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Studies on Isothiazoles. I. 3-Arylisothiazole-4-carboxylic Acids

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Preparations of 5-methyl-3-phenylisothiazole-4-carboxylic acid (Xa) and related compounds are described. 3-(Halogen-substituted phenyl)-5-methylisothiazole-4-carboxylic acids were also obtained by halogenation of 4-cyano-5-methyl-3-phenylisothiazole (VIIa), followed by hydrolysis. 5-Bromo-3-phenylisothiazole-4-carboxylic acid (XV) was prepared, and converted into the 5-methylthio derivative (XVI) which was oxidized to the corresponding sulfoxide (XVII) and sulfone (XVIII).

Since the first mononuclear isothiazole was prepared by Adams and Slack[2] in 1956, several synthetic methods and a variety of derivatives of isothiazole have been described.[3] The present paper reports the preparation of a series of 3-arylisothiazole-4-carboxylic acids which have been hitherto undescribed. Primary interest of the authors for these studies was to synthesize 5-methyl-3-phenylisothiazole-4-carboxylic acid (Xa) and the related compounds in connection with the new penicillin program. The semi-synthetic penicillins of isothiazole series will be reported elsewhere.

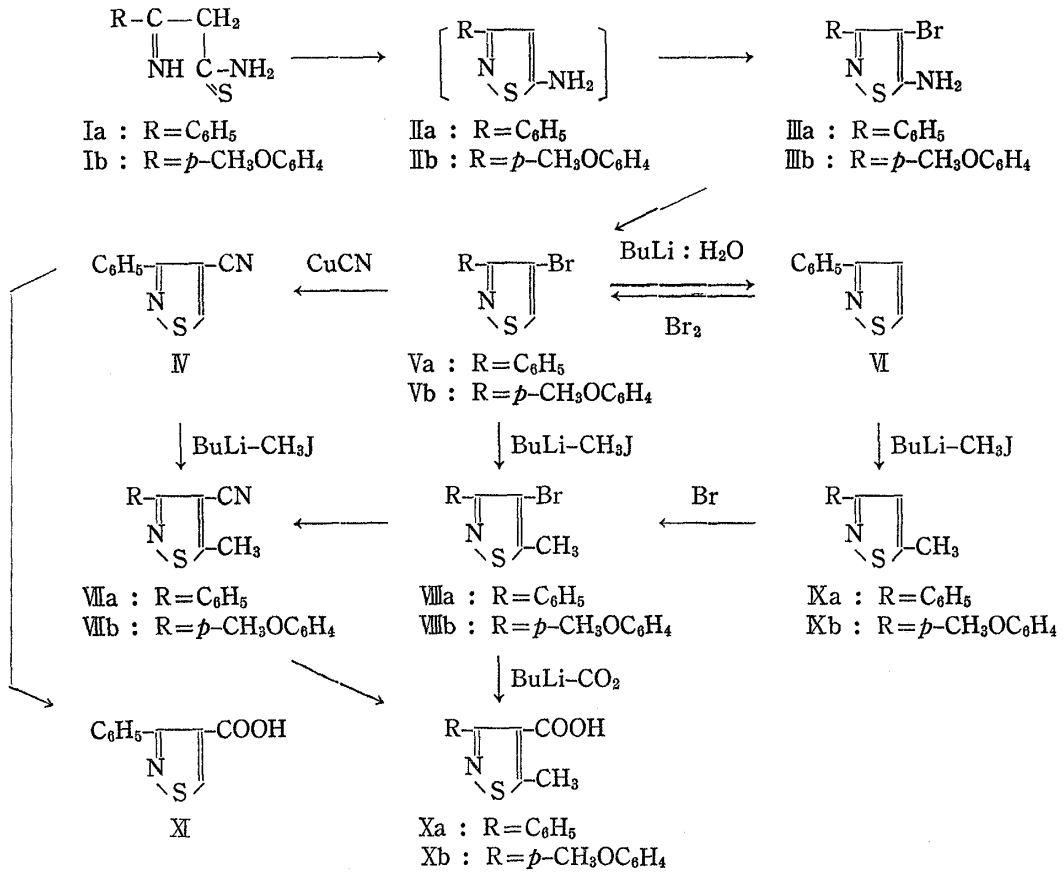


Chart 1

1) Location : *2-9-3, Shimo-meguro, Meguro-ku, Tokyo.*
2) A. Adams and R. Slack, *Chem. Ind.* (London), **1956**, 1232.
3) A.R. Katritzky, *Advances in Heterocyclic Chemistry*, **4**, pp. 107—120 (1965).

I. Preparation of 3-Arylisothiazole-4-carboxylic Acids

Bromination of 5-amino-3-phenylisothiazole[4] (IIa) with bromine gave with ease 5-amino-4-brome-4-phenylisothiazole (IIIa). Compound IIIa or IIIb could also be obtained directly from β-aryl-β-iminothiopropionamides (I) and bromine without isolating 5-amino-3-arylisothiazoles (II). 3-Aryl-4-bromoisothiazoles (V) were prepared by deamination of III according to the procedure of Buttimore[5] for 4-bromo-3-methylisothiazole.

Compound Va was reacted under reflux with cuprous cyanide in γ-picoline to afford 4-cyano-3-phenylisothiazole (IV). Methylation of IV was carried out with butyl lithium and methyl iodide at −70° according to the procedure for methylation in the 5-position of 4-bromo-3-methylisothiazole,[6] to give 4-cyano-5-methyl-3-phenylisothiazole (VIIa) in a low yield. Methylation of Va and Vb, however, yielded 3-aryl-4-bromo-5-methylisothiazoles (VIIIa,b) with higher yield. Conversion of VIII into VII was performed by refluxing with cuprous cyanide in quinoline. The nitriles (IV and VIIa) were hydrolyzed to the corresponding carboxylic acides (XI and Xa, respectively) by treating with concentrated sulfuric acid then with aqueous sodium nitrite. Hydrolysis of VIIb by this method was unsuccessful.

II. Reaction of 3-Arylisothiazoles with Butyl Lithium

In the course of methylation of Va with butyl lithium and methyl iodide, appreciable amounts of two by-products, VI and IXa, were isolated by fractional distillation and recrystallization. The nuclear magnetic resonance (NMR) spectrum[7] of VI shows an AB quartet (2H) at 7.48 (d) and 8.52 (d), J=5.0 cps, besides two sets of multiple lines (5H) at 7.23—7.40 and 7.77—7.96 assignable to phenyl ring protons. Identity of VI with 3-phenylisothiazole was established by a regeneration of Va by bromination of VI. While, the NMR spectrum of another by-product, IXa, shows a methyl singlet at 2.51 and a sharp singlet (1H) at 7.14 in addition to the ring proton multiplets (5H), and the bromination of IXa yielded VIIIa. Compound IXa was, therefore, determined to be 5-methyl-3-phenylisothiazole. The susceptibility of bromine atom at the 4-position to lithium reagent was confirmed by the following additional experiment: Va was treated with butyl lithium at −50° and decomposed with water to yield VI. Reaction of VI with butyl lithium and methyl iodide gave IXa without yielding any by-product. Methylation of Vb yielded a considerable amount of IXb as a by-product, which was converted into VIIIb with bromine. Reaction of VIIIb with butyl lithium at −50° gave 3-*p*-methoxyphenyl-5-methylisothiazol-4-yl lithium which was decomposed with Dry Ice to yield 3-*p*-methoxyphenyl-5-methylisothiazole-4-carboxylic acid (Xb). The NMR spectrum[8] of Xb agrees with the structure showing a methyl signal

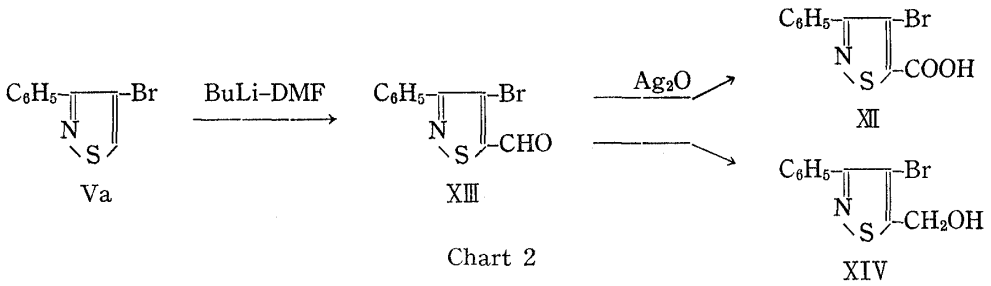


Chart 2

4) J. Goerdelar and H.W. Pohlond, *Chem. Ber.*, **94**, 2950 (1961).
5) D. Buttimore, D.H. Jones, R. Slack, and K.R.H. Wooldridge, *J. Chem. Soc.*, **1963**, 2032.
6) M.P.L. Caton, D.H. Jones, R. Slack, and K.R.H. Wooldridge, *J. Chem. Soc.*, **1964**, 446.
7) All NMR spectra were run by Varian HA-100 in Government Chemical Industrial Research Institute of Tokyo. The following abbreviations are used hereafter: singlet, (s); doublet, (d); double doublet, (dd); quartet, (q) and multiplet, (m). The measurements were carried out in 10% solution of either deuteriochloroform or carbon tetrachloride and chemical shifts are given in ppm from an internal reference, TMS, unless otherwise stated.
8) run in D_2O with K_2CO at 100 Mc. The chemical shifts were represented in cps from HOD.

at +214 (*ca.* 2.56), a methoxy signal at +87 (*ca.* 3.83) and ring proton signals (4H) as an AB quartet at −236 (d, *ca.* 7.06) and −318 (d, *ca.* 7.88), J_{AB}=8.9 cps.

Reaction of 4-bromo-3-phenylisothiazol-5-yl lithium prepared from Va with dimethylformamide (DMF) gave 4-bromo-5-formyl-3-phenylisothiazole (XIII), which was reduced to 4-bromo-5-hydroxymethyl-3-phenylisothiazole (XIV) with sodium borohydride. Oxidation of XIII afforded 4-bromo-3-phenylisothiazole-5-carboxylic acid (XII). These findings correlate well with those of Buttimore, *et al.*[5] and Caton, *et al.*[6] in the reactions of 3-methylisothiazol-5-yl lithium.

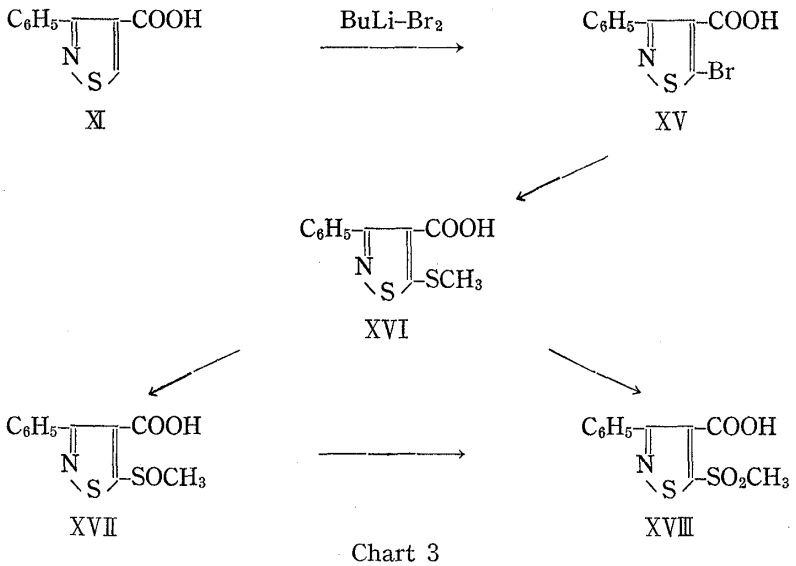


Chart 3

5-Bromo-3-phenylisothiazole-4-carboxylic acid (XV) was obtained by reaction of the 5-lithio derivative prepared from 3-phenylisothiazole-4-carboxylic acid (XI) with bromine. The bomine atom in the 5-position was fairly reactive and readily replaced by methylthio group by refluxing in a solution of sodium methyl mercaptide to afford 5-methylthio-3-phenylisothiazole-4-carboxylic acid (XVI), which was oxidized to 5-methylsulfoxy-3-phenylisothiazole-4-carboxylic acid (XVII) and 5-methylsulfonyl-3-phenylisothiazole-4-carboxylic acid (XVIII) with hydrogen peroxide or potassium permanganate.

III. Halogenation of 3-Arylisothiazoles

It has been reported that the brominations occur in the 4-position of 3-methylisothiazole, 5-amino-3-methylisothiazole[5] and 5-alkyl-3-methylisothiazole.[6] The similar reactivity was observed with 3-aryl-4-unsubstituted isothiazoles in the present study. Bromination of IIa, VI, IXa and IXb afforded the corresponding 4-bromo derivatives, IIIa, Va, VIIIa and VIIIb, respectively. In the course of bromination of IXb an appreciable amount of dibromo derivatives, mp 105—106°, was isolated, and the structure was considered to be A or B of Chart 4.

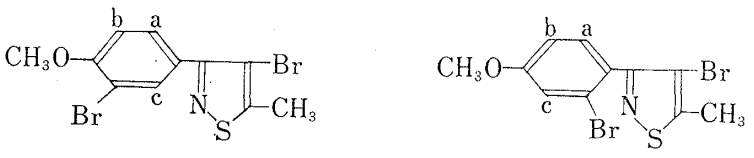


Chart 4

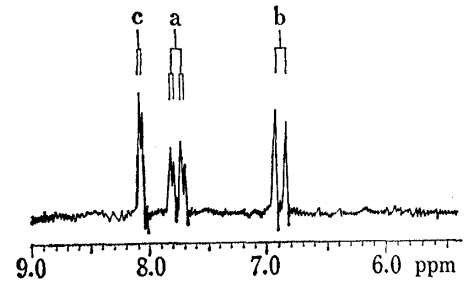


Fig. 1. Ring Proton Signals of 3-(3-Bromo-4-methoxyphenyl)-4-bromo-5-methylisothiazole

In either structure the NMR signal of H_b is to be expected to come to the highest field among the ring proton signals because of the electron donating effect of methoxy group. Since the *para*-coupling is generally weak or negligible, the signal of H_b in structure B should be split into four lines by an *ortho* hydrogen and a *meta* hydrogen, while in structure A the H_b signal is to be split into two lines by an *ortho*-coupling. As shown in Fig. 1, the actual signal consists of two lines separated by 8.3 cps, and therefore, the dibromo compound was determined to have structure A.

Halogenation of VIIa and IV also afforded compounds with halogen substitution(s) in the phenyl ring (Chart 5). Reaction of VIIa with chlorine in the presence of antimony trichloride yielded a mixture of *o*-chlorophenyl (XIXa), *p*-chlorophenyl (XIXb) and a small amount of 2,4-dichlorophenyl (XIXc) derivatives which were separated by fractional crystallization. Further chlorination afforded 2,4-dichlorophenyl (XIXc) and 2,4,5-trichlorophenyl (XIXd) derivatives.

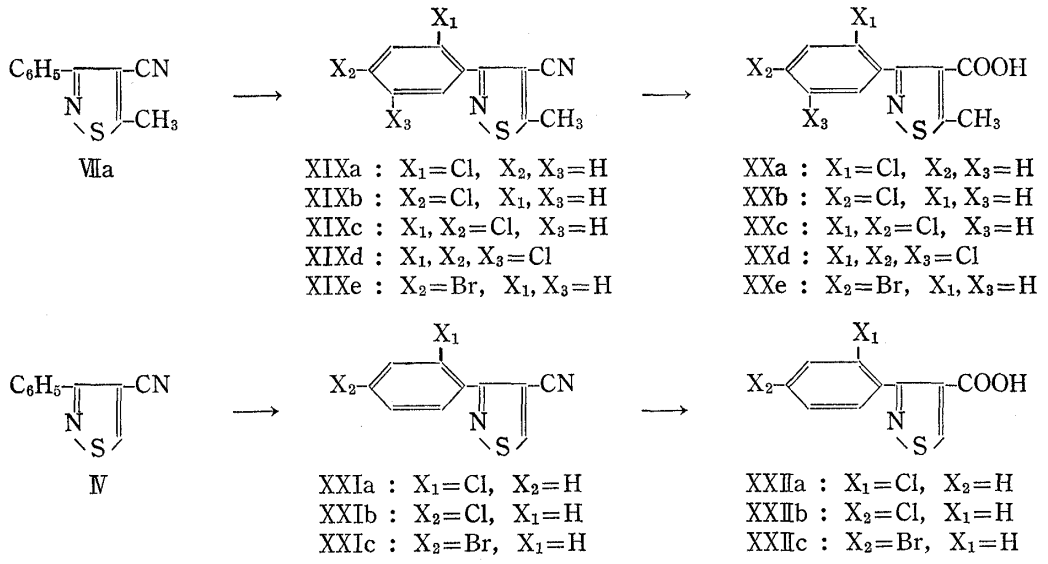


Chart 5

Similarly, 3-*o*-chlorophenyl-4-cyanoisothiazole (XXIa) and 3-*p*-chlorophenyl-4-cyanoisothiazole (XXIb) were obtained by chlorination of IV. Bromination of VIIa and IV with bromine in the presence of iron powder yielded 3-*p*-bromophenyl-4-cyano-5-methylisothiazole (XIXe) and 3-*p*-bromophenyl-4-cyanoisothiazole (XXIc), respectively. The NMR spectra were employed for assigning the halogen substitution(s) in the phenyl ring (Table III).

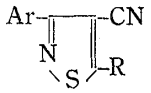
The 4-cyano-3-(halogen-substituted phenyl)isothiazoles were hydrolyzed to the corresponding carboxylic acid with sulfuric acid and sodium nitrite. Analytical and other data of the both series of compounds are shown in Table I and II.

IV. Spectroscopic Properties of 3-Arylisothiazoles

a. Nuclear magnetic resonance spectra

The NMR data of the 4-cyano-3-(halogen-substituted phenyl)isothiazoles are shown in Table III. The compounds with halogen substitution in the *para* position of the phenyl ring, XIXb, XIXe, XXIb and XXIc, were readily assignable because of the characteristic AB

Table I. 3-Aryl-4-cyanoisothiazoles



No.	Ar	R	mp (°C)	λ_{max}^{EtOH} mμ (ε)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
VIIa	C_6H_5	CH_3	79— 80	264 (11, 300)	$C_{11}H_8N_2S$	65.97	4.27	13.99	65.78	3.80	14.14
VIIb	*p*-$CH_3OC_6H_4$	CH_3	100—101	241.5 (10, 500) 280 (16, 800)	$C_{12}H_{10}ON_2S$	62.58	4.38	12.17	62.51	4.41	12.29
XIXa	*o*-Cl-C_6H_4	CH_3	78— 79	260.5 (8, 650)	$C_{11}H_7N_2SCl$	56.29	3.01	11.94	56.01	3.52	11.75
XIXb	*p*-Cl-C_6H_4	CH_3	114—115	267 (16, 200)	$C_{11}H_7N_2SCl$	56.29	3.01	11.94	56.02	2.71	11.81
XIXc	2,4-di-Cl-C_6H_3	CH_3	125—128	258.5 (10, 400)	$C_{11}H_6N_2SCl_2$	49.08	2.25	10.41	49.29	2.02	9.99
XIXd	2,4,5-tri-Cl-C_6H_2	CH_3	186—187	258.5 (11, 900)	$C_{11}H_5N_2SCl_3$	43.51	1.66	9.23	43.46	1.39	9.55
XIXe	*p*-Br-C_6H_4	CH_3	139	268.5 (18, 000)	$C_{11}H_7N_2SBr$	47.32	2.33	10.04	47.02	2.32	10.11
IV	C_6H_5	H	54— 55	256.5 (11, 800) 273 (10, 500)	$C_{10}H_6N_2S$	64.49	3.23	15.04	64.55	3.53	15.08
XXIa	*o*-Cl-C_6H_4	H	58— 60	260 (9, 700)	$C_{10}H_5N_2SCl$	54.42	2.28	12.70	54.30	2.53	12.37
XXIb	*p*-Cl-C_6H_4	H	148—150	265 (16, 400)	$C_{10}H_5N_2SCl$	54.42	2.28	12.70	54.18	2.46	12.81
XXIc	*p*-Br-C_6H_4	H	148—149	267 (18, 200)	$C_{10}H_5N_2SBr$	45.30	1.90	10.57	45.50	2.09	10.58

quartet (J=8.0—8.6 cps). The ring proton signals (4H) of XIXa and XXIa appears as a singlet-like multiplet, and XIXa was assigend to be an *ortho*-chloro compound because the corresponding carboxylic acid (XXa) derived from XIXa was differentiated by the IR and UV spectra from the authentic 3-*m*-chlorophenyl-5-methylisothiazole-4-carboxylic acid.[9] The ring proton signal (3H) of 2,4-dichloro derivative (XIXc), which was obtained by chlorination of *ortho* (XIXa) and *para*-chlorophenyl (XIXb) analogs, appears as a single line. The trichloro derivative (XIXd) derived from dichloro compound (XIXc) was found to have the substitutions at the 2,4 and 5 positions of phenyl ring, because the NMR signals for ring protons appeared as two separate singlets which are reasonable for 1,2,4,5-tetra-substituted benzene having negligible *para*-coupling.

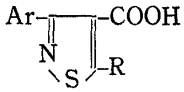
The phenyl ring proton signals of 3-phenylisothiazoles carrying no substitutent on the phenyl ring appear as two sets of multiplet at about 8.2—7.7 and 7.65—7.2, the chemical shifts being variable with the substituent in the 4- or 5-position of the isothiazole ring. The methyl signals of 3-aryl-5-methylisothiazoles are observed at about 2.8—2.2. In the 3-aryl-4-unsubstituted isothiazoles, the 4-H signal is observed at 7.5—7.0 with the exception of 4-amino-3-phenylisothiazole in which the 4-H signal appears at 6.17. In the 3-arylisothiazoles without substituent in the 5-position, the 5-H signal appears at 9.5—8.5. The coupling constant between 4-H and 5-H is 5 cps in general.

b. Ultraviolet absorption spectra

3-Phenylisothiazole has a strong absorption maximum at 272 mμ which shows a shift with substitution(s) in the isothiazole ring and/or the phenyl ring, the degree of the shift

9) T. Naito, S. Nakagawa, and K. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **16**, 160 (1968).

TABLE II. 3-Arylisothiazole-4-carboxylic Acids

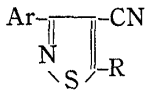


No.	Ar	R	mp (°C)	Yield (%)	λ_{max}^{EtOH} mμ (ε)	$\nu_{C=O}$ (cm^{-1})
Xa	C_6H_5	CH_3	153—154 *a*	87	264 (10,000)	1670
Xb	*p*-$CH_3OC_6H_4$	CH_3	148—150 *b*	54	276.5 (12,600)	1710
XXa	*o*-Cl-C_6H_4	CH_3	185—186 *b*	86	256 (9,500)	1670
XXb	*p*-Cl-C_6H_4	CH_3	181 *b*	80	262 (14,300)	1725
XXc	2,4-di-Cl-C_6H_3	CH_3	178—179 *b*	76	255 (8,800)	1670
XXd	2,4,5-tri-Cl-C_6H_2	CH_3	220 *c*	47	253 (10,100)	1670
XXe	*p*-Br-C_6H_4	CH_3	182—183 *b*	96	262 (16,400)	1720
XI	C_6H_5	H	165—166 *d*	81	259 (10,300)	1730
XXIIa	*o*-Cl-C_6H_4	H	175—177 *d*	92	258 (7,900)	1670
XXIIb	*p*-Cl-C_6H_4	H	172—174 *d*	34	259 (13,800)	1720
XXIIc	*p*-Br-C_6H_4	H	185—187 *c*	81	259 (15,700)	1695

No.	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Xa	$C_{11}H_9O_2NS$	60.26	4.14	6.39	60.26	4.22	6.36
Xb	$C_{12}H_{11}O_3NS$	57.81	4.45	5.62	57.92	4.11	5.51
XXa	$C_{11}H_8O_2NSCl$	52.07	3.18	5.52	52.26	3.30	5.84
XXb	$C_{11}H_8O_2NSCl$	52.07	3.18	5.52	52.29	3.40	5.41
XXc	$C_{11}H_7O_2NSCl_2$	45.85	2.45	4.86	45.52	2.55	4.91
XXd	$C_{11}H_6O_2NSCl_3$	40.95	1.86	4.34	40.83	2.20	4.96
XXe	$C_{11}H_8O_2NSBr$	44.31	2.71	4.70	44.31	2.73	5.25
XI	$C_{10}H_7O_2NS$	58.71	3.44	6.84	58.91	4.02	6.92
XXIIa	$C_{10}H_6O_2NSCl$	50.11	2.52	5.84	50.16	2.27	6.06
XXIIb	$C_{10}H_6O_2NSCl$	50.11	2.52	5.84	50.03	2.91	5.90
XXIIc	$C_{10}H_6O_2NSBr$	42.27	2.13	4.93	42.27	2.37	4.66

a : recrystallized from CCl_4 *b* : recrystallized from EtOH-H_2O
c : recrystallized from EtOH *d* : recrystallized for C_6H_6

TABLE III. NMR Data of 3-Aryl-4-cyanoisothiazoles



No.	Ar	R	Methyl proton (δ)	5-H (δ)	Phenyl ring proton (δ)
VIIa	C_6H_5	CH_3	2.73(s)	——	8.17—7.97(m) 7.6—7.4(m)
XIXa	*o*-Cl-C_6H_4	CH_3	2.74(s)	——	7.38(m)
XIXb	*p*-Cl-C_6H_4	CH_3	2.76(s)	——	7.45(d), 8.00(d) J_{AB}=8.4 cps
XIXc	2,4-di-Cl-C_6H_3	CH_3	2.81(s)	——	7.43(s)
XIXd	2,3,5-tri-Cl-C_6H_2	CH_3	2.74(s)	——	7.60(s), 7.53(s)
XIXe	*p*-Br-C_6H_4	CH_3	2.72(s)	——	7.85(d), 7.55(d) J_{AB}=8 cps
IV	C_6H_5	H	——	9.3(s)	8.25—8.0(m) 7.65—7.45(m)
XXIa	*o*-Cl-C_6H_4	H	——	9.27(s)	7.6—7.3(m)
XXIb	*p*-Cl-C_6H_4	H	——	9.23(s)	7.94(d), 7.30(d) J_{AB}=8 cps
XXIc	*p*-Br-C_6H_4	H	——	9.24(s)	7.88(d), 7.57(d) J_{AB}=8.6 cps

depending on the type and position of the substituents. Introduction of a methoxy group into the *para*-postion of the phenyl ring causes a bathochromic shift by *ca.* 10 mμ, while a halogen atom in the same position exerts a lesser effect on the UV absorption spectra, and an introduction of chlorine to the *ortho*-position of phenyl ring causes a hypochromic effect probable due to the steric hindrance.

c. Infrared absorption spectra

In the IR spectra of 3-phenylisothiazoles three bands of medium to weak intensity are observed in common in the 1520—1470 cm^{-1}, near 1450 cm^{-1} and 1400—1370 cm^{-1} regions. These bands often overlap with the absorptions of methyl deformation vibration and, therefore, are difficult to distinguish from those of 3-aryl-5-methylisothiazole. In 3-arylisothiazoles carrying no substitutent in the 5-position of isothiazole ring, characteristic C-H stretching vibrations give rise to a band at 3080—3120 cm^{-1}. The carbonyl stretching vibration of 3-arylisothiazole-4-carboxylic acids occurs at 1730—1670 cm^{-1}.

Experimental

β-Imino-β-phenylthiopropionamide (Ia)——A solution of 1340 g (9.3 moles) of β-imino-β-phenylpropionitrile[10] in 13 liter of methylene chloride was placed in a 20 liter stainless steel bottle. The bottle was chilled at −15° and hydrogen sulfide gas was bubbled into the solution until 1680 g of the gas was absorbed. After 18.5 g of powdered potassium hydroxide was added, the container was tightly stoppered and allowed to stand at room temperature for three days. The reaction mixture was then chilled to −10° and the crystals which separated were filtered and washed with ether. Yield 927 g (59%). mp 169—171° (lit.,[4] 174°).

β-Imino-β-*p*-methoxyphenylthiopropionamide (Ib)——β-Imino-β-*p*-methoxyphenylpropionitrile was prepared in a similar manner to the procedure of Holtzwart.[10] Yield 31%. mp 113—114°. *Anal.* Calcd. for $C_{10}H_{10}ON_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.76; H, 5.66; N, 16.05. IR cm^{-1}: $\nu_{C\equiv N}$ 2250. UV λ_{max}^{EtOH} mμ (ε): 255 (12,700), 295 (18,400).

A solution of 35 g (0.2 mole) of β-imino-β-*p*-methoxyphenylpropionitrile in 350 ml of methylene chloride was placed in a 500 ml pressure bottle and 0.3 g of powdered potassium hydroxide was added. The reaction mixture was chilled with Dry Ice-acetone. Dry hydrogen sulfide gas was passed into the solution until 27 g (0.8 mole) of the gas was absorbed. The bottle was tightly stoppered and allowed to stand for three days at room temperature. The separated bright yellow crystals were filtered and washed with ether. The analytical sample was recrystallized from methylene chloride. Yield 164 g (80%). mp 179—180°. *Anal.* Calcd. for $C_{10}H_{12}ON_2S$: C, 57.66; H, 5.81; N, 13.45. Found: C, 57.19; H, 5.69; N, 13.53. UV λ_{max}^{EtOH} mμ (ε): 273 (11,000), 352 (7,900).

5-Amino-4-bromo-3-phenylisothiazole (IIIa)——a) To a stirred solution of 30 g (0.17 mole) of IIa[4] in 100 ml of acetic acid and 300 ml of benzene was added dropwise 28 g (0.175 mole) of bromine at 5—10°. The separated hydrobromide was collected by filtration and stirred with excess 2N sodium carbonate solution for 3 hr at room temperature to give the free base, which was recrystallized from ligroin. Yield 35 g (81%). mp 84—85°. *Anal.* Calcd. for $C_9H_7N_2BrS$: C, 42.36; H, 2.77; N, 10.98. Found: C, 42.38; H, 2.69; N, 11.04. UV λ_{max}^{EtOH} mμ (ε): 236 (11,200), 259 (11,200).

b) To a stirred suspension of 800 g (4.5 moles) of Ia in 7.5 liter of ethanol was added dropwise 2160 g (13.5 moles) of bromine at about 10° over a period of 2 hr. After the addition was completed, stiring was continued for an hr. The precipitated hydrobromide was filtered and washed with 3 liter of cold ethanol. Yield 1059 g (70%). The hydrobromide was suspended in 5 liter of water and 5 liter of 10% aq. sodium carbonate was added with stirring. Stirring was continued for 2 hr at room temperature to afford free base, which was filtered, washed with water and air-dried. Yield 723 g (62%). mp 82—83°. This was identical by IR spectra with IIIa which was prepared by procedure-(a).

5-Amino-4-bromo-3-*p*-methoxyphenylisothiazole (IIIb)——To a stirred suspension of 150 g (0.72 mole) of Ib in 1.2 liter of ethanol was added dropwise 360 g (2.25 moles) of bromine at 15° during an hour. The reaction mixture was stirred for additional 2 hr at 20°. The separated hydrobromide was filtered, washed with cold ethanol and dried in the air. The hydrobromide was added with strring to 720 ml of 2N aq. sodium carbonate and stirring was continued for 2 hr to give the free amine, which was filtered, washed with water and dried. The analytical sample was recrystallized from ligroin. Yield 172 g (75%). mp 107—111°. *Anal.* Calcd. for $C_{10}H_9ON_2BrS$: C, 42.12; H, 3.18; N, 9.82. Found: C, 41.89; H, 2.79; N, 10.28. UV λ_{max}^{EtOH} mμ (ε): 234 (12,000), 274 (18,000).

4-Bromo-3-phenylisothiazole (Va)——a) A viscous solution of 57 g (0.224 mole) of IIIa in 100 ml of conc. sulfuric acid and 100 ml of conc. phosphoric acid was diazotized with 17 g (0.247 mole) of sodium

10) Holtzwart, *J. Prakt. Chem.*, [2] **39**, 230 (1889).

nitrite in 60 ml of water at 0—5°. The diazotized solution was added dropwise to a stirred suspension of 2 g of cuprous oxide in 240 ml of 30% hypophosphorous acid under cooling by running water. Two additional 7 g portions of cuprous oxide were added to the reaction mixture and stirring was continued for another one hour at room temperature. The reaction mixture was filtered with a Dicalite-precoated filter and the residue was washed with 500 ml of ether. The combined filtrate and washings were diluted with an equal volume of water and extracted with three 300 ml portions of ether. The combined ethereal solution was washed with two 50 ml portions of water and dried over anhydrous sodium sulfate. The ether was distilled off to give an oily residue, which was crystallized from petroleum ether using decolorizing carbon. Yield 39 g (73%). mp 55—56°. *Anal.* Calcd. for C_9H_2NBrS: Br, 33.28. Found: Br, 33.35. UV λ_{max}^{EtOH} mμ (ε): 274.5 (11,800).

b) To a mixture of 1.0 g (0.0062 mole) of VI, 0.8 g (0.01 mole) of sodium acetate and 20 ml of acetic acid was added 1.5 g (0.009 mole) of bromine. The reaction mixture was refluxed for 2 hr, evaporated under reduced pressure, treated with water and extracted with three 10 ml portions of ether. The combined ethereal solution was washed with aqueous sodium bicarbonate, then with 5 ml of water, dried on sodium sulfate and evaporated to give an oil, which was recrystallized from petroleum ether. Yield 0.7 g (48%). This was identical (IR, mp) with Va made by procedure-(a).

4-Bromo-3-*p*-methoxyphenylisothiazole (Vb)——Similary, Vb was prepared by deamination of 160 g (0.56 mole) of IIIb. Yield 92 g (61%). mp 40—41°. *Anal.* Calcd. for $C_{10}H_8ONBrS$: C, 44.46; H, 2.99; N, 5.19. Found: C, 44.45; H, 3.10; N, 5.19. UV λ_{max}^{EtOH} mμ (ε): 285 (14,300).

4-Bromo-5-methyl-3-phenylisothiazole (VIIIa)—a) To a stirred solution of 240 g (0.1 mole) of Va in 400 ml of dry THF was added dropwise *n*-butyl lithium prepared from 22 g (3 atoms) of lithium, 192 g (1.4 moles) of *n*-butyl bromide and 500 ml of dry ether, over a period of 3.5 hr at −70°, and stirring was continued for additional one hr. Then, 185 g (1.3 moles) of methyl iodide was added dropwise to the chilled reaction mixture, during which time temperature rose to −13°. When the exothermic reaction subsided the Dry Ice-acetone bath was removed. Stirring was continued for another hour and the temperature was allowed to rise to room temperature. The reaction mixture was poured into 500 ml of 2N hydrochloric acid. The ether layer was separated and the aqueous layer was extracted three times with 200 ml portions of ether. The combined ethereal solutions were washed with water dried over sodium sulfate and evaporated to give an oil, which was distilled *in vacuo*. A fraction, bp 117° (0.7 mm Hg) was collected. Upon standing the product (VIIIa) solidified. Yield 140 g (55%). mp 44—45°. *Anal.* Calcd. for $C_{10}H_8NBrS$: C, 47.25; H, 3.17; N, 5.51. Found: C, 47.51; H, 3.45; N, 6.07. UV λ_{max}^{EtOH} mμ (ε): 273.5 (12,800). NMR: 7.53 (CH_3, s), 7.85—7.7, 7.5—7.3 (ring protons, m).

The forerun was redistilled. A fraction. bp 125—130° (15 mm Hg), was collected and crystallized from petroleum ether to give 7.0 g (4%) of IXa, mp 47—48°. The forerun of IXa was redistilled and collected a fraction. bp 95—100° (0.8 mm Hg), which was redistilled to give 14 g (8.5%) of VI.

b) To a stirred solution of 4.0 g (0.0287 mole) of IXa in 50 ml of acetic acid was added 5.7 g (0.071 mole) of sodium acetate and then dropwise 6.5 g (0.071 mole) of bromine at room temperature. The reaction mixture was stirred for 3 hr, poured into 200 ml of water and extracted with three 50 ml portions of ether. The combined etheral solutions were neutralized with sodium bicarbonate, washed with two 20 ml portions of water, dried with sodium sulfate and evaporated to give an oily product, which was distilled *in vacuo*. A fraction, bp 130—132° (1.0 mm Hg), was collected. Yield 4.5 g (62%). This was identical (IR, GLC) with VIIIa made by an alternative synthesis.

4-Bromo-3-*p*-methoxyphenyl-5-methylisothiazole (VIIIb)——a) A solution of 81 g (0.3 mole) of Vb in 150 ml of dry THF was chilled to −70° with Dry Ice-acetone mixture. To the stirred solution was cautiously added *n*-butyl lithium perpared from 7.0 g (1 atom) of lithium, 70 g (0.51 mole) of *n*-butyl bromide and 150 ml of dry ether, maintaining the temperature below −65° over a period of 3 hr. To the reaction mixture was added 53.5 g (0.42 mole) of methyl iodide in three portions, during which time the temperature rose to −30°. The reaction mixture was allowed to stand overnight and poured into 300 ml of 2N hydrochloric acid. The ether layer was separated and the aqueous layer was extracted with two 200 ml portions of ether. The combined ethereal solution was washed with water, dried with sodium sulfate and evaporated. Distillation of the residual oil gave 62 g of colorless oil. bp 170—185° (5.0 mm Hg). The product showed two strong peaks by GLC. The product was treated with hot ligroin to afford crystalline 3-*p*-methoxy-5-methylisothiazole (IXb). Yield 12 g (18%). mp 82—83°. *Anal.* Calcd for $C_{11}H_{11}ONS$: C, 64.36; H, 5.40; N, 6.82. Found: C, 64.68; H, 5.53; N, 6.58. UV λ_{max}^{EtOH} mμ (ε): 282 (18,700). NMR: 2.50 (5-CH_3, s), 3.73 (OCH_3, s), 6.78 (phenyl ring protons, d), 7.78 (phenyl ring protons, d) J=9.7 cps, 7.08 (4-H, s). The mothor liquor was evaporated and the residue was distilled *in vacuo* to give VIIIb, bp 148—156° (1.3 mm Hg), mp 42—43°. Yield 28 g (33%). *Anal.* Calcd. for $C_{11}H_{10}ONBrS$: C, 46.49; H, 3.55; N, 4.93; S, 11.28. Found: C, 46.90; H, 3.00; N, 5.26; S, 10.93. UV λ_{max}^{EtOH} mμ (ε): 282 (17,300). NMR: 2.51 (5-CH_3, s), 3.81 (OCH_3, s), 6.91 (ring ptorons, d), 7.76 (ring protons, d) J=9.7 cps.

b) To a stirred solution of 10.7 g (0.053 mole) of IXb and 4 g (0.08 mole) of anhydrous sodium acetate in 100 ml of acetic acid was added 10.6 g (0.066 mole) of bromine at room temperature and stirring was continued for 3 hr. The reaction mixture was evaporated under reduced pressure. The residue was treated with 50 ml of water and extracted with two 50 ml portions of ether. The combined ether extracts were

washed with aq. sodium bicarbonate, dried with sodium sulfate and evaporated to dryness to give an oily product, which was dissolved in hot ligroin. On cooling 2.7 g (14%) of 4-bromo-3-(3-bromo-4-methoxyphenyl)-5-methylisothiazole, mp 105—106°, was obtained. *Anal.* Calcd. for $C_{11}H_9ONBr_2S$: Br, 44.02. Found: Br, 43.15. UV λ_{max}^{EtOH} mμ (ε): 282 (16,900). Evaporation of the filtrate gave 11.7 g (79%) of VIIIb. This was identical (IR, GLC) with VIIIb prepared by procedure-(a).

4-Cyano-3-phenylisothiazole (IV)——A mixture of 21 g (0.087 mole) of Va, 90 g (0.1 mole) of cuprous cyanide and 200 ml of γ-picoline was refluxed for 15 hr. The reaction mixture was poured into 200 ml ice water, acidified with conc. hydrochloric acid and extracted with three 100 ml portions of ether. The ethereal solution was washed with 20 ml portions of water, dried with sodium sulfate and evaporated to give an oil, which was crystallized from ligroin. Yield 12 g (74%). IR cm^{-1}: $\nu_{C\equiv N}$2280.

4-Cyano-5-methyl-3-phenylisothiazole (VIIa)——a) To a stirred solution of 186 g (0.1 mole) of IV in 100 ml of dry THF was added at −70° *n*-butyllithium which was prepared from 2.7 g (0.4 atom) of lithium, 30 g (0.22 mole) of *n*-butyl bromide and 100 ml of dry ether. After the addition was completed, the reaction mixture was stirred for another hour at −70° and then 28 g (0.2 mole) of methyl iodide was added dropwise at the rate to keep the temperature below −65°. Stirring was continued for additional two hours at −60° and the temprature was allowed to rise to room temperature. The reaction mixture was treated with 100 ml of water and acidified with conc. hydrochloric acid. The ether layer was separated and the aqueous layer was extracted twice with 50 ml protions of ether. The combined ethereal extracts were washed with 20 ml portions of water, dried with sodium sulfate and evaporated to give a brown viscous oil, which was fractionated by distillation. The fraction, bp 110—125° (0.2 mm Hg), was collected and recrystallized from ligroin. Yield 4.4 g (22%). IR cm^{-1}: $\nu_{C\equiv N}$ 2280.

b) A mixture of 14.7 g (0.058 mole) of VIIIa, 7.8 g (0.087 mole) of cuprous cyanide and 110 ml of quinoline was heated at 240—245° for 4.5 hr on an oil bath. The reaction mixture was poured into a mixture of 165 ml of conc. hydrochloric acid and 100 g of crushed ice and extracted with three 100 ml portions of chloroform. The chloroform extracts were washed with 20 ml of conc. hydrochloric acid and then with saturated aq. sodium bicarbonate, dried over sodium sulfate and evaporated to give a solid, which was recrystallized from ligroin,. Yield 8.6 g (74%).

4-Cyano-3-*p*-methoxyphenyl-5-methylisothiazole (VIIb)——A mixture of 17 g (0.06 mole) of VIIIb, 7.8 g (0.087 mole) of cuprous cyanide and 100 ml of quinoline was refluxed for 3.5 hr on an oil bath. The reaction mixture was poured into a mixture of 170 ml conc. hydrochloric acid and 100 g of crushed ice and extracted with three 100 ml portions of chloroform. The chloroform extract was washed with 50 ml of 20% hydrochloric acid followed with saturated aq. sodium bicarbonate, dried with sodium sulfate and evaporated. The residual oil was taken up in hot ligroin, decolorized with carbon to give a solid precipitate. The analytical sample was recrystallized from ligroin. Yield 6.95 g (51%).

3-Phenylisothiazole (VI)——To a stirred solution of 48 g (0.2 mole) of Va in 200 ml of dry THF was added dropwise over a period of 2 hr at −60 to −65° butyl lithium which was prepared from 8.5 g (1.2 atoms) of lithium, 85 g (0.62 mole) of *n*-butyl bromide and 300 ml of dry ether. The reaction mixture was stirred for one-half hour at −55～−60°, poured into a mixture of 500 g of crushed ice and 75 ml of conc. hydrochloric acid. The ether layer was separated and the aqueous layer was extracted with three 100 ml portions of ether. The combined etheral solution was washed twice with 50 ml portions of water and evaporated. The residual oil was fractionally distilled. Yield 14.2 g (39%). bp 142—144° (16 mm Hg). *Anal.* Calcd. for C_9H_7NS: C, 67.05; H, 4.38; N, 8.69. Found: C, 67.50; H, 4.15; N, 8.94. The product was identical (IR, GLC) with VI, which was obtained in methylation of Va. The starting material (20.5g, 43 %) was recovered from the after-run distillate and the residue.

5-Methyl-3-phenylisothiazole (IXa)——To a stirred solution of 31 g (0.193 mole) of VI in 80 ml of dry THF was added slowly at −60～−65° *n*-butyl lithium which was prepared from 4.4 g (0.6 atom) of lithium, 39 g (0.285 mole) of *n*-butyl bromide and 100 ml of dry ether. Then the reaction mixture was stirred for one-half hour at −65° and 28 g (0.2 mole) of methyl iodide was added. The temperature was allowed to rise to room temperature and the reaction mixture was stood overnight and poured into a mixture of 50 ml of conc. hydrochloric acid and 400 ml of ice water. The ether layer was separated and the aqueous layer was extracted with three 100 ml portions of ether. The combined ether extracts were washed twice with 50 ml of water, dried with sodium sulfate and evaporated under reduced pressure. The residual oil solidified on cooling. Yield 22 g (66%). The analytical sample was recrystallized from petroleum ether, mp 48—49°. *Anal.* Calcd. for $C_{10}H_9NS$: C, 68.58; H, 5.18; N, 7.99. Found: C, 68.95; H, 4.83; N, 7.97. The product was identical (IR, GLC) with IXa, which was obtained in methylation of Va. UV λ_{max}^{EtOH} mμ (ε): 272.5 (20,000), 292 (6,900).

5-Methyl-3-phenylisothiazole-4-carboxylic Acid (Xa)——A solution of 38.5 g (0.19 mole) of VIIa in 200 ml of conc. sulfuric acid was heated at 70° for 3 hr on a water bath and then chilled to −5°. A solution of 14 g (0.2 mole) of sodium nitrite in 30 ml of water was added slowly through a separatory funnel, the tip of which was dipped into the solution, the temperature being kept below 5°. The reaction mixture was stirred at 10° for an hour and at 50—60° for 2 hr, then poured into 100 g of crushed ice. The separated precipitate was filtered, washed with water and dissolved in aq. sodium bicarbonate. The insoluble material

was removed by filtration and the filtrate was acidified wtih 20% hydrochloric acid to afford the product, which was recrystallized from carbon tetrachloride. Yield 34.8 g (87%).

5-Methyl-3-phenylisothiazole-4-carboxamide——A solution of 100 mg (0.5 mmole) of XVIIa in 2 ml of conc. sulfuric acid was heated at 60—70° for 3 hr on a water bath. The reaction mixture was poured into 10 g of crushed ice. The separated precipitate was filtered, washed with water, dried and recrystallized from benzene. Yield 80 mg (73%). mp 194—196°. *Anal.* Calcd. for $C_{11}H_{10}ON_2S$: C, 60.53; H, 4.62; N, 12.84. Found: C, 60.54; H, 4.97; N, 12.92. UV λ_{max}^{EtOH} mμ (ε): 269. 5(14,000). IR cm^{-1}: $\nu_{C=O}$ 1640.

3-*p*-Methoxy-5-methylisothiazole-4-carboxylic Acid (Xb)——To a stirred solution of 6.5 g (0.023 mole) of VIIIb in 40 ml of dry ether was added dropwise at −50° *n*-butyl lithium prepared from 0.54 g (0.078 atom) of lithium, 5.35 g(0.039 mole) of *n*-butyl bromide and 30 ml of dry ether. The Dry Ice-acetone bath was removed and the temperature was allowed to rise to −30°. The reaction mixture was poured into 50 g of powdered Dry Ice. When the Dry Ice evaporated and the temperature rose to −10°, 50 ml of water was added and the mixture was well shaken in a separatory funnel. The water layer was separated and acidified with 20% hydrochloric acid to give a precipitate, which was filtered and recrystallized from ethanol–water (1:1).

4-Bromo-5-formyl-3-phenylisothiazole (XIII)——To a stirred solution of 12 g (0.05 mole) of Va in 30 ml of dry THF was added dropwise at −60° over a period of 3 hr *n*-butyl lithium which was prepared from 1.1 g (0.15 mole) of lithium, 10.3 g (0.075 mole) of *n*-butyl bromide and 30 ml of ether. The reaction mixture was stirred for half an hour at −60° and 4 g (0.055 mole) of DMF was added slowly in three portions. The temperature rose to −50°. After stirring for an hour, the reaction mixture was poured into a mixture of 20 ml of conc. hydrochloric acid and 80 ml of ice water to give a solid product, which was filtered, dried and recrystallized from ligroin. Yield 3.5 g (39%). mp 118—120°. *Anal.* Calcd. for $C_{10}H_6ONBrS$: C, 44.79; H, 2.26; N, 5.22. Found: C, 44.63; H, 1.98; N, 5.69. UV λ_{max}^{EtOH} mμ (ε): 275 (11,800). IR cm^{-1}: $\nu_{C=O}$ 1683.

Thiosemicarbazone——A mixture of 1.4 g (0.0052 mole) of XIII, 0.48 g (0.0052 mole) of thiosemicarbazide, 15 ml of ethanol and 4 drops of acetic acid was refluxed for 3 hr to give the product, which was recrystallized from DMF. Yield 1.1 g (62%). mp 205—208°. *Anal.* Calcd. for $C_{11}H_9N_4BrS_2$: N, 16.42. Found: N, 16.58. UV λ_{max}^{EtOH} mμ (ε): 253 (9,900), 345 (14,900).

4-Bromo-5-hydroxymethyl-3-phenylisothiazole (XIV)——To a stirred solution of 1.5 g (0.0056 mole) of XIII in 10 ml of methanol was added a solution of 0.076 g (0.002 mole) of sodium borohydride in 5 ml of 0.2N sodium hydroxide, and 5 ml of methanol. The reaction mixture was stirred for 3 hr and kept to stand for 1.5 days at room temperature. Most of the methanol was removed under reduced pressure to give an oil, which solidified on cooling. The solid was filtered, washed with water, dried and recrystallized from benzene. Yield 1.46 g (96%). mp 80—81°. *Anal.* Calcd. for $C_{10}H_8ONBrS$: C, 44.64; H, 2.98; N, 5.19. Found: C, 44.54; H, 3.08; N, 5.21. UV λ_{max}^{EtOH} mμ (ε): 274 (11,700).

N-Methylcarbamate——A solution of 1.0 g (0.0037 mole) of XIV and 0.22 g (0.0038 mole) of methylisocyanate in 27 ml of dry benzene was refluxed for 3 hr. The reaction mixture was concentrated to give the precipitate, which was filtered and recrystallized from benzene. Yield 1.06 g (87%). mp 141—143°. *Anal.* Calcd. for $C_{12}H_{11}O_2N_2BrS$: C, 44.05; H, 3.39; N, 8.56. Found: C, 44.44; H, 3.59; N, 8.75. UV λ_{max}^{EtOH} mμ (ε): 276 (12,000). IR cm^{-1}: ν_{N-H} 3460, $\nu_{C=O}$ 1685.

4-Bromo-3-phenylisothiazole-5-carboxylic Acid (XII)——To a stirred solution of silver oxide, which was prepared from 1.7 g (0.01 mole) of silver nitrate, 0.8 g (0.02 mole) of sodium hydroxide and 8 ml of water, was added 1.35 g (0.005 mole) of XIII in three portions. The reaction mixture was stirred for 2 hr at room temperature and filtered. The filter cake was well washed several times with 3 ml portins of hot water. The combined filtrate and washings were concentrated under reduced pressure to half the volume and acidified with 20% hydrochloric acid to give the product, which was recrystallized from alcohol. Yield 1.06 g (74%). mp 215—216° (decomp.). *Anal.* Calcd. for $C_{10}H_6O_2NBrS$: C, 42.42; H, 2.14; N, 4.95. Found: C, 42,48; H, 2.09; N, 4.97. UV λ_{max}^{EtOH} mμ (ε): 231 (16,200), 296 (7,850). IR cm^{-1}: $\nu_{C=O}$ 1685.

5-Bromo-3-phenylisothiazole-4-carboxylic Acid (XV)——To a stirred solution of 16.4 g (0.08 mole) of XI in 300 ml of dry THF was added dropwise *n*-butyl lithium, which was prepared from 2.2 g (0.32 atom) of lithium, 22 g (0.16 mole) of *n*-butyl bromide and 80 ml of dry ether, maintaining the temperature at −70 to −60° during the addition. Then 25.6 g (0.16 mole) of dry bromine was added dropwise at −65 to −60°. The Dry Ice-acetone bath was removed and the temperature was allowed to rise to room temperature. The reaction mixture was poured into 300 ml of 2N hydrochloric acid and extracted with two 200 ml portions of ether. The combined ether extracts were washed with water and the solvent was removed by distillation to give an oily residue, which was dissolved in sodium bicarbonate solution. The solution was decolorized with active carbon and acidified with dil. hydrochloric acid to afford the product. The analytical sample was recrystallized from ligroin. Yield 9.4g (41%). mp 126—127°. *Anal.* Calcd. for $C_{10}H_6O_2NBrS$: C, 42.27; H, 2.13; N, 4.93. Found: C, 42.41; H, 2.53; N, 4.91. UV λ_{max}^{EtOH} mμ (ε): 224 (13,800), 278 (11,600). IR cm^{-1}: $\nu_{C=O}$ 1725.

5-Methylthio-3-phenylisothiazole-4-carboxylic Acid (XVI)——A solution of 6.7 g (0.024 mole) of XV and 2.0 g (0.024 mole) of sodium bicarbonate in 10 ml of water was added to sodium methyl mercaptide solution made from 13.9 g (0.1 mole) of S-methylthiouronium sulfate and 4.0 g (0.1 mole) of sodium hydroxide.

The reaction mixture was refluxed for an hour and acidified with dil. hydrochloric acid to give a precipitate, which was recrystallized from benzene. Yield 2.2 g (37%). mp 179—180°. *Anal.* Calcd. for $C_{11}H_9O_2NS_2$: C, 52.57; H, 3.61; N, 5.77. Found: C, 51.94; H, 3.78; N, 5.56. UV λ_{max}^{EtOH} mμ (ε): 244 (15,500), 287 (10,600). IR cm^{-1}: $\nu_{C=O}$ 1660. NMR: 2.56 (S-CH_3, s), 7.6—7.3 (ring proton, m), 10.05 (COOH, s).

5-Methylsulfinyl-3-phenylisothiazole-4-carboxylic Acid (XVII)——To a stirred solution of 4.7 g (0.0187 mole) of XVI in 50 ml of acetic acid and 50 ml of acetic anhydride was added slowly 2.1 g (0.0187 mole) of 30% hydrogen peroxide. The reaction mixture was allowed to stand for 24 hr at room temperature, treated with 50 ml of water to decompose the acetic anhydride and evaporated to dryness under reduced pressure to give a solid, which was recrystallized from ethanol–water. Yield 4.0 g (80%). mp 193—196°. *Anal.* Calcd. for $C_{11}H_9O_3NS_2$: C, 49.42; H, 3.39; N, 5.24. Found: C, 49.86; H, 3.37; N, 5.40. UV λ_{max}^{EtOH} mμ (ε): 240 (11,400), 270 (7,900). IR cm^{-1}: $\nu_{C=O}$ 1700.

5-Methylsulfonyl-3-phenylisothiazole-4-carboxylic Acid (XVIII)——a) To a stirred solution of 5.0 g (0.02 mole) of XVI and 1.7 g (0.02 mole) of sodium bicarbonate in 50 ml of water was added a solution of 4.3 g (0.027 mole) of potassium permanganate in 50 ml of water. The reaction mixture was stirred at room temperature overnight and filtered with a Dicalite–precoated filter. The cake was washed with two 50 ml portions of hot water. The filtrate was combined with the washings and evaporated to one–third the volume. The concentrate was adjusted to pH 2.0 with 20% hydrochloric acid to give the product, which was crystallized from benzene containing a small amount of alcohol. Yield 4.0 g (71%). mp 184—187°. *Anal.* Calcd. for $C_{11}H_9O_4NS_2$: N, 4.94. Found: N, 5.17. UV λ_{max}^{EtOH} mμ (ε): 230 (15,300), 282 (6,700). IR cm^{-1}: $\nu_{C=O}$ 1685, ν_{SO_2} 1320, 1140.

b) To a solution of 100 mg (0.4 mmole) of XVI in 2 ml of acetic anhydride and 2 ml of acetic acid was added 100 mg (0.88 mmole) of 30% hydrogen peroxide. The reaction mixture was allowed to stand for 2 days at room temperature, treated with 2 ml of water and evaporated to dryness under reduced pressure to give the product, which was washed with water. Yield 70 mg (62%). The product was identical (IR) with XVIII made by procudure–(a).

c) To a stirred solution of 100 mg (0.375 mmole) of XVII and 32 mg (0.375 mmole) of sodium bicarbonate in 5 ml of water was added a solution of 41 mg (0.26 mmole) of potassium permanganate in 2 ml of water. The reaction mixture was allowed to stand overnight at room temperature and filtered. The cake was washed with a small amount of hot water. The filtrate was combined with the washings and concentrated to 3 ml. The concentrate was adjusted to pH 2.0 with 10% hydrochloric acid give the product. Yield 53 mg (50%). This was identical (IR) with XVIII made procedure–(a).

3-*p*-Chlorophenyl-4-cyano-5-methylisothiazole (XIXb)——A slow stream of chlorine gas was passed through a mixture of 54.6 g (0.27 mole) of VIIa and 13 g (0.057 mole) of antimony trichloride at 120° for 5 hr until the starting material was almost consumed, the progress of the reaction being checked by GLC every 30 minutes near the end of the reaction. The reaction mixture was taken up in 200 ml of chloroform. The solution was washed with 50 ml of 10% hydrochloric acid,then with aqueous sodium bicarbonate, dried with sodium sulfate and evaporated under reduced pressure to afford an oil, which was dissloved in hot ligroin. The solution was treated with decolorizing carbon, filtered with Dicalite and allowed to stand at room temperature to give product, which was recrystallized from ligroin. Yield 17 g (26.6%).

3-*o*-Chlorophenyl-4-cyano-5-methylisothiazole (XIXa)——Evaporation of the filtrate of XIXb to one–quarter volume gave the product, which was recrystallized from ligroin. Yield 4.8 g (7.5%).

3-(2,4-Dichlorophenyl)-4-cyano-5-methylisothiazole (XIXc)——The filtrate of XIXa was evaporated under reduced pressure. The oily product (13.9 g), which was a mixture of a small amount of VIIa, XIXa, XIXb and XIXc, was heated at 120—130°. Chlorine gas was then bubbled into the mixture in the presence of 3 g of antimony trichloride for 5 hr, and then the reaction mixture was dissolved in 50 ml of chloroform. The chloroform solution was washed successively with 20 ml of 20% hydrochloric acid, 20 ml of water and 20 ml of 5% sodium bicarbonate, dried with sodium sulfate and evaporated. The residue was dissolved in hot ligroin, decolorized with carbon, and allowed to stand to give 2.9 g of crude product, which was recrystallized from ligroin and then from ethanol. Yield 2 g.

3-(2,4,5-Trichlorophenyl)-4-cyano-5-methylisothiazole (XIXd)——Uncrystallized residue (6 g) of XIXc was further chlorinated in the manner similar to that in the above experiment, and the product was recrystallized from ethanol. Yield 0.8 g.

3-*p*-Bromophenyl-4-cyano-5-methylisothiazole (XIXe)——A mixture of 10 g (0.05 mole) of VIIa, 16 g (0.1 mole) of bromine and 1 g of iron powder was heated at 110° for 24 hr. The reaction mixture was poured into water and extracted with three 50 ml portions of chloroform . The combined extracts were washed with 10% hydrochloric acid, then with water and dried over anhydrous sodium sulfate. The filtrate was evaporated to give the solid residue, which was recrystallized from benzene. Yield 4.8 g (35%).

3-*p*-Chlorophenyl-4-cyanoisothiazole (XXIb)——Chlorine gas was passed into a mixture of 30 g (0.162 mole) of IV and 4 g (0.018 mole) of antimony trichloride for 4 hr at 120°. The reaction mixture was dissolved in 100 ml of chloroform. The solution was washed successively with 50 ml of 10% hydrochloric acid, 50 ml of water and 50 ml of 5% aqueous sodium bicarbonate, dried with anhydrous sodium sulfate and evaporated under reduced pressure to afford an oily mixture of the chlorinated products (GLC:SE-30, 4 mm, 225 cm;He 42 ml/min; retention time, *o*-Cl 2.45 min, *p*-Cl 3.1 min). The oily mixture was crystallized from

50 ml of toluene to give 9.7 g (28%) of the *para*-isomer as colorless needles, which was collected by filtration. The other isomer remained in the filtrate. The analytical sample was recrystallized from benzene–ligroin.

3-*o*-Chlorophenyl-4-cyanoisothiazole (XXIa)——The filtrate obtained from the above crystallization was evaporated into dryness. The residual oil was distilled under reduced pressure and divided into two fractions. The lower boiling fraction (XXIa rich, by GLC) was again subjected to distillation. The distillate was treated with ether to remove a small amount of the less soluble *para*-isomer, and then crystallized from ligroin to give 3.5 g (10%) of XXIa, which showed a single peak in GLC.

3-*p*-Bromophenyl-4-cyanoisothiazole (XXIc)——A mixture of 10 g (0.054 mole) of IV, 2 g of iron powder and 15 g (0.094 mole) of bromine was heated at 100—120° for 20 hr. The solid reaction mixture was treated with 100 ml of water and extracted with three 100 ml portions of chloroform. The chloroform extract was washed with saturated sodium bicarbonate solution until the washing became neutral, dried with sodium sulfate and evaporated to give a solid, which was recrystallized from alcohol. Yield 5.1 g (35%).

3-Arylisothiazole-4-carboxylic Acids——XI, XXa—e, XXIIa, b and c were prepared from the corresponding 4–carbonitriles by the procedure for preparation of Xa. The yields and properties are shown in Table II.

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