVII).

The nmr spectra of VIIa, VIIb, VIIc, and VIId exhibited coupling (17) between CH_3-4 and H-6. When R′ = CH_3, a doublet (J = 1.8 Hz) was observed and when R′ = H, a triplet (J = 1.8 Hz) was observed. Coupling was also observed in the nmr spectra of VIIIb and VIIId between

TABLE III

Spectral Values for the *N*-Oxides

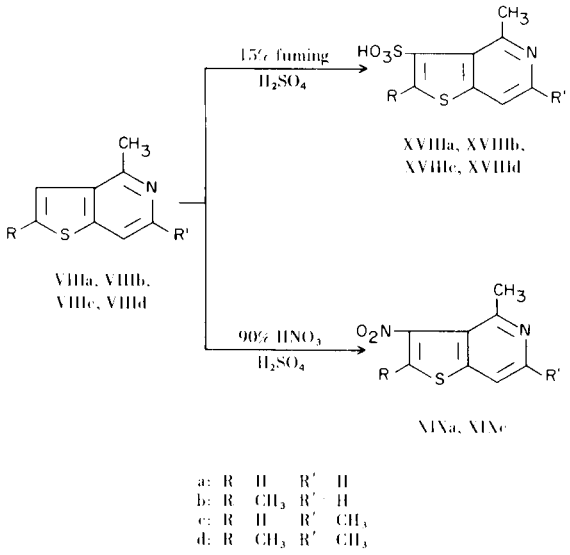
	NMR (a)									IR (b)
	2-H	3-H	4-H	5-H	6-H	7-H	$J_{2,3}$	$J_{4,5}$	$J_{6,7}$	νN→O (cm^{-1})
XXII	7.64	7.31	7.51	8.24	----	(CH_3) 2.77	5.4	7.0	---	1220
XXIIIa	7.65	7.35	(CH_3) 2.80	----	8.24	7.59	5.4	---	7.0	1245
XXIIIb	(CH_3) 2.61	7.00	(CH_3) 2.74	----	8.15	7.47	1.2	---	7.0	1215
XXIIIc	7.54	7.31	(CH_3) 2.85	----	(CH_3) 2.66	7.64	5.4	---	---	1245

(a) All NMR samples were run in deuteriochloroform. (b) All IR samples were run as potassium bromide pellets.

CH_3-2 and H-3 (18,12,13) (J = 1.0-1.2 Hz) and between H-3 and H-7 (J < 0.6 Hz) in VIIIa, VIIIb, VIIIc and VIIId. These observations helped to elucidate the nature of the product obtained after reaction with an electrophile.

The nitration and sulfonation of various substituted thieno[3,2-c]pyridines are shown in Scheme VI.

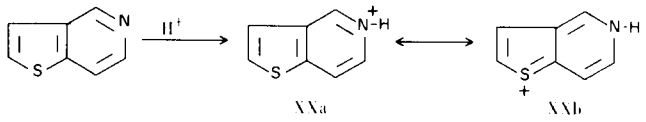
SCHEME VI

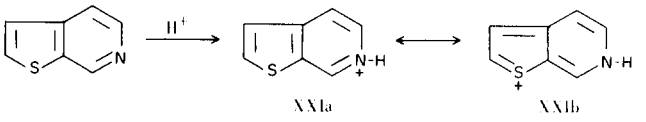


The nmr spectrum of the sulfonated and nitrated products exhibited no long range coupling between the aromatic singlet adjacent to the sulfonic acid or nitro group and H-7 in XVIIIa, XVIIIc, XIXa or XIXc. This substantiated the proton assignments in Table II and consequently electrophilic attack at C-3. The infrared spectra of XVIIIa and XIXa exhibited bands at 809 and 804 cm^{-1}, respectively, which are characteristic of two consecutive hydrogens on the pyridine moiety. Only the nmr spectrum of compounds XVIIIb, XVIIIc, XVIIId and XIXc was needed to determine where substitution had occurred. These nmr spectra further substantiated attack on the thiophene moiety.

Compounds II and VIIIa could not be formylated under Vilsmeier conditions. Attempts to acetylate VIIIa under Friedel-Crafts conditions also failed. These results may be rationalized in terms of the relative basicities of II and VIIIa.

In reactions where the attacking reagent is an electrophile such as nitration and sulfonation, protonation of the pyridine nitrogen precedes electrophilic attack on a carbon atom. The degree of protonation is a function of the basicity of the heteroaromatic amine. This basicity is dependent on the availability of the lone pair of electrons on nitrogen, which is related to the electronic distribution and degree of aromaticity of the molecule. The more basic the system, the more it will exist in a protonated

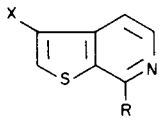




form. The *para*-quinoid resonance structures XXb and XXIb would be expected to be more stable than the corresponding *ortho*-quinoid structures which could be written for the protonated species of thieno[3,2-*b*]- and thieno[2,3-*b*]pyridines. The resulting increase in resonance stability observed for the thieno[3,2-c]- and thieno[2,3-c]pyridines allow these structures to act as stronger bases. A study of relative basicities in the azaindole series has shown that the basicities decrease in the order 1,5- > 1,6- > 1,4- > 1,7- azaindole (19). pK_a Measurements (Table V) have shown that 7-methylthieno[2,3-c]pyridine (pK_a = 5.81) is a weaker base than 4-methylthieno[3,2-c]-

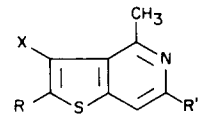
TABLE IV

Thieno[2,3-c]pyridines



Compound No.	X	R	R′	Method	Yield %	M.p.° (b.p.°/mm)	Formula	Analyses % Calcd. (Found) C	H	N	S
I(a)	H	H	---	A	< 1	58-59	C_7H_5NS	62.19 (62.01)	3.73 (3.65)	10.36 (10.18)	23.72 (23.65)
IX	SO_3H	H	---	B	54	399.5-401	$C_7H_5NO_3S_2$	39.06 (39.23)	2.34 (2.27)	6.51 (6.55)	29.70 (29.56)
II	H	CH_3	---	A	60	102-103/2.5mm	C_8H_7NS	64.40 (64.31)	4.73 (4.75)	9.39 (9.26)	21.49 (21.32)
Xa	SO_3H	CH_3	---	B	40	320-321	$C_8H_7NO_3S_2$	41.91 (42.07)	3.08 (3.18)	6.11 (6.13)	27.97 (27.92)
Xb	NO_2	CH_3	---	C	40	196-197	$C_8H_6N_2O_2S$	49.47 (49.36)	3.11 (3.25)	14.42 (14.59)	16.51 (16.39)
Xc	$COCH_3$	CH_3	---	D	40	170-170.5	$C_{10}H_9NOS$	62.80 (62.65)	4.74 (4.46)	7.32 (7.41)	16.77 (16.92)

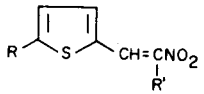
Thieno[3,2-c]pyridines



VIIIa (b)	H	H	H	E	100	52.5-54 (103/3.3mm)	C_8H_7NS	64.40 (64.24)	4.73 (4.92)	9.39 (9.22)	21.49 (21.31)
VIIIb	H	CH_3	H	E	73	75-76/0.11mm	C_9H_9NS	66.22 (66.13)	5.56 (5.69)	8.58 (8.72)	19.64 (19.48)
VIIIc	H	H	CH_3	E	82	64-65/0.18 mm	C_9H_9NS	66.22 (66.12)	5.56 (5.62)	8.58 (8.62)	19.64 (19.49)
VIIId	H	CH_3	CH_3	E	50	77/0.09mm	$C_{10}H_{11}NS$	67.76 (67.52)	6.25 (6.38)	7.90 (7.98)	18.09 (18.25)
XVIIIa	SO_3H	H	H	B	40	>400	$C_8H_7NO_3S_2$	41.91 (41.85)	3.08 (3.22)	6.11 (6.20)	27.97 (27.87)
XVIIIb	SO_3H	CH_3	H	B	30	291.5-292	$C_9H_9NO_3S_2$	44.41 (43.91)	3.76 (3.71)	5.75 (5.50)	26.34 (25.88)
XVIIIc	SO_3H	H	CH_3	B	42	>450	$C_9H_9NO_3S_2 \cdot H_2O$	41.36 (41.42)	4.24 (4.16)	5.36 (5.25)	24.54 (24.45)
XVIIId	SO_3H	CH_3	CH_3	B	50	294-296	$C_{10}H_{11}NO_3S_2 \cdot H_2O$	43.62 (43.85)	4.76 (4.96)	5.09 (4.96)	23.29 (23.56)
XIXa	NO_2	H	H	C	40	188-189	$C_8H_6N_2O_2S$	49.48 (49.39)	3.11 (3.22)	14.42 (14.33)	16.51 (16.41)
XIXc	NO_2	H	CH_3	C	33	138-139	$C_9H_8N_2O_2S$	51.91 (51.74)	3.87 (3.80)	13.45 (13.28)	15.40 (15.28)

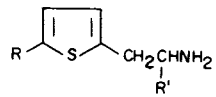
(a) See ref. 6. (b) See ref. 17.

Nitrovinyl Thiophenes



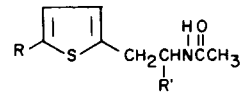
Compound No.	R	R′	Method	Yield (%)	M.p. (°C)	Formula	Analyses % Calcd. (Found) C	H	N	S
IVa	H	H	F	83	80-81	$C_6H_5NO_2S$	46.44 (46.45)	3.25 (3.19)	9.03 (8.90)	20.66 (20.50)
IVb	CH_3	H	F	76	82-82.5	$C_7H_7NO_2S$	49.69 (49.82)	4.17 (4.26)	8.28 (8.14)	18.95 (18.73)
IVc	H	CH_3	F	32	68-69	$C_7H_7NO_2S$	49.69 (49.63)	4.17 (4.04)	8.28 (8.46)	18.95 (19.15)
IVd	CH_3	CH_3	F	46 (c)	—	$C_8H_9NO_2S$	—	—	—	—

Thiopheneethylamines



					B.p. °/mm					
Va	H	H	G	80	66-67/3.75	C_6H_9NS	56.65 (56.80)	7.13 (7.31)	11.01 (11.12)	25.21 (24.98)
Vb	CH_3	H	G	71	75-76/3.5	$C_7H_{11}NS$	59.53 (59.37)	7.85 (7.99)	9.92 (9.83)	22.70 (22.50)
Vc	H	CH_3	G	37	70-71/4.75	$C_7H_{11}NS$	59.53 (59.59)	7.85 (7.94)	9.92 (9.81)	22.70 (22.56)
Vd	CH_3	CH_3	G	66	87-88/4.1	$C_8H_{13}NS$	61.88 (61.75)	8.44 (8.30)	9.02 (8.91)	20.65 (20.58)

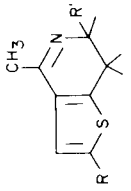
Acetamides of Thiopheneethylamines



VIa	H	H	H	60	50-51	$C_8H_{11}NOS$	—	—	—	—
VIb	CH_3	H	H	52	117-118/0.12	$C_9H_{13}NOS$	58.98 (59.00)	7.15 (7.33)	7.64 (7.50)	17.50 (17.61)
VIc	H	CH_3	H	62	113/0.11	$C_9H_{13}NOS$	58.98 (59.13)	7.15 (7.22)	7.64 (7.78)	17.50 (17.63)
VId	CH_3	CH_3	H	50 (c)	50/0.12	$C_{10}H_{15}NOS$	—	—	—	—

TABLE IV (Continued)

6,7-Dihydrothieno[3,2-*c*]pyridines



VIIa	H	H	J	60	62/0.16	C_8H_9NS	63.54 (63.33)	6.00 (6.19)	9.26 (9.16)	21.20 (21.06)
VIIb	CH_3	H	J	55	62-64/0.11	$C_9H_{11}NS$	65.41 (65.21)	6.71 (6.74)	8.48 (8.60)	19.40 (19.17)
VIIc	H	CH_3	J	82	58/0.17	$C_9H_{11}NS$	65.41 (65.33)	6.71 (6.83)	8.48 (8.55)	19.40 (19.41)
VIId	CH_3	CH_3	J	70	54/0.11	$C_{10}H_{13}NS$	66.99 (66.76)	7.31 (7.29)	7.81 (7.99)	17.88 (17.96)

(c) Crude yield.

TABLE V

Dissociation Constants of Thienopyridines

Compounds	pK_a
XI	2.80
I	5.25
II	5.81
VIIIa	6.17
VIIIb	6.43
VIIIc	6.75
VIIId	6.77

pyridine (pK_a 6.17). These values agree closely with those found for the corresponding 1,6- and 1,5-azaindoles (7.95 and 8.26, respectively), but are of a lower magnitude because of the higher degree of aromaticity of the thienopyridines compared to the pyrrolopyridines.

The greater the basicity of VIIIa as compared to II indicates that a higher concentration of the former molecule will exist as the protonated species. This has the effect of lowering the reactivity of VIIIa towards electrophilic attack at the 3-position. The difference in reactivity between II and VIIIa cannot be observed in nitration and sulfonation since the corresponding attacking agents NO_2^+ and SO_3, are extremely strong electrophiles and thus not very selective. When protonation takes the form of complex coordination between the thienopyridine nitrogen atom and an electrophilic species as in Friedel-Crafts acetylations, this complex will exist in larger concentrations if a more basic thienopyridine is used. Thus, VIIIa, which should form this complex in greater concentration, will be less reactive towards acetylation than II

SCHEME VII

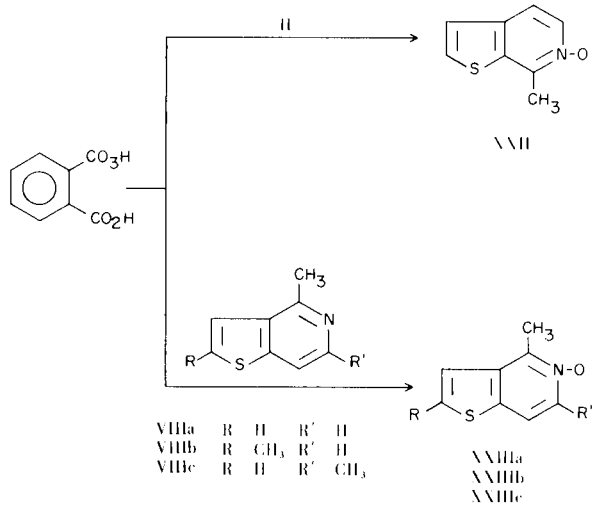


TABLE VI

Thienopyridine *N*-Oxides

Compound	Yield (%)	M.p. (°C)	Formula	Analyses % Calcd. (Found) C	H	N	S
XXII	70	118-119	C_8H_7NOS	58.16 (57.89)	4.27 (4.40)	8.49 (8.36)	19.41 (19.19)
XXIIIa	75	106-107.5	C_8H_7NOS	58.16 (57.96)	4.27 (4.20)	8.49 (8.33)	19.41 (19.44)
XXIIIb	60	103-106	C_9H_9NOS	60.31 (60.11)	5.06 (4.89)	7.81 (7.69)	17.89 (17.69)
XXIIIc	55	86-87.5	C_9H_9NOS	60.31 (60.23)	5.06 (5.17)	7.81 (7.78)	17.89 (18.05)

since II under the same conditions will exist to a greater extent in the uncomplexed form. The electrophilic species involved in formylation using dimethylformamide and phosphorus oxychloride is resonance-stabilized and a less potent electrophile than the species resulting from the reaction of acetyl chloride and aluminum chloride. Thus, it is unable to attack either II or VIIIa.

The thienopyridines prepared in this study were oxidized with monoperphthalic acid to form the *N*-oxides as shown in Scheme VII. Under these conditions only the pyridine nitrogen was oxidized as shown by their infrared spectra which exhibited no absorptions attributable to a sulfoxide or a sulfone. In addition, a band characteristic of a nitrogen oxide was present in these compounds (Table III).

EXPERIMENTAL

Elemental analyses were performed by Alfred Bernhardt Microanalytical Laboratories, Mulheim, West Germany, or Galbraith Laboratories, Knoxville, Tennessee. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were determined on a Perkin-Elmer double beam 521 recording spectrophotometer as potassium bromide disks unless otherwise noted. NMR spectra were determined on a Varian A-60A spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane as an internal standard (δ). Mass spectra were recorded by the Morgan Schaffer Corporation, Montreal, Canada. Unless otherwise noted, all reaction flasks were fitted with either a mechanical or magnetic stirrer, a reflux condenser, a drying tube and an addition funnel with or without a pressure equilibrating side arm.

The pK_a measurements were performed on the thienopyridine hydrochlorides which were analytically pure after repeated recrystallizations and after being dried in an Abderhalden drying pistol under reduced pressure. The samples were weighed on a microanalytical balance and dissolved in approximately 25 ml. of ion-free water in a 50 ml. beaker which was kept at a constant temperature of 20.0 ± 0.1°. While stirring the hydrochloride salt solution magnetically, 0.20 *N* sodium hydroxide was added from a burette to the acid solution in small increments. The resulting *p*H readings were observed on a Beckman Expanded Scale *p*H Meter using a combination glass electrode #39142 B5. The meter was calibrated in 0.1 *p*H units, allowing estimation to 0.01 *p*H units. It was standardized with aqueous buffers (*p*H 4.00 ± 0.01 @ 20°, *p*H 7.02 ± 0.01 @ 20°, and *p*H 10.05 ± 0.01 @ 20°) supplied by Arthur H. Thomas and the standardization was rechecked after the titrations.

[(α-Methyl-2-thenylidene)amino]acetaldehyde Diethyl Acetal (IIIb).

To a mixture of 2-acetylthiophene (114.3 g., 0.905 mole) and 200 ml. of toluene in a 500 ml. one-necked, round-bottomed flask was added β,β-diethoxyethylamine (133.19 g., 1.00 mole) in one portion. The flask was then fitted with a Dean-Stark trap and reflux condenser. After the mixture was heated overnight, the theoretical amount of water was collected in the trap. The reaction mixture was cooled, dried over magnesium sulfate, and concentrated under reduced pressure. Distillation of the residue gave the Schiff's base as a yellow liquid, b.p. 130-135° (0.15 mm), 85% yield; NMR δ (neat), singlet at 2.05 (CH_3–C=N), triplets at 1.13 (2x-CH_3, CH_2 = 6.0 Hz), 4.73 (–C(O)(O)–H, $J_{CH,\ CH_2}$ = 5.0 Hz), multiplets at 3.55 (3x-CH_2-), 6.91 (H-4) and 7.23 (H-3, H-5).

Anal. Calcd. for $C_{12}H_{19}NO_2S$: C, 59.72; H, 7.93; N, 5.80; S, 13.28. Found: C, 59.52; H, 8.06; N, 5.90; S, 13.08.

Preparation (20) of Thieno[2,3-c]pyridine (I) and 7-Methylthieno-[2,3-c]pyridine (II). Method A.

Polyphosphoric acid (400 g.) was placed in a 500 ml. three-necked, round-bottomed flask. The acid was stirred and heated at 120° and the amino acetal (20) (0.083 mole) was added to this dropwise. After the addition was completed, the mixture was heated at 120° for 20 minutes, cooled, and added to 500 g. of cracked ice. This acidic solution was extracted with ether to remove any unreacted starting material. The aqueous layer was then made basic with concentrated sodium hydroxide solution and extracted again with ether. The ether extracts were washed with water and dried overnight with magnesium sulfate. The organic layer was concentrated under reduced pressure and distilled *in vacuo* to yield the thienopyridine as a clear liquid.

Preparation of Thienopyridine-3-Sulfonic Acids (IX, Xa, XVIIIa, XVIIIb, XVIIIc, and XVIIId). Method B.

The thienopyridine (0.02 mole) was placed in a 25 ml. two-necked round-bottomed flask. The flask was immersed in an ice bath and 10 ml. of 15% fuming sulfuric acid was added dropwise to the thienopyridine. After the addition was completed, the mixture was heated to 90° for 10 minutes, cooled and a solution of 3.5 g. sodium bicarbonate and 10 g. sodium chloride in 50 ml. of water was added to it slowly. The product precipitated before the solution was completely neutralized. The solid was collected, washed with water, and recrystallized from water, using decolor-

izing carbon, to give the sulfonic acid as white crystals.

Preparation of 3-Nitrothienopyridines (Xb, XIXa, and XIXc). Method C.

Concentrated sulfuric acid (35 ml.) was added dropwise to the thienopyridine (0.066 mole) in a 250 ml. three-necked, round-bottomed flask which was cooled in an ice bath. A mixture of 35 ml. of concentrated sulfuric acid and 35 ml. of 90% nitric acid was added slowly to the acidic solution of thienopyridine. After heating the reaction to 90° for four hours, it was cooled, poured on 100 g. of cracked ice and neutralized with 30% potassium hydroxide solution. This solution was continously extracted with ether. After drying the ether layer over magnesium sulfate, the ether was evaporated under reduced pressure to give a tan solid. This solid was recrystallized from ethanol, using decolorizing carbon to produce the yellow nitro product.

Methyl 7-Methylthieno[2,3-*c*]pyridin-3-yl Ketone (Xc). Method D.

7-Methylthieno[2,3-*c*]pyridine (4.47 g., 0.03 mole) and 50 ml. of carbon disulfide were placed in a 100 ml. three-necked, round-bottomed flask. The solution was stirred and aluminum chloride (9.32 g., 0.07 mole) was added all at once, then acetyl chloride (5.50 g., 0.07 mole) was added dropwise while the mixture was cooled in an ice bath. After the addition was completed, the reaction was refluxed for one hour, then cooled and a gum was separated by decantation. The semi-solid was washed with carbon disulfide and added portionwise to 100 ml. of dilute hydrochloric acid. This solution was made basic with 10% potassium hydroxide solution, and the inorganic precipitate was extracted with ether (the filtrate contained no organic material). The ether extract was dried over magnesium sulfate and a precipitate formed when hydrogen chloride was added to the ether solution (hydrochloride m.p. 270-272°, 2-propanol). The hydrochloride was dissolved in water and neutralized with sodium bicarbonate solution. The precipitate which formed was collected and recrystallized from carbon tetrachloride, using decolorizing carbon, to yield the ketone as a white solid, m.p. 170-170.5°, yield 40%.

Preparation (21) of Thieno[3,2-*c*]pyridines (VIIIa, VIIIb, VIIIc, and VIIId). Method E.

The dihydrothienopyridine (0.12 mole) was added to 1000 ml. of dry xylene in a 2000 ml. one-necked, round-bottomed flask. The catalyst, 10% Palladium on Carbon (7.0 g.), was added to the stirred solution and this mixture was refluxed for 12 hours. After the solution was cooled and the solids were collected, the filtrate was dried over magnesium sulfate and concentrated under reduced pressure. Distillation of the residue gave the thienopyridine as a clear liquid.

Preparation (22) of Nitrovinyl Thiophenes (IVa, IVb, IVc, and IVd). Method F.

In a 3000 ml. two-necked, round-bottomed flask were placed 1500 ml. of methanol, the thiophene-2-carboxaldehyde (0.71 mole) and the appropriate nitro compound (2.2 moles). When the stirred mixture was cooled to −5°, 750 ml. of 50% sodium hydroxide solution was added dropwise at 0°. This mixture was stirred for one hour at 10° and then added to three liters of concentrated hydrochloric acid in five liters of water cooled to 0°. The crude product separated as a yellow solid, which was collected and dried. The solid was recrystallized from methanol, using decolorizing carbon, to give the nitrovinyl thiophene as a yellow solid.

Preparation (22) of Thiopheneethylamines (Va, Vb, Vc, and Vd). Method G.

In a 500 ml. three-necked, round-bottomed flask fitted with a Dewar condenser were placed 100 ml. of anhydrous ether and lithium aluminum hydride (10.0 g., 0.26 mole). The nitrovinyl thiophene (0.06 mole), dissolved in a minimum amount of anhydrous ether, was added dropwise to the vigorously stirred mixture. This mixture was refluxed for six hours, then cooled and water added cautiously until the lithium complex was destroyed. The inorganic salts were collected and extracted with 2-propanol. The alcohol extracts were combined with the ether layer, dried-over sodium sulfate and concentrated under reduced pressure. Distillation of the residue yielded the amine as a clear liquid.

Preparation (23) of Acetamides of Thiopheneethylamines (VIa, VIb, VIc, and VId). Method H.

In a 2000 ml. two-necked, round-bottomed flask were placed the amine (0.42 mole) and 800 ml. of 20% sodium hydroxide solution. Acetic anhydride (200.0 g., 1.99 mole) was added dropwise and the reaction mixture stirred for one hour. The product was extracted with benzene, the benzene extract was dried over sodium sulfate and the solvent was evaporated under reduced pressure. Distillation of the residue yielded the amide.

Preparation (21) of 6,7-Dihydrothieno[3,2-*c*]pyridines (VIIa, VIIb, VIIc, and VIId). Method J.

In a 3000 ml. three-necked, round-bottomed flask were placed the amide (0.214 mole) and one liter of dry benzene. The mixture was stirred and heated to boiling. Phosphorus oxychloride (87.3 g., 0.571 mole) in 400 ml. of dry benzene then was added to it dropwise. The mixture was heated for two hours, cooled and poured onto 2000 g. of cracked ice. The aqueous layer was separated, made basic with concentrated sodium hydroxide solution, and extracted with ether. The organic layer was washed with water, dried over magnesium sulfate and concentrated under reduced pressure. Distillation of the residue yielded the dihydrothienopyridine as a clear liquid.

7-Styrylthieno[2,3-*c*]pyridine (XI).

This procedure was a modification of the method of Kaslow and Stayner (16). A solution of 7-methylthieno[2,3-*c*]pyridine (3.0 g., 0.02 mole), benzaldehyde (2.43 g., 0.02 mole; freshly distilled) and acetic anhydride (1.02 g., 0.01 mole) was placed in a 10 ml. one-necked, round-bottomed flask and heated to 160° for 22 hours. The hot solution was poured into 15 ml. of 10% sodium hydroxide solution and was stirred for five minutes to give an oil which gradually solidified at room temperature. The precipitate was collected, washed with water and cold absolute ethanol. The solid was recrystallized from absolute ethanol. using decolorizing carbon, to give 7-styrylthieno[2,3-*c*]pyridine as a yellow solid, m.p. 69-70°, yield 82%; NMR δ (deuteriochloroform), doublet at 8.76 (H-5, $J_{5,4}$ = 5.2 Hz) and multiplet at 7.6 (C_6H_5, H-2, H-3, H-4 and –CH=CH–).

Anal. Calcd. for $C_{15}H_{11}NS$: C, 75.92; H, 4.67; N, 5.90; S, 13.51. Found: C, 75.93; H, 4.86; N, 5.90; S, 13.45.

Thieno[2,3-*c*]pyridine-7-carboxaldehyde (XII).

This procedure is a modification of the method of Tarbell, *et al.* (24). To a magnetically stirred solution of 7-styrylthieno-[2,3-*c*]pyridine (1.18 g., 0.005 mole) and 4 mg. of osmic anhydride in 18 ml. of dioxane and 6 ml. of water contained in a 50 ml. one-necked, round-bottomed flask was added powdered sodium metaperiodate (2.25 g., 0.0105 mole) portion-wise over a 20 minute period. This mixture was stirred for two hours. The

precipitated sodium iodate was collected and washed with ether. The ether washings and the filtrate were combined and evaporated to dryness. The solid residue was sublimed at room temperature (0.1 mm). For analysis, the aldehyde was sublimed at 40° (1.7 mm), m.p. 73-74°, yield 30%; NMR δ (deuteriochloroform), singlet at 10.28 (–CH), doublets at 7.44 (H-3, $J_{3,2}$ = 5.7 Hz), 7.86 (H-2), 7.90 (H-4, $J_{4,5}$ = 5.3 Hz), and 8.70 (H-5).

Anal. Calcd. for C_8H_5NOS: C, 58.88; H, 3.08; N, 8.58; S, 19.65. Found: C, 58.65; H, 3.16; N, 8.43; S, 19.47.

α,α-Diphenylthieno[2,3-c]pyridine-7-ethanol (XIII).

In a 250 ml. three-necked, round-bottomed flask fitted with a mechanical stirrer, a Dewar condenser with a potassium hydroxide drying tube, and an addition funnel, was added 125 ml. of condensed ammonia. Sodamide (0.78 g., 0.02 mole) was added to the liquid ammonia and the mixture stirred. After 30 minutes, 7-methylthieno[2,3-c]pyridine (3.7 g., 0.025 mole) was added all at once. After 30 minutes, finely divided benzophenone (4.55 g., 0.025 mole) was added at once and stirring was continued for an additional two hours. The ammonia was then evaporated by a stream of nitrogen gas, and 100 ml. of ether followed by 50 ml. of water were added to the residue. The ether layer was separated, the water layer was extracted with ether and all the organic extracts were combined and dried over sodium sulfate. After concentration of the ether extract under reduced pressure, unreacted starting material and a solid remained. The solid was recrystallized from carbon tetrachloride, using decolorizing carbon, to yield the alcohol as a white crystalline solid, m.p. 193-194° (sublimes at 150° at 0.5 mm), yield 15%; NMR δ (DMSO-d_6), singlets at 2.64 (-CH_2-), 3.39 (-OH), 7.33 (2x -C_6H_5-), doublets at 7.11 (H-3, $J_{3,2}$ = 3.0 Hz), 7.54 (H-4, $J_{4,5}$ = 5.5 Hz), 8.30 (H-5) and H-2 hidden under the phenyl absorption.

Anal. Calcd. for $C_{21}H_{17}NOS$: C, 76.10; H, 5.17; N, 4.23; S, 9.67. Found: C, 75.98; H, 5.14; N, 4.14; S, 9.61.

7,7′-Ethylene bis[Thieno[2,3-c]pyridine] (XIV).

Gaseous ammonia (200 ml.) was condensed in a 500 ml. three-necked, round-bottomed flask equipped as described in the previous experiment. Sodium (0.57 g., 0.025 g.a.) was added to the liquid ammonia and after stirring for one hour, 7-methylthieno-[2,3-c]pyridine (4.47 g., 0.03 mole) was added and the mixture stirred for another hour. Either benzophenone (5.46 g., 0.03 mole) or benzaldehyde (3.18 g., 0.03 mole) was then added and the mixture stirred for four hours while being cooled in a dry ice-2-propanol bath. After the ammonia was evaporated, 200 ml. of ether followed by 100 ml. of water was added. The ether was decanted and the water was extracted with ether. The ether extracts were combined, dried over magnesium sulfate, and concentrated *in vacuo* to yield a solid which was recrystallized from ethyl acetate, m.p. 175-176°, yield 6%. The infrared spectrum of the product showed no absorption for -OH. No phenyl protons were observed in the NMR spectrum and the elemental analysis did not agree with the calculated values for α,α-diphenylthieno-[2,3-c]pyridine-7-ethanol. The mass spectrum indicated the molecular weight was 296. The analytical data agreed with the values calculated for 7,7′-ethylene bis[thieno[2,3-c]pyridine]. NMR δ (deuteriochloroform), singlet at 3.72 (2x-CH_2-), doublets at 7.30 (H-3[3′], $J_{3,2}$ = 5.8 Hz), 7.52 (H-4[4′], $J_{4,5}$ = 5.8 Hz), 7.60 (H-2[2′]), and 8.46 (H-5[5′]).

Anal. Calcd. for $C_{16}H_{12}N_2S_2$: C, 64.83; H, 4.08; N, 9.45; S, 21.63. Found: C, 64.69; H, 4.24; N, 9.28; S, 21.50.

6,7-Dimethylthieno[2,3-c]pyridinium Iodide (XV).

7-Methylthieno[2,3-c]pyridine (5.0 g., 0.034 mole), 10.0 ml. of methyl iodide and 20 ml. of methanol were placed in a 50 ml. flask and heated for two hours. The mixture was cooled and then concentrated under reduced pressure. The solid residue obtained was recrystallized from ethanol, using decolorizing carbon, to yield the pyridinium iodide as tan crystals, m.p. 201-202°, yield 90%; NMR δ (deuterium oxide), singlets at 3.12 (CH_3-7), 4.41 (CH_3-6), doublets at 7.75 (H-3, $J_{3,2}$ = 5.4 Hz), 8.16 (H-5, $J_{5,4}$ = 7.0 Hz), 8.58 (H-4), and 8.60 (H-2).

Anal. Calcd. for $C_9H_{10}INS$: C, 37.12; H, 3.46; N, 4.81; S, 11.01; I, 43.59. Found: C, 36.96; H, 3.62; N, 4.75; S, 11.13; I, 43.72.

4,5,6,7-Tetrahydro-6,7-dimethylthieno[2,3-c]pyridine Monopicrate (XVI).

This method is a modification of a procedure by Mirza (25). 6,7-Dimethylthieno[2,3-c]pyridinium iodide (540 mg.), sodium borohydride (500 mg.), 10.0 ml. of methanol and 1.0 ml. of water were placed in a 25 ml. one-necked, round-bottomed flask equipped with a magnetic stirrer. The mixture was heated to boiling for 10 minutes, then cooled, diluted with 50 ml. of water and extracted with chloroform. The organic extract was dried over magnesium sulfate and evaporated under reduced pressure. The residue obtained was dissolved in methanol and a saturated picric acid solution was added to it to give the picrate which was recrystallized from absolute ethanol, m.p. 187-188°, yield 60%.

This tetrahydrothienopyridine was also prepared using a procedure of Kost and Yudin (26). 6,7-Dimethylthieno[2,3-c]-pyridinium iodide (1.13 g., 0.004 mole) and 1.0 ml. of triethylamine were heated in a 10 ml. one-necked, round-bottomed flask fitted with a reflux condenser. To this stirred mixture, formic acid (1.84 g., 0.04 mole) was added through the condenser and this was heated to boiling for 10 hours. This mixture was cooled, made basic with 10% sodium hydroxide solution, diluted with 10 ml. of water and extracted with chloroform. The chloroform extract was dried over sodium sulfate and evaporated under reduced pressure. The residue was dissolved in absolute ethanol and saturated picric acid solution was added. The precipitate was recrystallized from ethanol, using decolorizing carbon, to yield the picrate as a yellow solid, m.p. 187-188°; NMR δ (DMSO-d_6), singlets at 2.95 (CH_3-6), 8.60 (2 H's on picrate function), doublets at 1.64 (CH_3-7, $J_{CH_3, H-7}$ = 6.8 Hz), 6.94 (H-3, $J_{3,2}$ = 5.2 Hz), 7.54 (H-2), multiplets at 2.94 (CH_2-4), 3.59 (CH_2-5), 4.78 (N-H), and 3.08 (H-7).

Anal. Calcd. for $C_{15}H_{16}N_4O_7S$: C, 45.45; H, 4.06; N, 14.13; S, 8.09. Found: C, 45.47; H, 4.35; N, 14.02; S, 8.09.

α,α-Diphenylthieno[3,2-c]pyridine-4-ethanol (XVII).

In a 250 ml. three-necked, round-bottomed flask equipped as described in the preparation of XIII was added 125 ml. of condensed ammonia. While stirring the ammonia, sodamide (0.39 g., 0.01 mole) was added and after 30 minutes, 4-methylthieno[3,2-c]-pyridine (2.0 g., 0.013 mole) was added all at once. After 30 minutes, finely divided benzophenone (2.0 g., 0.011 mole) was added all at once and stirring continued for an additional two hours. The ammonia was then evaporated by a stream of nitrogen gas and 100 ml. of ether followed by 50 ml. of water were added to the residue. The ether layer was separated, the water layer was extracted with ether and all the organic extracts were combined and dried over sodium sulfate. After concentration of the ether extract under reduced pressure, the residue was sublimed for three

days at 175° (0.05 mm), m.p. 232-233°, yield 10%; NMR δ (deuteriochloroform), singlets at 3.32 (-OH), 3.63 (-CH_2-), 7.36 (2x C_6H_5-), doublets at 8.23 (H-6, $J_{6,7}$ = 5.8 Hz), 7.72 (H-7), 7.12 (H-3, $J_{3,2}$ = 5.0 Hz), H-2 hidden under phenyl absorption.

Anal. Calcd. for $C_{21}H_{17}NOS$: C, 76.10; H, 5.17; N, 4.23. Found: C, 75.81; H, 5.03; N, 4.09.

Preparation of Amine Oxides (XXII, XXIIIa, XXIIIb, and XXIIIc). Table VI.

This product is a modification of the method of Ochiai, *et al.* (27). In a 50 ml. two-necked, round-bottomed flask were added the thienopyridine (0.007 mole), 0.5 ml. of glacial acetic acid and 3 ml. of methanol. An ether solution of monoperphthalic acid (28) (10 ml.) was added in one portion and white crystals began to precipitate after 10 minutes. After one hour, an additional 30 ml. of monoperphthalic acid was added. After the solution stood for 30 hours at room temperature, the crystals were collected. They were dissolved in a minimum amount of 10% sodium hydroxide solution and this solution was extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from carbon tetrachloride, using decolorizing carbon, to give the oxide as a white solid. More product was isolated from the ether filtrate extracting it with 10% sodium hydroxide solution. The aqueous layer was extracted with chloroform, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was recrystallized from carbon tetrachloride and combined with the oxide separated previously.

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