Aromatic Substitution of 4-Phenylisothiazole

Joseph H. Finley and Gert P. Volpp

FMC Corporation, Central Research Department

Aromatic substitutions on 4-phenylisothiazole by nitric acid, halogens, chlorosulfonic acid and acetic anhydride take place under relatively mild conditions to give predominantly *para* and *ortho* substitution on the benzene ring. By contrast, the 3-isothiazolyl group has been shown to be *meta* directing. Several derivatives of 4-phenylisothiazole are described.

INTRODUCTION

Mononuclear isothiazoles were first prepared by Adams and Slack (1a,b) in 1956. A variety of substituted isothiazoles including arylisothiazoles have been synthesized by catalytic vapor phase reactions of olefins, ammonia and sulfur dioxide (2,3). In this way, 4-phenylisothiazole could be prepared from α-methylstyrene; a mixture of 3- and 5-phenylisothiazole was obtained from β-methylstyrene.

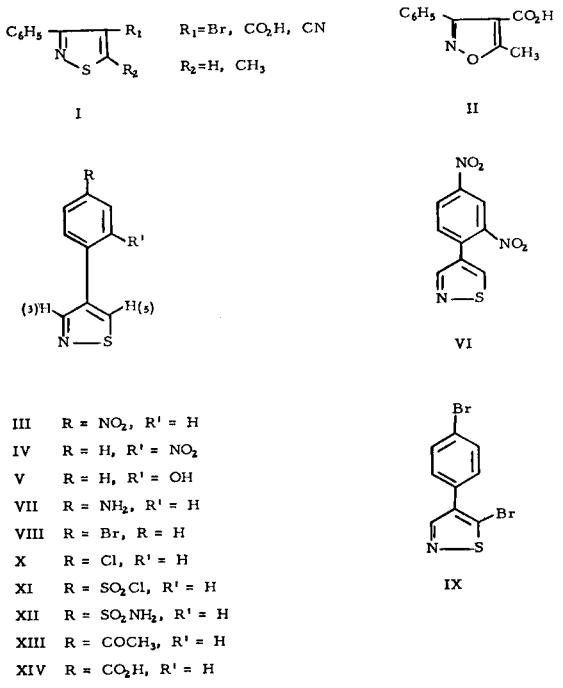
No systematic study of aromatic substitution on phenylisothiazoles has been carried out to date (4). Naito and co-workers (5) studied the nitration of 3-phenylisothiazoles (I) in which the 4-position of the isothiazole ring was blocked by substitution. The reaction was conducted at low temperatures with fuming acid and yielded 3-(*m*-nitrophenylisothiazoles as major products. Caradonna and coworkers (6a) obtained *meta* substitution on nitrating a similarly substituted 3-phenylisoxazole (II). However, Lynch (6b) obtained 5-(*p*-nitrophenyl)isoxazole by nitration of 5-phenylisoxazole.

The present studies were directed toward the aromatic substitution reactions of 4-phenylisothiazole. Of the three possible sigma intermediates which can be considered for electrophilic substitutions taking place in isothiazole, it is easily seen that substitution on the 4-position is of lowest energy. Therefore, if this position is phenyl substituted, it is expected that a vinylogous effect can operate and substitution of 4-phenylisothiazole will be directed to the *ortho* and *para* positions, and will take place under milder conditions than with 3-phenylisothiazole.

RESULTS AND DISCUSSION

At 0°, 4-phenylisothiazole reacted with concentrated nitric acid in sulfuric acid. The major product (70-85% by glpc, 50-58% isolated) was 4-(*p*-nitrophenyl)isothiazole (III). Its proton nmr spectrum (Table I) contained the AA'BB' pattern characteristic of *p*-disubstituted benzene derivatives. Singlet absorptions for the isothiazole H-3 and H-5 protons were found at lower field. Assignment of the signals at 9.16 ppm and 8.96 ppm in DMSO-d_6 and deuteriochloroform, respectively, to H-3 was based on their relative broadening due to quadrupole coupling with the adjacent nitrogen.

In one reaction, a small quantity (16%) of 4-(*o*-nitrophenyl)isothiazole (IV) was isolated after removal of the *para* isomer by repeated recrystallizations. Both the H-3 and H-5 signals in IV occur at much higher field than those of III. In deuteriochloroform these absorptions are found at *ca.* 0.1 ppm higher field than those of 4-phenylisothiazole despite the substitution of the aryl group in IV with an electron withdrawing group. This shielding by the *ortho* nitro group is attributed to the close proximity of the isothiazole hydrogens to the negative charge on oxygen



of the nitro group. The isothiazole hydrogens in 4-(*o*-hydroxyphenyl)isothiazole (V) have chemical shifts comparable to the *o*-nitrophenylisothiazole (IV) which is indicative of a similar shielding effect by the hydroxy

TABLE I

Nmr Data of Various 4-Phenylisothiazoles (a)

Compound	R	R′	Aryl Protons	H_5	H_3	Solvent	Other Absorptions ppm
4-phenylisothiazole	H	H	7.2-7.8 (m)	8.76	8.60	$CDCl_3$	
III	NO_2	H	7.86 (d); 8.30 (d)	8.86	8.96	$CDCl_3$	
III	NO_2	H	8.1 (d); 8.4 (d)	9.66	9.16	DMSO-d_6	
IV	H	NO_2	7.5-7.92 (m)	8.66	8.49	$CDCl_3$	
IV	H	NO_2	7.4-8.0 (m)	9.16	8.76	DMSO-d_6	
V	H	OH	7.05-7.63 (m)	9.18	8.94	DMSO-d_6	9.94 (s) (OH)
VI	NO_2	NO_2	7.75 (d); 8.56 (q); 8.8 (s)	8.78	8.56	$CDCl_3$	
VI	NO_2	NO_2	7.98 (d); 8.56 (q); 8.87 (s)	9.32	8.74	DMSO-d_6	
VII	NH_2	H	7.36 (d); 6.72 (d)	8.50	8.72	$CDCl_3$	3.56 (s) (NH_2)
VIII	Br	H	7.98 (s)	9.56	9.04	DMSO-d_6	
IX	Br	H	7.40 (d); 7.62 (d)	---	8.48	$CDCl_3$	
X	Cl	H	7.44 (d); 7.63 (d)	8.74 (b)	8.80 (b)	$CDCl_3$	
XI	SO_2Cl	H	7.88 (d); 8.20 (d)	8.90	8.96	$CDCl_3$	
XII	SO_2NH_2	H	7.98 (s)	9.56	9.04	DMSO-d_6	7.42 (s) (NH_2)
XIII	$COCH_3$	H	7.69 (d); 8.08 (d)	8.87	8.87	$CDCl_3$	2.12 (s) (CH_3)
XIV	CO_2H	H	8.0 (s)	9.6	9.14	DMSO-d_6	CO_2H not visible

(a) Chemical shifts in ppm downfield from tetramethylsilane as internal standard. (b) Assignment by quadrupole broadening is uncertain and was not verified by solvent-shift study.

(d) apparent doublet (m) multiplet (q) apparent quartet (s) apparent singlet

group on both the 3- and 5-hydrogens. If resonance charge delocalization was solely responsible for the effect, only H-5 in V would be expected to be at higher field.

The broadening of the H-3 signal in IV due to quadrupole coupling with the adjacent ring nitrogen was not very distinct and the assignment doubtful. Assignment of the signals could be made by determining the solvent shift in going from deuteriochloroform to DMSO-d_6. The downfield shift of *ca.* 0.5 to 0.8 ppm for H-5 and 0.2 to 0.3 ppm for H-3 in 4-(*p*-nitrophenyl)isothiazole (III), for which the peak assignment seemed secure, was used to correlate the observed absorptions with H-3 and H-5 of IV.

Nitration of a mixture of III and IV with concentrated nitric acid at 60° gave as the major product 4-(2,4-dinitrophenyl)isothiazole (VI). The structure assignment was based on elemental analysis and the proton nmr spectrum (Table I) which is consistent in all respects with that expected for VI. The isothiazole H-3 and H-5 of VI were found to absorb at 8.74 ppm and 9.32 ppm respectively, in DMSO-d_6. These assignments which are based on the observed solvent shift as discussed for IV are close to those found for the isothiazole protons of 4-(*o*-nitrophenyl)-isothiazole (IV) and further illustrate the shielding effect of *ortho* nitro substituents in IV and VI.

Further reactions were carried out on 4-(*p*-nitrophenyl)-isothiazole. Reduction with stannous chloride and hydrochloric acid gave 4-(*p*-aminophenyl)isothiazole (VII). The diazonium salt of VII reacted with copper(I) bromide to give a dark red insoluble complex to which no definite structural assignment could be made. The expected Sandmeyer product 4-(*p*-bromophenyl)isothiazole (VIII) could be set free by warming the complex with dilute nitric acid followed by adjustment of the solution to *p*H 12 with ammonium hydroxide.

Another route to VIII was found in brominating the complex of 4-phenylisothiazole and copper(I) bromide with excess bromine in acetic acid at room temperature. Treatment of the brominated complex with nitric acid followed by ammonium hydroxide gave, in addition to the blue copper tetraamine complex, a mixture of bromophenylisothiazoles containing 83% (by glpc) of 4-(*p*-bromophenyl)isothiazole (VIII). The AA′BB′ pattern in the nmr spectrum of VIII appeared as a broad singlet (Table I) indicating that bromine and 4-isothiazolyl have similar

chemical shifts.

While bromination of the copper complex is a good procedure to obtain VIII in relatively high yield, the bromination does not depend on the presence of copper; 4-phenylisothiazole reacts with excess bromine under conditions similar to those used to brominate the complex. In glacial acetic acid containing 5% water the major product was 4-(*p*-bromophenyl)isothiazole (VIII) (> 85% yield by glpc). Bromination in glacial acetic acid gave 4-(*p*-bromophenyl)-5-bromoisothiazole (IX) as a second product in 20% yield. Substitution by the second bromine atom on the isothiazole nucleus rather than on phenyl was deduced from the nmr spectrum of IX which contained only one broadened H-3 signal in the downfield region at 8.48 ppm. The phenyl protons appeared as two doublets centered at 7.40 and 7.62 ppm. Integration of the peak areas showed the expected 4:1 ratio of phenyl:isothiazolyl hydrogens. It is possible that formation of significant amounts of IX was due to the greater solubility of initially formed VIII in glacial *versus* moist acetic acid.

Synthesis of 4-(*p*-chlorophenyl)isothiazole (X) was carried out by treating the diazonium salt of 4-(*p*-aminophenyl)isothiazole (VII) with copper(I) chloride. The metal complex formed initially was decomposed to X by treatment with nitric acid followed by ammonium hydroxide.

Further aromatic substitution reaction on 4-phenylisothiazole gave isolable *p*-substituted products. For example, chlorosulfonation at 80°, gave 4-(isothiazol-4-yl)benzenesulfonyl chloride (XI) as the major product (57% isolated). The acid chloride XI was converted to the sulfonamide XII with ammonia gas in benzene solution. Acylation of 4-phenylisothiazole with acetic anhydride in the presence of aluminum chloride at 100° led to a mixture of *p*-(isothiazol-4-yl)acetophenone XIII (75%), 4-phenylisothiazole (20%) and 5% of an unknown. The ketone XIII was isolated in 49% yield. It was converted by the haloform reaction to *p*-(isothiazol-4-yl)benzoic acid (XIV).

EXPERIMENTAL

Nuclear magnetic resonance (nmr) spectra were recorded on a Varian Model A-60 spectrometer. Values are reported in part-per-million (ppm) versus internal TMS. Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrometer. Ultraviolet spectra were recorded on a Perkin-Elmer Model 202 spectrometer. All reported melting points were taken in capillaries in a Mettler FP-1 melting point apparatus and are uncorrected.

4-(*p*-Nitrophenyl)isothiazole (III).

To a chilled solution containing 200 ml. of concentrated sulfuric acid and 20 g. (0.373 mole) of 4-phenylisothiazole, a solution containing 25 ml. (0.39 mole) of concentrated nitric acid in 200 ml. of concentrated sulfuric acid was added dropwise with stirring. After *ca.* two hours, the reaction mixture was poured into 2 l. of ice water and was brought to *p*H 12 by addition of dilute ammonium hydroxide. The solid was collected by filtration, dried and was then dissolved in 900 ml. of boiling benzene and filtered while hot. Evaporation of the filtrate gave 70 g. of a yellow crystalline product. Glpc analysis (5 ft. x 1/4 in. SE-30, 200°) showed two major components: 4-(*o*-nitrophenyl)isothiazole (IV) and 4-(*p*-nitrophenyl)isothiazole (III) at 1.8 and 3.0 minutes. Their relative ratios varied from 30:70 to 12:88 in different experiments.

Pure III (m.p. 179-180°) was obtained by recrystallization from 500 ml. of benzene and 200 ml. of cyclohexane in 50-58% yield. Ir (potassium bromide) 6.62, 7.5 μm (NO_2); uv max (ethanol) 204 nm (ε, 22,000), 219 nm (ε, 12,100), 307 nm (ε, 16,700).

Anal. Calcd. for $C_9H_6N_2O_2S$: C, 52.43; H, 2.93; N, 13.59. Found: C, 52.49; H, 2.91; N, 13.61.

4-(*o*-Nitrophenyl)isothiazole (IV).

After removal of III from the above mixture by recrystallizations from benzene-cyclohexane, IV was isolated (*ca.* 90% pure) in 16% yield, m.p. 59.5-62.5°; ir (potassium bromide) 6.6, 7.5 mμ (NO_2).

Anal. Calcd. for $C_9H_6N_2O_2S$: C, 52.43; H, 2.93; N, 13.59. Found: C, 52.10; H, 3.03; N, 13.32.

4-(2,4-Dinitrophenyl)isothiazole (VI).

To 12.1 g. (0.059 mole) of the above crude mononitrated mixture and 100 ml. of concentrated sulfuric acid, a solution containing 3.7 g. (0.059 mole) of concentrated nitric acid in 32 ml. of sulfuric acid was added while stirring at 0°. After addition was complete, the mixture was warmed to 60-70° for 3.5 hours and then worked up as described for III. Recrystallization from benzene afforded VI (66%), m.p. 147.5-148.5°; ir (potassium bromide) 6.6, 7.5 μm (NO_2); uv max (ethanol) 214.5 nm (ε, 14,480), 240.5 nm (ε, 13,900), 290 nm (ε, 10,300).

Anal. Calcd. for $C_9H_5N_3O_4S$: C, 43.04; H, 2.01; N, 16.73. Found: C, 42.80; H, 1.89; N, 16.57.

4-(*p*-Aminophenyl)isothiazole (VII).

To 20.0 g. (0.097 mole) of III in 900 ml. of methanol, a solution containing 87.5 g. (0.34 mole) of stannous chloride dihydrate in 175 ml. of concentrated hydrochloric acid was added dropwise. The reaction mixture was warmed to 60-70° with stirring until all of the solid material was dissolved (*ca.* 0.5 hour). Methanol was then removed *in vacuo*. The slurry was poured into ice, brought to *p*H 12 with 20% sodium hydroxide solution. The crude amine VII was removed by filtration, dried and recrystallized from benzene-cyclohexane. The product was obtained as an orange solid (76% yield), m.p. 138.7-139.7°; ir (potassium bromide) 2.9-3.3 μm (NH_2); uv max (ethanol) 226 nm (ε, 11,600), 266 nm (ε, 14,220), 287 nm (ε, 12,390).

Anal. Calcd. for $C_9H_8N_2S$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.50; H, 4.41; N, 15.51.

4-(*o*-Hydroxyphenyl)isothiazole (V).

To a stirred slurry of 6.1 g. (0.041 mole) of 4-(*o*-nitrophenyl)-isothiazole (IV) containing *ca.* 10% of the *p*-isomer III in 280 ml. of methanol, a solution of stannous chloride dihydrate (26.6 g., 0.011 mole) in 53 ml. of concentrated hydrochloric acid was added dropwise. The mixture was warmed to 75° for 0.25 hour. Methanol was removed *in vacuo*. The residual slurry was adjusted to *p*H 12 with 20% sodium hydroxide solution and extracted with ether. The combined ethereal extracts were washed with water and dried. Evaporation *in vacuo* gave 4.5 g. (61%) of crude 4-(*o*-aminophenyl)isothiazole; ir (chloroform) 2.8 μm (N-H). A solution of 1.8 g. (0.027 mole) of sodium nitrite in 50 ml. of water was added dropwise to an ice cold solution of amine in 200 ml. of water and

5 ml. of concentrated sulfuric acid. An additional 80 ml. of concentrated sulfuric acid was added and the mixture was heated to 80°. After the diazonium salt was completely hydrolyzed, the mixture was poured into ice and extracted with ether. Evaporation of the ether left a brown oil, which was chromatographed on an 85 x 30 mm alumina column using benzene followed by solutions of benzene containing more polar solvents. Fraction 30 (10% methanol: 90% benzene v/v) contained a solid (1.36 g.) which on recrystallization from methanol gave 0.4 g. (14%) of pure V, m.p. 136-138°; ir (potassium bromide) 3.3 μm (OH).

Anal. Calcd. for C_9H_7NOS: C, 61.01; H, 3.98; N, 7.91. Found: C, 60.81; H, 3.89; N, 7.77.

4-(*p*-Bromophenyl)isothiazole (VIII).

Compound VIII was synthesized by a modified version of the Sandmeyer reaction (Method A), by bromination of a copper complex of 4-phenylisothiazole (Method B) or by direct bromination of 4-phenylisothiazole (Method C).

Method A.

4-(*p*-Aminophenyl)isothiazole (7.0 g., 0.04 mole) in 35 ml. of hydrobromic acid was diazotized at 0° by dropwise addition of a solution of 2.9 g. (0.042 mole) of sodium nitrite in 25 ml. of water. The diazonium salt was rapidly added under stirring to a fresh solution of copper(I) bromide (7) at 85°, followed by addition of 10 ml. of hydrobromic acid and stirring at 75° for 0.25 hour. After cooling, the red solid was filtered, washed with water and dried giving 12.0 g. of the copper(I)-4-(*p*-bromophenyl)isothiazole complex. This material was insoluble in a variety of organic solvents and water. It was found to contain 20.4% copper and 33.9% carbon. Treatment of the complex with ammonium hydroxide failed to give any reaction. It was warmed to 50° with 1:1 nitric acid and then treated with ammonium hydroxide. A deep blue solution of copper(II) tetraamine and a precipitate resulted. The latter was filtered and purified by distribution between water and chloroform. Evaporation of the dried chloroform left crude VIII, which was sublimed at 90-120°/< 10 mm (31% overall yield). Analytical data are reported under Method B.

Method B.

Addition of 10 g. (0.062 mole) of 4-phenylisothiazole in 50 ml. of acetone to a freshly prepared copper(I) bromide solution (7) gave an insoluble copper(I)-4-phenylisothiazole complex which after filtration and drying was dissolved in 50 ml. of glacial acetic acid. Excess bromine (93.5 g., 0.585 mole) was added dropwise. After one hour, the mixture was diluted with water and excess bromine was reduced with sodium thiosulfate. The complex was worked up as above. Glpc analysis of the resulting oil (20% SE 30, 6 ft. x 1/4 in., 230°, He=60 ml/min) showed that 4-(*p*-bromophenyl)isothiazole (VIII) comprised *ca.* 83% of the mixture. In addition, two other products and *ca.* 11% unreacted 4-phenylisothiazole were present.

From the oily crude product, VIII was sublimed at 130° (<10 mm) and recrystallized from chloroform-cyclohexane giving 3.0 g. (22%) of pure VIII, m.p. 94-96.5°; uv max (ethanol) 206 nm (ε, 22,650), 248 nm (ε, 15,250), 270 nm (ε, 16,350).

Anal. Calcd. for C_9H_6BrNS: C, 45.02; H, 2.52; N, 5.82. Found: C, 45.30; H, 2.48; N, 5.95.

Method C.

To a solution containing 20 ml. of acetic acid, 1 ml. of water and 1.45 g. (0.009 mole) of 4-phenylisothiazole, 5.8 g. (0.072 mole) of bromine was added at room temperature. After 1.5 hours the mixture was diluted with 20 ml. of water. The precipitate was filtered, washed with water and dried. It was dissolved in 60 ml. of hot benzene-cyclohexane (5:1 v/v) and filtered. Evaporation of the filtrate gave 1.97 g. of solids, m.p. 65-75°. Recrystallization (chloroform-cyclohexane) gave 0.58 g. (27%) VIII, m.p. 80-84°. The proton nmr and ir spectra of this material were identical with those obtained from pure VIII (Method B).

Glpc analysis of the chloroform-cyclohexane mother liquor from the recrystallization showed the presence of additional VIII (86%), two minor products (11.4%) and unreacted 4-phenylisothiazole (3%).

4-(*p*-Bromophenyl)-5-bromoisothiazole (IX).

To a solution of 4-phenylisothiazole (5.0 g., 0.031 mole) in 70 ml. of glacial acetic acid, bromine (34.6 g., 0.31 mole) was added dropwise at 25° and the mixture stirred for 1.5 hours. Addition of the mixture to water gave a solid which was filtered and washed. Its glpc chromatogram (5 ft. x 1/8 in. Carbowax 20 M, 250°) showed VIII (59%), three uncharacterized materials (37.2%), and 4-phenylisothiazole (4.1%). On recrystallization from chloroform-cyclohexane, 2.0 g. (20%) of 4-(*p*-bromophenyl)-5-bromoisothiazole (IX), m.p. 136-139° was isolated.

Anal. Calcd. for $C_9H_5Br_2NS$: C, 33.78; H, 1.58; N, 4.39. Found: C, 33.48; H, 1.68; N, 4.15.

4-(*p*-Chlorophenyl)isothiazole (X).

A solution of 4-(*p*-aminophenyl)isothiazole (VII, 7.0 g., 0.04 mole) in 35 ml. of concentrated hydrochloric acid was diazotized by dropwise addition of a solution of 2.9 g. (0.04 mole) of sodium nitrite in 25 ml. of water. The diazonium salt was added to a freshly prepared copper(I) chloride solution (8) at 80° followed by addition of 45 ml. of concentrated hydrochloric acid and stirring at 70-80° for 0.25 hour. The insoluble copper(I) complex was filtered, dried, treated with nitric acid and ammonia, and worked up with chloroform as described above. A chloroform solution of the oily residue (2.7 g.) was passed over a 6 x 1 in. alumina column to remove impurities. Crude X (1.63 g.) was obtained as a yellow solid, m.p. 71-75.8°. Sublimation at 80-120° (<10 mm) gave 1.4 g. (18%) of X, m.p. 74-76.5°.

Anal. Calcd. for C_9H_6ClNS: C, 55.26; H, 3.09; N, 7.15. Found: C, 55.14; H, 3.41; N, 6.91.

4-(Isothiazol-4-yl)benzenesulfonyl Chloride (XI).

4-Phenylisothiazole (5 g., 0.031 mole) was added slowly with cooling to 18 g. (0.155 mole) of chlorosulfonic acid. The mixture was heated at 90° for four hours and poured into ice. A white solid was collected and dried. Tlc analysis (90% cyclohexane: 10% ethanol v/v) showed the presence of a small quantity of 4-phenylisothiazole (R_f 0.5) and one additional material (R_f 0.1). The solid was recrystallized from chloroform-cyclohexane giving 4.6 g. (57%) of XI, m.p. 139-141.5°.

Anal. Calcd. for $C_9H_6ClNO_2S_2$: C, 41.63; H, 2.32; N, 5.40. Found: C, 41.63; H, 2.24; N, 5.28.

4-(Isothiazol-4-yl)benzenesulfonamide (XII).

To a solution of 5.0 g. (0.019 mole) of XI in 100 ml. of benzene, ammonia gas was added at 60° for four hours. After this time, tlc analysis (90% benzene: 10% ethanol v/v) showed that XI (R_f 0.8) was almost completely reacted. The solid was filtered, washed with warm water and dried *in vacuo* at 60°. Recrystallization (acetone-cyclohexane) gave 2.9 g. (63%) of XII, m.p. 163.5-166.5°. One further recrystallization gave pure XII, m.p. 164.5-166.5°; ir (potassium bromide) 3.0-3.3 μm (amine N-H).

Anal. Calcd. for $C_9H_8N_2O_2S_2$: C, 45.01; H, 3.36; N, 11.67. Found: C, 45.37; H, 3.47; N, 11.34.

p-(Isothiazol-4-yl)acetophenone (XIII).

A mixture of 94 g. (0.70 mole) of anhydrous aluminum chloride, 25.2 g. (0.25 mole) of acetic anhydride and 4-phenylisothiazole (20.0 g., 0.124 mole) was prepared at low temperature and heated at 100° for four hours. After this time, starting material was shown by tlc (benzene solvent) to be absent. The mixture was poured into ice water containing 200 ml. of concentrated hydrochloric acid. The solution was extracted with chloroform. The combined extracts were washed with dilute sodium hydroxide and water and dried (sodium sulfate). The residue after evaporation was crystallized from chloroform-cyclohexane giving 12.2 g. (49%) of XIII, m.p. 90-94°. One further recrystallization afforded pure XII, m.p. 90-92°; ir (potassium bromide) 6.08 μm (C = O); uv max (ethanol) 210 nm (ε, 16,200), 285 nm (ε, 16,750).

Anal. Calcd. for $C_{11}H_9NOS$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.30; H, 4.52; N, 6.86.

In another synthesis of XIII, the crude product obtained by chloroform extraction was analyzed by glpc (5 ft. x 1/4 in., 20% SE 30, 190°). The mixture consisted of 20% unreacted 4-phenylisothiazole, 75% XIII (enrichment) and 5% of an uncharacterized product.

p-(Isothiazol-4-yl)benzoic Acid (XIV).

To 40 ml. of a sodium hypochlorite solution (1.58*M*) (9) 4.0 g. (0.02 mole) of XIII was added. The suspension was warmed to 70° for one hour during which time the solid material dissolved and a new substance was precipitated. A small portion of the reaction mixture (treated with sodium bisulfite and hydrochloric acid) was analyzed by tlc (20% ethanol: 80% benzene v/v) and gave a single spot (R_f 0.2). No starting material (R_f for XIII= 0.8) was detected.

After cooling to 25°, 5.0 g. of solid sodium bisulfite was added to the reaction mixture to destroy excess sodium hypochlorite. After acidification with concentrated hydrochloric acid the crude product was filtered and dried *in vacuo* at 80°. Recrystallization from ethanol gave pure XIV (60%) which sublimed at 282-284°; ir (potassium bromide) 3.0-3.5 (OH), 5.95 μm (C = O).

Anal. Calcd. for $C_{10}H_7NO_2S$: C, 58.54; H, 3.44; N, 6.83. Found: C, 58.80; H, 3.44; N, 6.63.

REFERENCES

(1a) A. Adams and R. Slack, *Chem. Ind.*, 1232 (1956). (b) A. Adams and R. Slack, *J. Chem. Soc.*, 3061 (1959).

(2) F. Hübenett, F. H. Flock and H. Hofmann, *Angew Chem.*, 74, 674 (1962).

(3) H. Hübenett and H. Hofmann, *ibid.*, 75, 420 (1963).

(4) See reviews by H. Hübenett and F. H. Flock, *Angew Chem.*, 75, 1189 (1963); R. Slack and K. R. H. Wooldridge, *Adv. of Heterocyclic Chemistry*, 4, 107 (1965).

(5) T. Naito, S. Nakagawa and K. Takahashi, *Chem. Pharm. Bull.*, (Tokyo), 16, (1), 160 (1968).

(6a) C. Caradonna and M. L. Stein, *Farmaco Ed. Sci.*, 15, 647 (1960). (b) B. M. Lynch and L. Shiu, *Can. J. Chem.*, 43, 2117 (1965).

(7) "Organic Synthesis," Coll. Vol. II, 6th Printing, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 132.

(8) *Ibid.*, p. 131.

(9) "Organic Synthesis," Coll. Vol. I, 7th Printing, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 309.

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