Chemistry of Thienopyridines. XVIII. Lithiation as a Route to 2- and 3-Substituted Thieno[2,3-*b*]pyridines (1)

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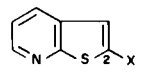
Treatment of thieno[2,3-*b*]pyridine (Ia) with *n*-butyllithium in hexane-tetramethylethylenediamine at -70° plus subsequent addition of dimethylformamide produced 2-formyl-Ia (66%). Halogen-metal exchange between 3-bromothieno[2,3-*b*]pyridine and *n*-butyllithium was effected in ether at -70°. Further reaction of the 3-lithio-Ia intermediate with a variety of carbonyl compounds gave 3-substituted thieno[2,3-*b*]pyridines bearing formyl (77%), acetyl, benzoyl, chloroacetyl, ethoxycarbonyl, *N*-phenylcarbamyl, and diphenyl hydroxymethyl groups. Common characteristics of these derivatives in pmr and mass spectra are noted.

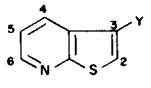
The formyl derivatives were condensed with various reagents in order to modify the carbon functional group present.

In continuation of our studies on the chemistry of thieno[2,3-*b*]pyridine (Ia) (3-9), we wished to develop additional methods for introducing a carbon functional group at either C-2 or C-3. Only three such derivatives



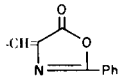
a: X = H
b: X = Li
c: X = CHO

d: X = Ac
e: X = -CH=CHNO$_2$
f: X = -CNHPh (O)



a: Y = Br
b: Y = Li
c: Y = CHO
d: Y = CN
e: Y = Ac
f: Y = -CCH$_2$Cl (O)
g: Y = CO$_2$Et
h: Y = -CPh (O)

i: Y = -CNHPh (O), OH
j: Y = -CPh$_2$, OH
k: Y = -CH=CHNO$_2$, OH
l: Y = -CHCN, OH



m: Y = -CH= (O, O, N, Ph)

have been described previously. The 2-acetyl derivative Id was obtained by constructing a pyridine ring onto 2-acetylthiophene (3). Treatment of 3-bromothieno[2,3-*b*]-pyridine (IIa) with cuprous cyanide gave the 3-cyano derivative IId, convertible to the 3-acetyl compound IIe by means of methylmagnesium iodide (9). In other preliminary studies, direct lithiation of Ia was accomplished by means of methyllithium in ether at -25°, but concurrent addition of the reagent to the azomethine function of the pyridine ring occurred (3). We now report lithiation routes which can be used to accomplish the desired goal of carbon functionalization.

Treatment of Ia with *n*-butyllithium (molar ratio BuLi:Ia = 1.25) in *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (10) and hexane at -70° gave the 2-lithio derivative Ib *in situ*, as evidenced by the isolation of 2-formylthieno[2,3-*b*]pyridine (Ic) in 66% yield upon subsequent addition of *N,N*-dimethylformamide (DMF). Under these conditions, no addition to the azomethine linkage is noted. A crucial point in the lithiation process seems to be that Ia must be kept finely dispersed in the reaction medium.

The 3-lithio derivative of Ia was prepared by means of halogen-metal exchange between 3-bromothieno[2,3-*b*]-pyridine (IIa) and *n*-butyllithium in ether at -70° (or even at *ca.* 15° in one case). The resultant IIb reacted *in situ* with a variety of carbonyl compounds, as indicated in Table I. Examination of the table shows that the method works well for the production of the aldehyde IIc. Other products were obtained in only fair to poor yields. Nonetheless, the 44% yield of 3-acetyl derivative IIe obtained from reaction of IIb with acetic anhydride is a marked improvement over that of 8% (overall) for the two-step route IIa → IId → IIe previously reported (9).

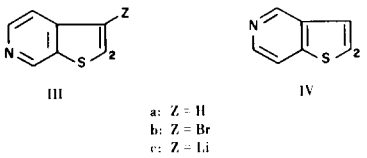
Direct lithiation of Ia at C-2 is analogous to the reaction of the isosteric benzo[*b*]thiophene (11). However, metalation of the latter compound is not complicated by a competitive addition reaction. Gronowitz and Sandberg (12) reported that attempts to metalate thienopyridines IIIa and IV at C-2 gave only addition to the azomethine linkage, even at -70°. These workers did find, however, that halogen-metal exchange occurs between bromo compound IIIb and ethyllithium in ether at -70° to give IIIc (susceptible to carboxylation with

TABLE I

Products Formed from Reaction of 3-Lithiothieno[2,3-*b*]pyridine (IIb) with Various Reagents

Reagent Used Formula	Molar Ratio (a)	Procedure (b)	Compound Formed No.	M.p., °C (c)	% Yield (c,d)
Me_2NCHO	1.2	A	IIc	92-93	77
AcCl	5	B	IIe	108.5-111	27
Ac_2O	1.2	B	IIe	106-109	44
$ClCH_2\overset{O}{\overset{\|\|}{C}}Cl$	5	B	IIf	165-167.5	17
EtO_2CCl	5	C	IIg	68.5-70.5	13
PhCCl (O)	1.2	B	IIh	115-117	33
PhN=C=O	1.2	A	IIi	137-139	41
Me_2NAc	10	D	Id	121-123	9
$Ph_2C=O$	1	E	IIj	166-168.5	7
			Ia	--------	28 (e)

(a) Ratio of reagent to IIb. (b) In cases A-D, IIb was formed at *ca.* -70°; in case E, it was formed at *ca.* 15°. See Experimental for details. (c) After preliminary purification involving crystallization and/or evaporative distillation. (d) Only for reaction with *N,N*-dimethylformamide was an effort made to obtain a maximal yield. Every other yield is based on a single experiment. (e) Crude liquid product.



III IV

a: Z = H
b: Z = Br
c: Z = Li

carbon dioxide). However, 30% of unreacted IIIb was recovered, despite the fact that a 60% excess of ethyllithium was used. With only the 20% excess of *n*-butyllithium generally used in our experiments, no unreacted IIa was found amongst the products isolated. In a single experiment with 100% excess of *n*-butyllithium on IIa plus subsequent treatment of the cold mixture with *N,N*-dimethylacetamide (see Table I) a low yield of 2-acetylthieno[2,3-*b*]pyridine (Id) (instead of the expected 3-isomer) was isolated. A chemical rationale for this transformation has not yet been established. However, it appears to be associated with the use of a large excess of *n*-butyllithium rather than with a thermally induced rearrangement such as occurs with 3-lithiobenzo[*b*]thiophene (13). Thus, treatment of IIa with only the usual 20% excess of *n*-butyllithium and then warming this solution to -20° before addition of *N,N*-dimethylacetamide gave only Ia, *sans* acetylation.

Pearson *et al.* (14) reported that halogen-metal exchange was highly successful between *n*-butyllithium and bromoquinolines or bromoisoquinolines in THF-ether at -70° only if a 100% excess of lithium reagent was used. They proposed that coordination of RLi with the heterocyclic nitrogen atom competes with metal-halogen exchange (15). If we assume that the extent of complexation at the heterocyclic nitrogen atom falls in the same general order as the basicities of the parent ring systems, we can rationalize the gross differences observed in lithiation reactions in system Ia (on the one hand) and IIIa and IV (on the other) (16). Complexation should be significant for IIIa (pK_a = 5.58) and IV (5.67) (17,18), which are more basic than quinoline (4.9) and isoquinoline (5.40) (19), but may be of little pertinence for the considerably less basic Ia (2.75) (20).

The availability of good synthetic routes to aldehydes Ic and IIc presented the possibility of preparing a multitude of derivatives of thieno[2,3-*b*]pyridine with substituents at C-2 and C-3 *via* condensation reactions. Only a few of these possibilities have been investigated. Both aldehydes condensed with nitromethane [*via* the intermediate aldimine produced with *n*-butylamine (21)] to give the β-nitrovinyl derivatives Ie and IIk. In addition, the 3-aldehyde was converted to the cyanohydrin III and to the azlactone IIm. These reactions were effected in yields of 50 ± 6%.

In previous papers, we noted the marked downfield chemical shift in the nuclear magnetic resonance of H-4 upon substitution of a nitro group at C-3 in the parent thienopyridine Ia (6) and in its 5-ethyl derivative (8). In fact, in these 3-nitro compounds, the signal for H-4 falls downfield from that for H-6--an inversion in order from that found in Ia, in 5-ethyl-Ia, and in their 3-acetylamino derivatives (3,8). Contrariwise, substitution of a nitro

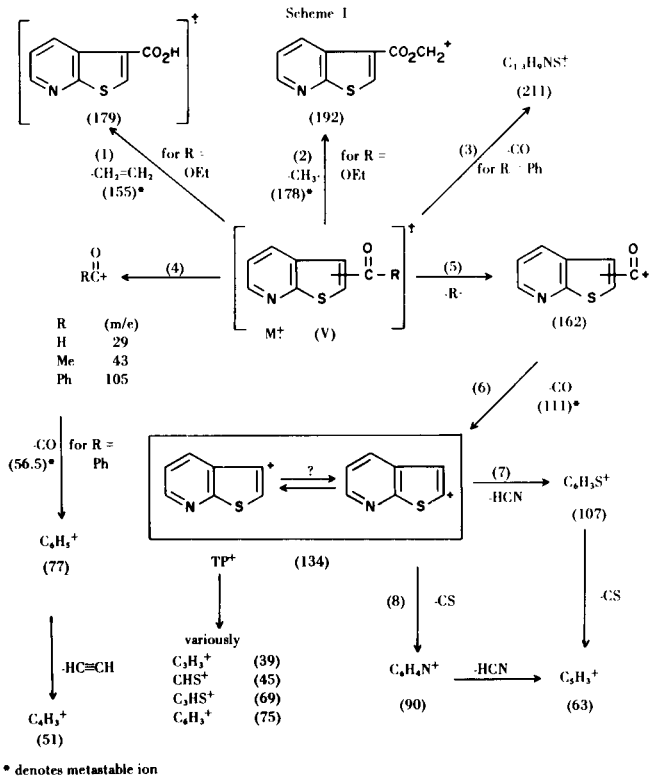
TABLE II

Proton Magnetic Resonance Data for Thieno[2,3-*b*]pyridines Substituted in the 2- or 3-Position (a)

Compound Number	Solvent (b)	Substituent	Chemical Shift, in δ				Coupling Constant, in Hz			Other Signals
			H-2 or H-3	H-4	H-5	H-6	$J_{4,5}$	$J_{5,6}$	$J_{4,6}$	
Ic	F	2-CHO	7.99	8.24	7.48	8.68	8.1	4.6	1.5	10.09 (c)
IIc	F	3-CHO	8.48	8.94	7.45	8.70	8.2	4.6	1.8	10.14 (c)
IIf	G	3-C(=O)CH_2Cl	9.16	8.87	7.61	8.71	8.0	4.6	1.5	4.27 (d)
IIg	F	3-CO_2Et	8.44	8.80	7.39	8.62	8.2	4.7	1.6	1.43 (e)
IIh (f)	H	3-C(=O)Ph	8.44	8.81	7.4-8.1	8.67	8.1	4.5	1.6	(g)
IIi (f)	H	3-C(=O)NHPh	8.57 8.16	8.86 8.27	7.0-8.0	*ca.* 8.63	8.2	4.6	1.6	9.65 (h)
IIj	F	3-C(OH)Ph_2	6.90	7.95	7.2-7.6	8.55	8.0	5	1.6	3.38 (i)
Ie	G	2-CH=$CHNO_2$	8.15	8.38	7.52	8.68	8.0	4.5	1.5	8.02 (j)
IIk	K	3-CH=$CHNO_2$	8.10	8.82	7.77	8.62	8.0	6.0	1.5	7.52 (k)
IIl	G	3-CH(OH)CN	8.10	8.42	7.55	8.68	8.5	4.5	1.7	6.22 (l)
IIm	K	3-CH=$C_9H_5NO_2$	9.4	9.3-9.5	7.4-8.4	8.9-9.1	*ca.* 8	*ca.* 5	?	(m)

(a) Unless otherwise noted, the spectrum was determined by means of a Varian Associates A-60 instrument with tetramethylsilane as internal standard. (b) Solvents used: F, deuteriochloroform; G, hexadeuteriodimethyl sulfoxide; H, hexadeuterioacetone; K, trifluoroacetic acid. (c) (s, 1, CHO). (d) (s, 2, methylene). (e) (t, 3, J = 7.2 Hz, Me), 4.44 (q, 2, methylene). (f) Spectrum determined by means of a Varian Associates XL-100 instrument with pentadeuterioacetone (center of multiplet taken as δ 2.05 ppm *vs.* tetramethylsilane) as internal standard. (g) The signal for the phenyl group overlaps that for H-5. (h) (broad s, NH). (i) (broad s, OH), 7.43 (s, phenyl) which is superimposed on signal for H-5. (j) (d, 1, J = 12.5 Hz, H-α), 8.53 (d, 1, H-β) which overlaps signals for H-4 and H-6. (k) (d, 1, J = 14.5 Hz, H-α), 8.08 (d, 1, H-β). (l) (broad s, 1, CH)–sharpens on addition of deuterium oxide, 7.30 (broad s, 1, OH)–disappears on addition of deuterium oxide. (m) Phenyl and vinyl proton signals are superimposed on the signal for H-5.

Scheme I



* denotes metastable ion

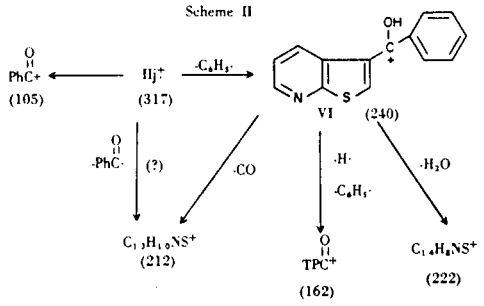
group at C-2 in a series of 3-halothieno[2,3-*b*]pyridines did not alter the order of appearance of signals for H-4 and H-6 (9). Analogously, 2-acetyl-Ia showed the "normal" order of Ia, while 3-acetyl-Ia exhibited the "inverted" order. Additional examples of the large deshielding effect on H-4 by means of carbonyl groups at C-3 in Ia are seen in Table II. The inverted order is found for the 3-formyl, 3-chloroacetyl, 3-ethoxycarbonyl, and 3-benzoyl derivatives, while the normal order occurs for the 2-formyl derivative, as well as for the carbinol IIj and the cyanohydrin III. Inverted orders are also noted for the vinylogous 3-derivatives IIk and IIm (but not for the 2-derivative Ie), though use of the strongly acidic solvent trifluoroacetic acid in the first two cases could confuse relative shielding effects on the various proton substituents. Analytically pure amide IIi shows two singlets at δ 8.16 and 8.57 (relative areas 3.3:1) for one proton on the thiophene ring and two sets of doublets of doublets of the same relative areas at δ 8.27 and 8.86, respectively, for one proton at C-4. The signal for H-6 consists of two closely overlapping doublets of doublets--again for one proton. While structural elucidation of this spectrum must await further investigation, it is tentatively proposed that either the sample contains 23% of the 2-isomer If as an impurity or it consists of a ratio of magnetically distinguishable *s-trans:s-cis* = 3.3:1 rotamers of the single isomer IIi.

The major mass spectral fragmentation pathways for carbonyl compounds Ic, Id, IIc, and IIe-IIi are summarized in Scheme I and data on intensities of common ionic fragments are presented in Table III (Experimental). The molecular ion M^+ (V) is the most abundant one in the spectra for the two aldehydes (Ic and IIc) and for the benzoyl derivative IIh. In all other cases, the thienopyridoylium ion ($TPCO^+$, m/e 162) which results from loss of the radical R from the molecular ion (process 5), is the most abundant one. The aldehydes (where R is a hydrogen atom) are special in that the thienopyridoylium ion is nearly as abundant (80-90%) as the parent ion. Only in the case of IIh is the bond between the thieno[2,3-*b*]pyridyl group (TP) and the carbonyl carbon atom broken (to form the benzoyl cation) in preference to the one between R and the carbonyl carbon atom. Ion 162 emits carbon monoxide (process 6), as corroborated by the presence of a metastable ion peak at *ca.* m/e 111 in every spectrum, to give TP^+ (m/e 134). The 3-TP cation was previously postulated as an intermediate in the degradation of molecular ions from 3-halothieno[2,3-*b*]-pyridines (9). Similar characteristic decompositions of ion 134 are noted here, even where this ion is derived from a 2-substituted thieno[2,3-*b*]pyridine compound. On this basis, it seems likely that the 2- and 3-TP cationic structures are interconvertible in the chamber of the mass spectrometer (22). Specifically, ion 134 undergoes loss of either a molecule of hydrogen cyanide (process 7) or one of carbon monosulfide (process 8). In the spectrum of amide IIi, in fact, metastable ion peaks are observed at *ca.* 85.5 and 60.5 for these two processes. Appearance of the ion $C_5H_3^+$ (m/e 63) in every spectrum likewise seems characteristic of the presence of the TP cation. While no corroborating metastable ions were noted, it is likely that ion 63 results from successive losses of both hydrogen cyanide and carbon monosulfide (in either order) from ion 134 (as depicted in Scheme I). Ion fragments at m/e 39, 45, 69, and 75 probably also arise from ion 134.

As expected, the benzoyl cation (from process 4) undergoes successive losses of carbon monoxide and acetylene (23). Acetyl and formyl cations also result (albeit to a much smaller extent) from process 4. No major differences are apparent in the mass spectra of the isomeric aldehydes Ic and IIc or of the isomeric acetyl derivatives Id and IIe (22). Benzoyl derivative IIh (analogous to benzophenone) (23) loses carbon monoxide directly from the parent ion (process 3). Processes 1 and 2 are also significant transformations of the molecular ion from ethyl ester IIg.

The mass spectrum of carbinol IIj exhibits many of the features shown by that of the benzoyl derivative IIh (see Scheme II). The benzoyl cation is the most abundant

Scheme II



ion fragment. Its presence is supported by ions at m/e 77 and 51 (Scheme I). The carbinol molecular ion emits a phenyl radical to give VI (formulated as protonated IIh) which can lose water, the elements of benzene (to form the thienopyridoylium ion and, thence, the thienopyridyl cation), or (as for step 3, Scheme I) carbon monoxide (to form ion 212). Alternatively ion 212 could arise directly from the molecular ion by loss of a benzoyl radical. No metastable peaks to support these pathways were observed, however.

EXPERIMENTAL (24)

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

In an atmosphere of nitrogen, a mixture of 15.6 ml. (25 mmoles) of 1.6 *M* *n*-butyllithium in hexane and 3.8 ml. (40 mmoles) of *N,N,N',N'*-tetramethylethylenediamine was stirred magnetically at room temperature for 30 minutes, diluted with 50 ml. of hexane, cooled in a bath of Dry Ice-ethanol, and treated (with vigorous stirring) dropwise (from a syringe with a small needle) with 2.7 g. (20 mmoles) of thieno[2,3-*b*]pyridine (Ia) (3). The mixture was stirred in the bath for 7 hours longer and then for 12 hours while it warmed to room temperature. It was cooled in ice, treated with 1.8 g. (25 mmoles) of dimethylformamide, stirred for one hour, and then treated successively with 10 ml. of ethanol, 40 ml. of saturated aqueous ammonium chloride solution, and 50 ml. of water. The layers were separated. The organic layer (plus chloroform extracts of the aqueous layer) was dried (magnesium sulfate) and evaporated. The residue was triturated with hexane to give 2.16 g. (66%) of brown solid, m.p. 132.5-133.5°. Recrystallizations from ethanol (once with charcoal) gave white needles of Ic, m.p. 141.5-142°; ir (chloroform): 1680 cm^{-1} (carbonyl).

Anal. Calcd. for C_8H_5NOS: C, 58.9; H, 3.1; N, 8.6; S, 19.7. Found: C, 58.6; H, 3.0; N, 8.6; S, 19.8.

3-Lithiothieno[2,3-*b*]pyridine (IIb) Reactions.

Procedure A.

To a vigorously stirred, cold (Dry Ice-ethanol bath) mixture of 7.5 ml. (12 mmoles) of 1.6 *M* *n*-butyllithium (in hexane) and 100 ml. of dry ether was added 2.14 g. (10 mmoles) of 3-bromothieno[2,3-*b*]pyridine (9). The mixture was stirred for one hour, the cooling bath was removed, 12 millimoles of reactant (*N,N*-dimethylformamide or phenylisocyanate) was added, and stirring was continued for another hour. A saturated aqueous solution (50 ml.) of ammonium chloride was added. Separation of layers, extraction, and evaporation were conducted as in the preparation of Ic. Further processing of the residue is indicated in subsequent paragraphs.

Procedure B.

Procedure A was modified (in some cases) by the quantity of reagent used (see Table I) and (in all cases) by the hydrolytic agent used (50 ml. of saturated aqueous sodium bicarbonate for reactions with acetyl chloride and chloroacetyl chloride, 50 ml. of 1% aqueous sodium bicarbonate for reaction with benzoyl chloride, and 50 ml. of water for reaction with acetic anhydride).

Procedure C.

The method was the same as used for acetyl chloride (Procedure B), except that the cooling bath was Dry Ice-2-propanol and stirring was conducted for 25 hours after the reagent (ethyl chloroformate) was added.

3-Formylthieno[2,3-*b*]pyridine (IIc).

The crude product was evaporatively distilled at 100-120° (0.1 mm.), crystallized from ethanol, and finally sublimed up to 100° (0.15 mm.) to give needles, m.p. 108-108.5° (phase change at *ca.* 95°); ir (chloroform): 1680 cm^{-1} (carbonyl).

Anal. Calcd. for C_8H_5NOS: C, 58.9; H, 3.1; N, 8.6; S, 19.7. Found: C, 58.8; H, 3.1; N, 8.5; S, 19.5.

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

The residue from reaction of IIb with acetic anhydride was recrystallized from ethanol; that from reaction of IIb with acetyl chloride was evaporatively distilled at 90-150° (0.15 mm.) and then recrystallized from ethanol - identified by direct spectral comparisons with an authentic sample of IIe, previously obtained by reaction of 3-cyanothieno[2,3-*b*]pyridine with methylmagnesium iodide (9).

3-(Chloroacetyl)thieno[2,3-*b*]pyridine (IIf) (25).

Repetitive crystallizations of the residue from carbon tetrachloride-chloroform and sublimations at 90-125° (0.6 mm.) gave prisms, m.p. 169.5-170.5° dec.; ir (acetonitrile): 1690 cm^{-1} (carbonyl).

Anal. Calcd. for C_9H_6ClNOS: C, 51.1; H, 2.9; Cl, 16.8; N, 6.6; S, 15.2. Found: C, 51.1; H, 2.7; Cl, 16.9; N, 6.6; S, 15.1.

Ethyl Thieno[2,3-*b*]pyridine-3-carboxylate (IIg).

One crystallization of the residue from carbon tetrachloride-hexane plus repetitive evaporative distillations at 60-100° (0.5 mm.) gave prisms, m.p. 72.5-73.5°; ir (chloroform): 1720 cm^{-1} (carbonyl).

Anal. Calcd. for $C_{10}H_9NO_2S$: C, 58.0; H, 4.4; N, 6.8; S, 15.5. Found: C, 58.0; H, 4.2; N, 6.9; S, 15.6.

3-Benzoylthieno[2,3-*b*]pyridine (IIh).

Crystallization of the residue from chloroform-hexane plus evaporative distillation at 120-145° (0.6 mm.) gave prisms, m.p. 121.5-123°; ir (chloroform): 1655 cm^{-1} (carbonyl).

Anal. Calcd. for $C_{14}H_9NOS$: C, 70.3; H, 3.8; N, 5.9. Found: C, 70.3; H, 3.8; N, 5.9.

N-(Phenyl)thieno[2,3-*b*]pyridine-3-carboxamide (IIi).

Recrystallizations of the residue from chloroform-hexane plus evaporative distillation at 150-225° (0.6 mm.) gave fine needles, m.p. 137-138.5°; ir (chloroform): 1680 cm^{-1} (carbonyl).

Anal. Calcd. for $C_{14}H_{10}N_2OS$: C, 66.1; H, 4.0; N, 11.0. Found: C, 65.8; H, 4.0; N, 10.8.

Reaction of IIb with Benzophenone.

Procedure E.

To a vigorously stirred, cold (3°) suspension of 2.14 g. (10 mmoles) of 3-bromothieno[2,3-*b*]pyridine in 50 ml. of ether was

added 6.3 ml. (10 mmoles) of 1.6 *M* *n*-butyllithium in hexane. The temperature rose to 15°, whereupon the mixture was stirred for 6 minutes, then was treated with a solution of 1.82 g. (10 mmoles) of benzophenone in 35 ml. of ether, stirred at room temperature for 7 hours longer, and finally treated with 30 ml. of water. The ether layer (plus ether extracts of the aqueous layer) was extracted with 2 *M* hydrochloric acid, dried, and evaporated. The residue was partially sublimed at 60-130° (0.15 mm.). The sublimate was discarded. The residue from sublimation was crystallized repetitively from ethanol and then sublimed at 140-160° (0.2 mm.) to yield nearly white prisms of diphenyl 3-thieno-[2,3-*b*]pyridyl carbinol (IIj), m.p. 168-168.5°.

Anal. Calcd. for $C_{20}H_{15}NOS$: C, 75.7; H, 4.8; N, 4.4; S, 10.1. Found: C, 76.0; H, 4.7; N, 4.3; S, 10.1.

The preceding acidic extract was basified with sodium hydroxide and extracted with dichloromethane. Evaporation of the dried organic phase gave thieno[2,3-*b*]pyridine (Ia), identified by pmr spectrum (3).

Reaction of IIb with *N,N*-Dimethylacetamide.

Procedure D.

Organolithium compound IIb was prepared exactly as in Procedure A, except that 12.5 ml. (20 mmoles) of 1.6 *M* *n*-butyllithium (molar ratio BuLi:IIa = 2) was used and the cold mixture was treated with a solution of 9.3 ml. (100 mmoles) of *N,N*-dimethylacetamide in 15 ml. of ether, followed (after 20 minutes) by 10 ml. of ethanol and 50 ml. of saturated aqueous ammonium chloride solution. The dichloromethane extract (dried) of the mixture was evaporated and the residual oil was crystallized from carbon tetrachloride to give 2-acetylthieno[2,3-*b*]pyridine (Id), identified by direct comparison (m.p., mixture m.p., ir, and pmr spectra) with an authentic sample (3).

In a second experiment, the solution of IIb (prepared exactly as in Procedure A) was warmed to -20° before the dimethylacetamide (10 mmoles) was added. The mixture was stirred and refluxed for 4 hours, and then hydrolyzed to form Ia as the only isolable product.

3-(β-Nitrovinyl)thieno[2,3-*b*]pyridine (IIk) (25).

A mixture of 1.63 g. of 3-aldehyde IIc, 2 ml. of *n*-butylamine, and 60 ml. of benzene was refluxed in an apparatus with a water trap for 3.5 hours. The residual liquid from evaporation of the solvent was heated with 10 ml. of glacial acetic acid and 2 ml. of nitromethane on a steam bath for 20 minutes. The mixture was poured into water. The precipitated solid was collected and crystallized from chloroform to give 1.14 g. (55%) of IIk, m.p. 172-174°, raised to 177.5-178° on recrystallizations from acetonitrile-chloroform plus sublimations at 100-145° (0.5 mm.), obtained as canary yellow prisms; ir (chloroform): 1525 and 1345 (nitro group), 965 cm^{-1} (*trans*-CH=CH).

Anal. Calcd. for $C_9H_6N_2O_2S$: C, 52.4; H, 2.9; N, 13.6; S, 15.6. Found: C, 52.4; H, 2.6; N, 13.4; S, 15.8.

2-(β-Nitrovinyl)thieno[2,3-*b*]pyridine (Ie) (25).

Repetition of the preceding reaction but with 2-aldehyde Ic (instead of IIc) gave crude precipitate Ie, m.p. 167-174.5° dec. (44%). Recrystallization from chloroform plus repetitive sublimations at 60-150° (0.5 mm.) produced canary yellow prisms, m.p. 184.5-185.5°; ir (chloroform): 1525 and 1340 (nitro group), 950 cm^{-1} (*trans*-CH=CH).

Anal. Calcd. for $C_9H_6N_2O_2S$: C, 52.4; H, 2.9; N, 13.6; S, 15.6. Found: C, 52.5; H, 2.7; N, 13.7; S, 15.7.

α-Hydroxy-α-(3-thieno[2,3-*b*]pyridyl)acetonitrile (III).

TABLE III

Significant Mass Spectral Ion Fragments from 2- and 3-Substituted Thieno[2,3-*b*]pyridines of General Formula TPC(=O)R (a)

Compound Number (b)	R Group	Mol. Wt. M	Source Temp., °C	Relative Abundance of Ion, % M^+ (m/e)	$TPCO^+$ (162)	TP^+ (134)	$(TP-HCN)^+$ (107)	$(TP-CS)^+$ (90)	$C_5H_3^+$ (63)	RCO^+	Other
Ic	H	163	100	100	82	25	6	10	15	8	(c)
Id	Me	177	80	59	100	27	7	11	13	13	(d)
IIc	H	163	90	100	90	32	8	8	12	3	(e)
IIe	Me	177	105	43	100	33	5	5	7	7	(f)
IIf	CH_2Cl	213 211	125	9 25	100	34	6	6	9	---	(g)
IIg	OEt	207	110	63	100	22	5	5	9	---	(h)
IIh	Ph	239	140	100	9	28	6	7	11	56	(i)
IIi	NHPh	254	175	37	100	28	5	6	8	---	(j)

(a) TP = 2- or 3-thieno[2,3-*b*]pyridyl. (b) Compounds I are substituted at C-2; compounds II are substituted at C-3. (c) All peaks of relative abundance ≥ 5% are reported as (m/e) %: (165) 6, (164) 15, (135) 17, (91) 6, (82) 7, (81) 6, (69) 8, (64) 6, (50) 7, (45) 6, (39) 6; metastable ions at 161 (163 → 162) and 111 (162 → 134, for all compounds). (d) Also (179) 5, (178) 8, (164) 5, (163) 13, (135) 8, metastable ion at 148 (177 → 162). (e) Also (165) 6, (164) 14, (135) 10, (81) 5, (75) 7, (69) 6, (50) 5, (45) 6; metastable ion at 161. (f) Also (164) 6, (163) 10, (135) 6; metastable ion at 148. (g) Also (164) 6, (163) 9, (148) 6, (75) 6; metastable ions at 124 (211 → 162) and 123 (213 → 162). (h) Also (208) 9, (192) 8, (179) 23, (164) 6, (163) 14, (135) 9. (i) Also (241) 6, (240) 17, (238) 33, (211) 8, (210) 5, (164) 5, (163) 10, (106) 5, (77) 54, (76) 5, (75) 7, (74) 5, (51) 25, (50) 10, (39) 7. (j) Also (255) 6, (164) 5, (163) 10, (65) 8, (39) 8; metastable ions at 103-104 (254 → 162), 85-86 (134 → 107), and 60-61 (134 → 90).

A suspension of 0.81 g. of aldehyde IIc in 10 ml. of ether was stirred with a mixture of 0.27 g. of ammonium chloride and 0.33 g. of potassium cyanide (equimolar amounts) in 4 ml. of water for 15 minutes. The precipitate was crystallized from ethyl acetate-chloroform to give 0.43 g. (45%) of crude cyanohydrin III, m.p. 132-136°, converted to tan globules (m.p. 139-140.5°) on recrystallization; ir (pyridine): 3190 cm^{-1} (OH).

Anal. Calcd. for $C_9H_6N_2OS$: C, 56.8; H, 3.2; N, 14.7. Found: C, 56.5; H, 3.2; N, 14.7.

2-Phenyl-4-(3-thieno[2,3-*b*]pyridyl)ethylidene-5-oxazolone (IIm).

A mixture of 0.81 g. of aldehyde IIc, 0.9 g. (equimolar amount) of hippuric acid, and 5 ml. of acetic anhydride was heated on a steam bath for 85 minutes, diluted with 10 ml. of ethanol, cooled to -20°, and filtered to give crude IIm, 0.75 g. (49%), m.p. 273-276.5° dec., converted to canary yellow needles after recrystallizations from *n*-pentanol and *n*-pentanol-ethyl acetate as well as sublimation at 160-210° (0.7 mm.): m.p. 279.5-281°; ir (chloroform): 1795 (carbonyl), 1655 cm^{-1} (C=N).

Anal. Calcd. for $C_{17}H_{10}N_2O_2S$: C, 66.7; H, 3.3; N, 9.2; S, 10.5. Found: C, 66.7; H, 3.3; N, 9.1; S, 10.5.

Mass Spectra.

Mass spectra of the eight compounds listed in Table III were determined by Dr. Susan Rottschaefer by means of a CEC model 21-110 instrument at 70 eV.

Likewise obtained for carbinol IIj was the spectrum, m/e (relative abundance, for peaks $\geq$ 7%) 319 (7), 318 (25), 317 (44), 241 (15), 240 (34), 222 (9), 214 (7), 213 (24), 212 (55), 211 (10), 165 (7), 163 (10), 162 (22), 135 (7), 134 (10), 106 (9), 105 (100), 78 (7), 77 (55), 51 (11).

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(25) This compound is a skin irritant.