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Studies on Isothiazoles. II.[1] Nitration of 3-Phenylisothiazoles[2]

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Nitration of 4-substituted-3-phenyliosthiazoles (I, II, III, and IV) with fuming nitric acid and sulfuric acid yielded exclusively the corresponding 3-*m*-nitrophenyl derivatives (VI, VII, VIII and IX), while nitration of 3-phenylisothiazole (V) gave 3-*p*-nitrophenylisothiazole (Xa) and 3-*m*-nitrophenylisothiazole (Xb). Reduction of 5-methyl-3-*m*-nitrophenylisothiazole-4-carboxylic acid (IX) afforded the corresponding amino derivative (XII), which was diazotized and subjected to the Sandmeyer Reaction to give the corrsponding 3-*m*-chlorophenyl (XIV) and 3-*m*-bromophenyl(XV) derivatives. Preparation of the 3-*m*-methoxyphenyl derivative (XVII) was also described.

There have been several works published concerning the nitration of 3-phenylisoxazole. Musante[4] reported that 3-phenylisoxazole was nitrated to 3-*p*-nitrophenylisoxazole, while Langella, *et al.*[5] obtained 3-*p*-nitrophenylisoxazole and 3-*m*-nitrophenylisoxazole with mixed nitric and sulfuric acids, and 5-nitro-3-phenylisoxazole with nitric and acetic acids mixture. Caradonna, *et al.*[6] obtained 5-methyl-3-*m*-nitrophenylisoxazole-4-carboxylic acid by nitration of 5-methyl-5-phenylisoxazole-4-carboxylic acid with nitric and sulfuric acids mixture. The purpose of this paper is to report the nitration of 3-phenylisothiazoles which have a sulfur atom in place of oxygen in the heterocyclic ring system.

Among the substrates were 4-bromo-5-methyl-3-phenylisothiazole (I),[7] 4-bromo-3-phenylisothiazole (II),[7] 4-cyano-5-methyl-3-phenylisothiazole (III),[7] 5-methyl-3-phenyl-isothiazole-4-carboxylic acid (IV)[7] and 3-phenylisothiazole (V).[7] Fuming nitric acid and sulfuric acid was employed as a nitrating agent. The reaction was carried out in the cold (*ca.* 0°), and the reaction mixture was stirred for 2 hours at room temperature. Nitration of I gave a mononitro product (VI), mp 122—123°, which was determined to be a *m*-nitrophenyl derivative as discussed below.

I : R_1=Br, R_2=CH_3
II : R_1=Br, R_2=H
III : R_1=CN, R_2=CH_3
IV : R_1=COOH, R_2=CH_3

VI : R_1=Br, R_2=CH_3
VII : R_1=Br, R_2=H
VIII : R_1=CN, R_2=CH_3
IX : R_1=COOH, R_2=CH_3

Chart 1

1) Part I: T. Naito, S. Nakagawa, and K. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **16**, 148 (1968).
2) A part of this work was presented at the 24th General Meeting of the Pharmaceutical Society of Japan (April, 1967, Kyoto).
3) Location: *2-9-3, Shimo-meguro, Meguro-ku, Tokyo.*
4) C. Musante, *Farm. sci. e tec.* (Pavia), **6**, 32 (1951) (*Chem. Abst.*, **45**, 5879*f* (1951)).
5) M.R. Langella and P.R. Finzi, *Chim. Ind* (Milan), **47**, 996 (1965) (*Chem. Abst.*, **63**, 16324*h* (1965)).
6) C. Caradonna and M.L. Stein, *Farmaco.* (Pavia) *Ed. Sci.*, **15**, 647 (1960) (*Chem. Abst.*, **58**, 2441*c* (1963)).
7) T. Naito, S. Nakagawa, and K. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **16**, 148 (1968).

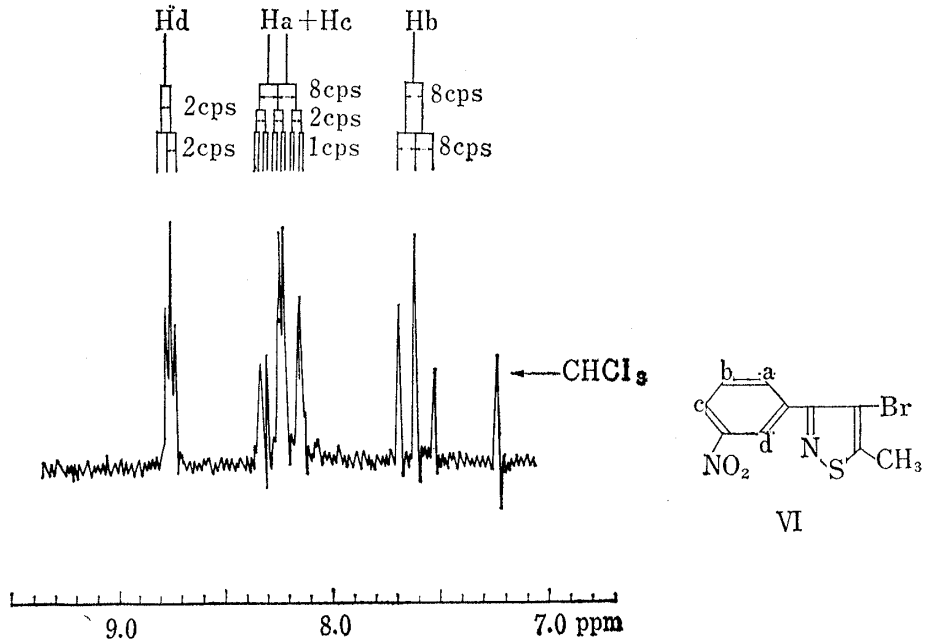
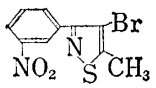
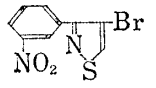
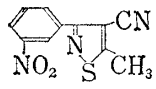
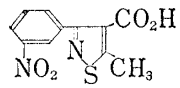
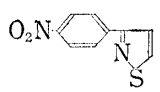
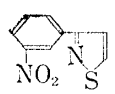


Fig. 1. Ring Proton Signals of 4-Bromo-5-methyl-3-phenylisothiazole (VI)

In the nuclear magnetic resonance (NMR) spectrum[8] of VI (Fig. 1), a methyl singlet appeared at 2.53, and signals of ring protons, H_b, H_a+H_c and H_d (Chart 1), were observed at 7.60 (t), 8.22(m) and 8.74 (t), respectively. The H_d signal shifted to the lowest field by the deshielding effect of both a neighboring nitro group and an isothiazole nucleus, and split into three lines by *meta*-couplings ($J_{ad}=J_{cd}=2$[9]). The H_b signal came at the highest field among the

Table I. 3-(Nitrophenyl)isothiazoles

No.	Compound	Yield (%)	mp (°C)	λ_{max}^{EtOH} mμ (ε)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VI		70	122—123[a]	271 (16500)	$C_{10}H_7O_2N_2BrS$	40.15	2.36	9.37	40.35	2.64	9.24
VII		88	115—116[b]	271 (15100)	$C_9H_5O_2N_2BrS$	37.91	1.77	9.83	37.64	1.59	9.40
VIII		93	138—139[b]	219 (14700) 257 (12300)	$C_{11}H_7O_2N_3S$	53.87	2.88	17.13	54.11	3.02	17.07
IX		80	235—236[c]	260 (18000)	$C_{11}H_8O_4N_2S$	49.99	3.05	10.64	49.68	2.67	10.51
Xa		21	183—186[c]	307 (20400)	$C_9H_6O_2N_2S$	52.42	2.93	13.59	52.40	3.04	13.67
Xb		30	81[b]	271 (22000)	$C_9H_6O_2N_2S$	52.42	2.93	13.59	52.21	2.95	13.64

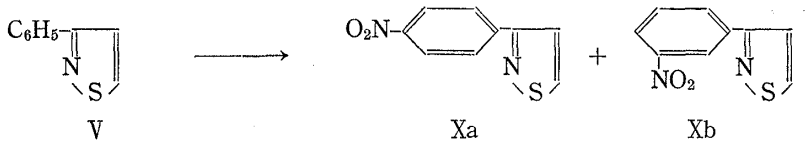
Recrystallization solvent: *a*, ligroin; *b*, benzene; *c*, ethanol

8) All NMR spectra in this paper were recorded on Varian HA-100 spectrometer, and the chemical shifts are represented in ppm from an internal reference, TMS.
9) Apparent coupling constant in cps.

Table II. The NMR Data of 3-*m*-Nitrophenylisothiazoles

Compound	Solvent	Ring protons: chemical shift (ppm) b	a+c	d	coupling constant (cps) *ortho*	*meta*	*para*	Other protons
VI	$CDCl_3$	7.60(t)	8.22(m)	8.74(t)	$J_{ab}=J_{bc}=8$	$J_{ad}=J_{cd}=2$ $J_{ac}=1$	$J_{bd}=0$	5-CH_3 2.53
VII	$CDCl_3$	7.60(t)	8.22(m)	8.74(t)	$J_{ab}=J_{bc}=8$	$J_{ad}=J_{cd}=2$	$J_{bd}=0$	5-H 8.70
VIII	$CDCl_3$	7.65(t)	8.30(m)	8.85(q)	$J_{ab}=J_{bc}=8$	$\left\{\begin{array}{l}J_{ad}=3,\ J_{cd}=2\\ \text{or}\\ J_{ad}=2,\ J_{cd}=3\end{array}\right\}$ $J_{ac}=1$	$J_{bd}=0$	5-CH_3 2.78
IX	$D_2O+K_2CO_3$	7.71(t)	8.06(q) 8.31(q)	8.50(t)	$J_{ab}=J_{bc}=8$	$J_{ad}=J_{cd}$ $J_{ad}=\sim 1$	$J_{bd}=0$	5-CH_3 2.63
Xb*	C_2D_6SO	7.94(t)	8.46(m)	8.96(t)	$J_{ab}=J_{bc}=8$	$J_{ad}=J_{cd}=$ $J_{ac}=\sim 1$	$J_{bd}=0$	4-H 8.28(d) 5-H 9.44(d) $J_{4,5}=4.6$

* measured at 60 Mc.



V Xa Xb

Chart 2

ring proton signals and spin-coupled by *ortho* hydrogens ($J_{ab}=J_{bc}=8$). The signals of the remaining protons, H_a and H_c, adjacent to either nitro group or isothiazole ring, appeared as a multiplet between the H_d and H_b signals. Therefore, VI was determined to be 4-bromo-5-methyl-3-*m*-nitrophenylisothiazole. Nitrations of II, III and IV were carried out in a similar manner to give mono nitro compounds, VII, VIII and IX, respectively. Table I shows the yields and properties of these compounds, and Table II summarizes the NMR data which are indicative of the substitution of nitro group in compounds VII, VIII and IX also to be at the *meta*-position.

Nitration of V, however, gave two kinds of mono nitro compound, Xa and Xb (Chart 2). In the NMR spectrum of Xa, the phenyl ring protons appeared as a singletl at 8.28, and the isothiazole ring protons at 4 and 5-positions gave rise to an AB quartet centered at 8.04 (d) and 9.15 (d), respectively, ($J_{4,5}=5$). Compound Xa was, therefore, determined to be *p*-nitrophenylisothiazole and, incidentally because of the apparent magnetic equivalence of nitro group and isothiazole ring, the phenyl ring protons should have appeared as a singlet. In order to verify this, Xa was reduced with ferrous sulfate and ammonia to the corresponding amino compound (XI) melting at 87—88°. As was expected, the singlet signal of phenyl ring protons of Xa now became a four-proton AB quartet at 6.84 (d) and 7.96 (d), $J_{ab}=9$, in XI. The signal of amino hydrogens appeared at 3.84, and 4-H and 5-H signals at 7.64(d) and 8.78 (d) as a two-proton AB quartet ($J_{4,5}=5$). The ring proton signals of another nitration product, Xb, showed the same pattern as that of other 3-*m*-nitrophenyl compounds, and Xb was determined to be 3-*m*-nitrophenylisothiazole.

Reduction of IX with ferrous sulfate and ammonium hydroxide afforded 3-*m*-aminophenyl-5-methylisothiazole-4-carboxylic acid (XII), which was diazotized with sodium nitrite in a usual manner. The resulting diazotized solution was reacted with cuprous chloride or cuprous bromide to give 3-*m*-chlorophenyl-5-methylisothiazole (XIV) or 3-*m*-bromophenyl-5-methylisothiazole-4-carboxylic acid (XV), respectively. Hydrolysis of the diazotized solution yielded 3-*m*-hydroxyphenyl-5-methylisothiazole-4-carboxylic acid (XVI),

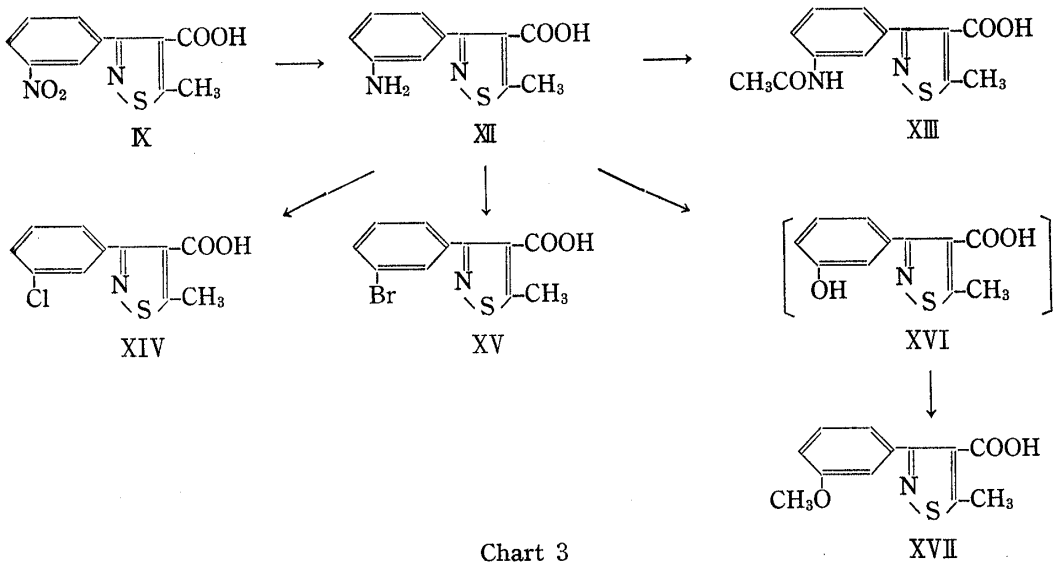


Chart 3

which was methylated with dimethyl sulfate to give 3-*m*-methoxyphenyl-5-methylisothiazole-4-carboxylic acid (XVII).

Experimental

General Procedure for Nitration of 3-Phenylisothiazoles——To a stirred solution of 3-phenylisothiazoles (0.01 mole) in 10—20 ml of conc. sulfuric acid was added dropwise an equimolar amount of fuming nitric acid at 0°. The reaction mitxture was stirred for 2 hr at room temperature and poured onto 100 g of crushed ice. The precipitated product was filtrerd, washed with water, dried and recrystallized from an appropriate solvent.

3-*p*-Aminophenylisothizole (XI)——To a stirred solution of 1.7 g (6 mmole) of ferrous sulfate heptahydrate in 5 ml of water were added portionwise 200 mg (1 mmole) of Xa in 20 ml of hot ethanol and 6 ml of conc. ammonium hydroxide at 80°. The reaction mixture was stirred for 2 hr at 80° and filtered. The filter cake was washed five times with 3 ml portions of hot ethanol. The filtrate and washings were combined and concentrated under reduced pressure to give a heterogeneous solution, The oil was extracted with three 10 ml portions of ether. The ethereal solution was washed with water, dried with sodium sulfate and evaporated to dryness. The residual solid was recrystallized from ligroin to afford 87 mg (49%) of needles, mp 87—88°. *Anal.* Calcd. for $C_9H_8N_2S$: C, 61.33; H, 4.58; N, 15.90. Found: C, 61.37; H, 4.84; N, 15.83. UV λ_{max}^{EtOH} mμ (ε): 294 (17,500), 301 (17,500).

3-*m*-Aminophenyl-5-methylisothiazole-4-carboxylic Acid (XII)——To a stirred solution of 1.0 g (0.0038 mole) of IX in 20 ml of 28% ammonium hydroxide was added in portions 10 g (0.036 mole) of ferrous sulfate heptahydrate at 60°. The reaction mixture was stirred for an hour at 70° and filtered. The filter cake was washed with 5 ml portions of hot water. The filtrate and washings were combined and excess ammonia was removed under reduced pressure. The solution was adjusted to pH 3.0 with dil. hydrochloric acid to give the product, which was filtered, washed with water and recrystallized from methanol. Yield 0.74 g (83%). mp 213—214°. *Anal.* Calcd. for $C_{11}H_{10}O_2N_2S$: C, 56.39; H, 4.30; N, 11.96. Found: C, 56.88; H, 4.13; N, 11.92. UV λ_{max}^{EtOH} mμ (ε): 271 (11,400).

3-*m*-Acetylaminophenyl-5-methylisothiazole-4-carboxylic Acid (XIII)——A mixture of 1.8 g (0.0076 mole) of XII and 20 ml of acetic anhydride was heated at 120° for an hour. The excess acetic anhydride was decomposed with water, and the aqueous mixture was concentrated under reduced pressure. The residual solid was recrystallized from ethanol to give 1.44 g (65%) of plates, mp 263—264°. *Anal.* Calcd. for $C_{13}H_{12}O_3N_2S$: C, 56.51; H, 4.38; N, 10.14. Found: C, 56.80; H, 4.61; N, 10.16. IR cm^{-1}: ν_{NH} 3300, $\nu_{C=O}$ 1680.

3-*m*-Chlorophenyl-5-methylisothiazole-4-carboxylic Acid (XIV)——A suspension of 4.6 g (0.02 mole) of XII in 80 ml of conc. hydrochloric acid was diazotized with 1.6 g (0.023 mole) of sodium nitrite in 6 ml of water at 0—5°. The diazotized solution was slowly added to cuprous chloride in 20 ml of conc. hydrochloric acid at 5°. (The cuprous chloride was prepared from 7.5 g (0.03 mole) of cupric sulfate and 2 g (0.034 mole) of sodium chloride in 25 ml of hot water, and 1.6 g (0.15 mole) of sodium bisulfite and 1 g (0.025 mole) of sodium hydroxide in 12 ml of water.) The reaction mixture was stirred for 3 hr at 5°, stored overnight at room temperature, heated to 60° for half an hour and extracted three times with 50 ml portions of chloroform. The combined chloroform extracts were washed with 50 ml of water and shaken with two 30 ml portions of 5% aq. sodium bicarbonate. The combined aqueous solution was acidified with 20% hydrochloric aicd to give a precipitate, which was filtered, washed with water and recrystallized from water–ethanol (2:1).

Yield 2.3 g (40%). mp 147—148°. *Anal.* Calcd. for $C_{11}H_8O_2NClS$: C, 52.07; H, 3.18; N, 5.52. Found: C, 52.41; H, 3.47; N, 5.69. UV λ_{max}^{EtOH} mμ (ε): 261 (11,000). IR cm^{-1}: $\nu_{C=O}$ 1720.

3-*m*-Bromophenyl-5-methylisothiazole-4-carboxylic Acid (XV)——A solution of 3.8 g (0.015 mole) of XII in 40 ml of 48% hydrobromic acid was diazotized with 1.05 g (0.015 mole) of sodium nitrite in 4 ml of water at 0—5°. The diazotized solution was added dropwise at 0° to a stirred solution of cuprous bromide (prepared from 7.5 g (0.03 mole) of copper sulfate and 4.5 g (0.043 mole) of sodium bromide in 12 ml of hot water and 1.9 g (0.015 mole) of sodium bisulfite) in 20 ml of 48% hydrobromic acid. The reaction mixture was stirred for 3 hr at 0—5°, overnight at room temperature and for half an hour at 60°, then diluted with an equal volume of water and shaken with two 50 ml portions of chloroform. The combined chloroform extracts were washed with water and shaken with 2 g of sodium bicarbonate in 50 ml of water. The water layer was acidified with 20% hydrochloric acid to afford the product, which was recrystallized from benzene–ligroin. Yield 3.0 g (68%). mp 132—133°. *Anal.* Calcd. for $C_{11}H_8NBrS$: C, 44.31; H, 2.71; N, 4.70. Found: C, 44.68; H, 3.06; N, 4.67. UV λ_{max}^{EtOH} mμ (ε): 262 (9,800). IR cm^{-1}: $\nu_{C=O}$ 1690.

3-*m*-Methoxyphenyl-5-methylisothiazole-4-carboxylic Acid (XVII)——A solution of 2.3 g (0.01 mole) of XII in 30 ml of 50% sulfuric acid was diazotized with 0.69 g (0.01 mole) of sodium nitrite in 5 ml of water at 0—5°. The diazotized solution was slowly added to 50 ml of stirred 50% sulfuric acid at 70°. The reaction mixture was stirred for an hour at 70°, coloed to 5° and adjusted to pH 2.0 with 40% sodium hydroxide to afford the intermediate (XVI) 1.6 g (68%). To a stirred solution of 1.6 g (0.0069 mole) of XVI and 0.92 g (0.023 mole) of sodium hydroxide in 20 ml of water was added dropwise 1.77 g (0.014 mole) of dimethyl sulfate at room temperature. The reaction mixture was stirred for 2 hr at room temperature, for an hour at 70° and then acidified with 20% hydrochloric acid to give viscous precipitate, which was recrystallized from water–ethanol (1:1). Yield 0.75 g (43%). mp 140—141°. *Anal.* Calcd. for $C_{12}H_{11}O_3NS$: C, 57.81; H, 4.45; N, 5.62. Found: C, 57.80; H, 4.84; N, 6.04. UV λ_{max}^{EtOH} mμ (ε): 264 (9,500). IR cm^{-1}: $\nu_{C=O}$ 1710.

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