# Synthesis of 2-Chloro-2-imidazoline and its Reactivity with Aromatic Amines, Phenols, and Thiophenols

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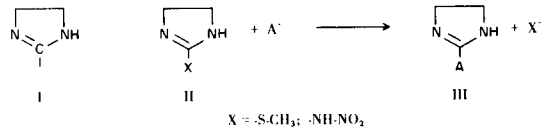
2-Chloro-2-imidazoline has been synthesized by the reaction of ethylene-thiourea with chlorine in aqueous solution at 50°. The compound was reacted with aromatic amines, phenols, and thiophenols.

Several syntheses to introduce the 2-imidazolinyl group (I) in organic molecules are reported in the literature: a) ring cyclization of ethylenediamine (1,2) or substituted ethylenediamines (3,4,5); b) nucleophilic displacement reaction on 2-substituted imidazolines (II) (6,10) (Scheme I). None of these methods allow a

SCHEME I

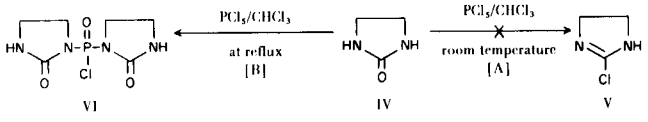


general approach. Nucleophilic displacements should be easier when X = Cl (Scheme I) since chlorine is a better leaving group.

In a Japanese patent (11), K. Suzuki described the synthesis of 2-chloro-2-imidazoline (V) according to Scheme IIA; analysis, m.p. and other physico-chemical data were not given. Suzuki reported that the compound reacted with benzyl chloride in the presence of sodium, to give 2-benzylimidazoline.

Najer *et al.* (12), repeating Suzuki's reaction (Scheme IIB) isolated as the main product, compound VI, instead of V, and found that it gave, by reaction with aromatic amines, 2-arylaminoimidazolines.

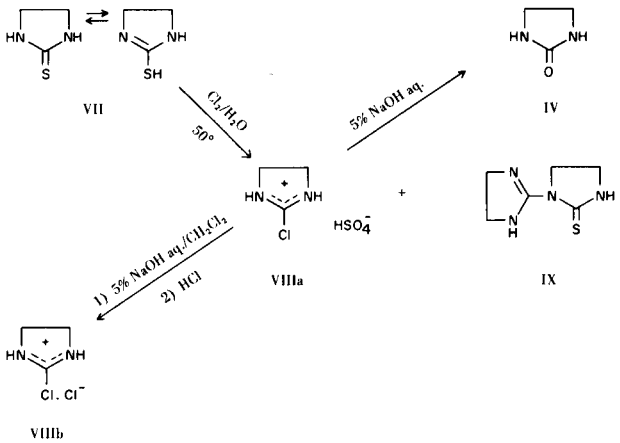
SCHEME II



Repeating the Suzuki's reaction, we have confirmed these results. The desired 2-chloro-2-imidazoline was obtained by chlorination of ethylenethiourea (VII) in water solution, according to the well known procedure for displacement of mercapto groups by chlorine (13,14,15) (Scheme III). With our experimental conditions, we obtained a mixture of the sulfate and hydrochloride salts of the 2-chloro-2-imidazoline. The sulfate was isolated in good yield by treating the mixture with concentrated sulfuric acid, removing "*in vacuo*" the hydrogen chloride evolved and pouring the solution into acetone.

We have occasionally isolated in low yield the Jaffé's base (IX) (9). The 2-chloro-2-imidazoline sulfate (VIIIa) can be recrystallized from methanol, but it decomposes after long heating in this solvent. The rate of hydrolysis of compound VIIIa to imidazolidin-2-one (IV) in 5% sodium hydroxide solution was studied by titration of the chloride ion. After 50 hours at room temperature, only 6% had hydrolyzed, while at 90° after one hour, 53% had hydrolyzed. The potentiometric titration showed two end points ($pK_{a_1}$ = 2.65; $pK_{a_2}$ = 6.4 neutral equiv. 202), in agreement with the proposed hemisulfate VIIIa.

SCHEME III

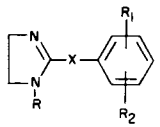


Compound VIIIa like all 2-substituted-2-imidazolines is more stable as a salt, than as the free base.

A solution of the free base X was obtained by treatment of the hemisulfate VIIIa with a cold 5% sodium hydroxide solution and extraction with methylene chloride. The 2-chloro-2-imidazoline base (X) could not be characterized

TABLE I

2-Substituted-2-imidazolines



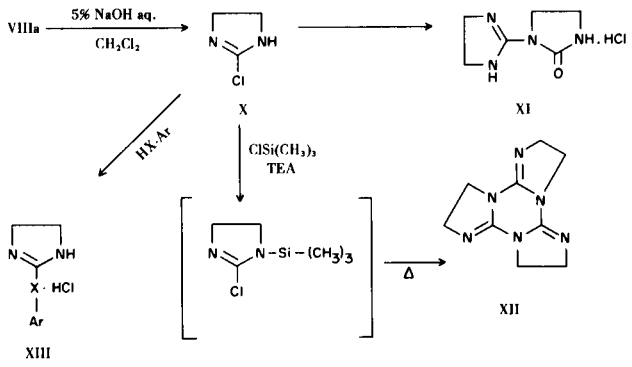
| Compound Number | X | R | $R_1$ | $R_2$ | Yield Purified % | M.p., °C | Purificn. Solvent | Method |
|---|---|---|---|---|---|---|---|---|
| **1** | NH | H | H | H | 67 | 214 (a) | EtOH | A |
| **2** | NH | H | H | 4-$CH_3$ | 50 | 125-127 (b) | $C_6H_6$/ciclohex | A |
| **3** | S | H | H | H | 15 | 91-92 | isoPrOH | C |
| **4** | S | $C_3H_5N_2$ (d) | H | H | (e) | 142-143 | isoPrOH | D |
| **5** | S | H | 2-Cl | 6-Cl | 47 | 218-219 | EtOH/ether | B |
| **6** | S | $C_3H_5N_2$ (d) | 2-Cl | 6-Cl | (e) | 175 | non cryst. | D |
| **7** | O | H | 2-Cl | 6-Cl | 45 | 192-194 | EtOH/ether | B |
| **8** | O | H | 2-$OCH_3$ | 6-$OCH_3$ | 30 | 191-193 | isoPrOH/ether | B |
| **9** | O | H | 2,3-CH=CH-CH=CH (f) | | 24 | 192-195 | isoPrOH | B |
| **10** | O | H | H | H | 11 | 182-183 | isoPrOH | B |
| **11** | O | H | 2-$OCH_3$ | 4-$CH_2$=CH-$CH_2$ | 44 | 186-187 | isoPrOH | B |
| **12** | O | H | 2-$CH_3$ | H | 37 | 192-194 | isoPrOH/ether | B |
| **13** | O | H | 2-$CH_3$ | 6-$CH_3$ | 10 | 198-201 | isoPrOH/ether | B |

TABLE I (continued)

| Compound Number | Empirical Formula | Analysis % Calcd. C | H | N | Cl | S | Found C | H | N | Cl | S |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $C_9H_{11}N_3$·HCl | | | | | | | | | | |
| 2 | $C_{10}H_{13}N_3$ | | | | | 10.89 | 53.00 | 4.57 | 9.40 | | 10.82 |
| 3 | $C_9H_{10}N_2S$·$C_4H_4O_4$ (c) | 53.04 | 4.79 | 9.52 | | 13.01 | 58.16 | 5.82 | 22.43 | | 12.81 |
| 4 | $C_{12}H_{14}N_4S$ | 58.50 | 5.73 | 22.74 | | 11.31 | 37.96 | 3.25 | 9.83 | 37.38 | 11.22 |
| 5 | $C_9H_8Cl_2N_2S$·HCl | 38.15 | 3.17 | 9.88 | 37.52 | 10.17 | 45.57 | 3.81 | 17.80 | 22.45 | 10.22 |
| 6 | $C_{12}H_{12}Cl_2N_4S$ | 45.72 | 3.84 | 17.77 | 22.50 | | 40.62 | 3.50 | 10.54 | 39.71 | |
| 7 | $C_9H_8Cl_2N_2O$·HCl | 40.39 | 3.39 | 10.47 | 39.75 | | 50.96 | 6.03 | 11.00 | 13.70 | |
| 8 | $C_{11}H_{14}N_2O_3$·HCl | 51.10 | 5.84 | 10.83 | 13.72 | | 62.26 | 5.57 | 11.10 | 14.10 | |
| 9 | $C_{13}H_{12}N_2O$·HCl | 62.77 | 5.26 | 11.26 | 14.25 | | 53.15 | 5.92 | 13.89 | 17.35 | |
| 10 | $C_9H_{10}N_2O$·HCl·½$H_2O$ | 53.21 | 5.57 | 13.81 | 17.45 | | 57.56 | 6.49 | 10.62 | 13.59 | |
| 11 | $C_{13}H_{16}N_2O_2$·HCl | 58.09 | 6.37 | 10.42 | 13.19 | | 56.59 | 6.28 | 13.05 | 16.60 | |
| 12 | $C_{10}H_{12}N_2O$·HCl | 56.47 | 6.16 | 13.17 | 16.66 | | 57.60 | 6.69 | 12.23 | 15.78 | |
| 13 | $C_{11}H_{14}N_2O$·HCl | 58.27 | 6.66 | 12.35 | 15.63 | | | | | | |

(a) Lit. (17) m.p. 212°. (b) Lit. (12) m.p. 129°. (c) Maleate. (d) 2-Imidazolin-2-yl. (e) Intermolecular reaction product. (f) α-Naphthyl.

SCHEME IV



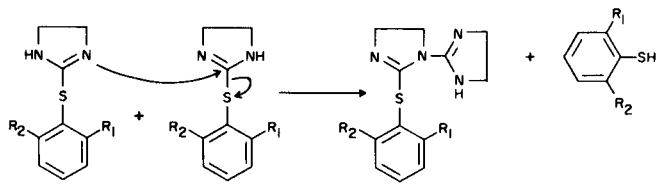

XIII = No. 1-3, 5, 7-13, Table I
X = NH, S, O

because of its decomposition at room temperature with loss of hydrogen chloride and formation of 1-(2′-imidazolin-2′-yl)imidazolidin-2-one (XI) (9). Reaction of X in methylene chloride with trimethylsilyl-chloride in the presence of triethylamine results in trimerization and formation of XII (16). We have tested the reactivity of X with some nucleophiles such as aromatic amines, phenols, and thiophenols.

Aniline and *para*-toluidine gave 2-arylamino-2-imidazoline (XIII) (no. 1, 2, Table I) in 67% and 50% yield, respectively. (Procedure A); this class of compounds is well known and obtained also by the reaction of amines with 2-methylmercapto-2-imidazoline (12).

However, we were not able to obtain the unknown 2-arylthio and 2-aryloxy-2-imidazolines (XIII) (X = S or O) by reaction of the 2-methylmercapto-2-imidazoline with phenols and thiophenols. In the chemical literature, only 2-alkylthio and 2-alkoxy-2-imidazolines have been reported, the former were obtained by alkylation of *N,N′*-ethylenethiourea (VII) (20), the latter by reaction of 2-methylmercapto-2-imidazoline with sodium alkoxides (9). On the other hand, the arylthio (XIII, X = S) and aryloxy (XIII, X = O) analogues could be obtained by the reaction of phenols and thiophenols with 2-chloro-2-imidazoline (X) (Scheme IV) in sodium hydroxide solution at room temperature (Procedure B). 2-Phenylthio-2-imidazoline (No. 3, Table I) was obtained either in 2-propanol solution (Procedure C) or according to the general procedure B. Arylthioimidazolines are less stable then the aryloxy analogues since they react intermolecularly with loss of one molecule of thiophenol and formation of XIV (Scheme V) either in solution (benzene, methylene chloride) (Procedure D), or in the solid state. Compounds XIV are in turn sensitive to moisture and decompose with loss of thiophenol. The intermediate arylamines, phenols, and thiophenols were known and commercially available, 2,6-dichloro-thiophenol, described previously as a meta-

SCHEME V



XIII XIV

$R_1 = R_2 = H$ No. 3, Table I $R_1 = R_2 = H$ No. 4, Table I
$R_1 = R_2 = Cl$ No. 5, Table I $R_1 = R_2 = Cl$ No. 6, Table I

bolite (21), was prepared by reduction of the corresponding sulfochloride with lithium aluminum hydride.

## EXPERIMENTAL

Melting points are uncorrected. The ir spectra were obtained in mineral oil on a Perkin-Elmer model 137 spectrophotometer. The nmr spectra were determined on a Varian A 60 spectrometer using tetramethylsilane as the internal reference. Interpretation of nmr: $\delta$ chemical shift ppm (multiplicity, number of protons), s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. The reported yields are the result of single experiments and no attempts were made to optimize them.

2-Chloro-2-imidazoline Sulfate (VIIIa).

Thirty g. of ethylenethiourea (18) (VII) was added to 50 ml. of water. A stream of chlorine gas was passed into the stirred suspension. A water-ice bath was used to maintain the temperature below 50°. After 30 minutes, all the starting material had dissolved. The bubbling of chlorine was continued for 5 hours. Then the solution was heated at 50° for one hour. The solution was concentrated under reduced pressure and the residue triturated first with 200 ml. of hot acetone then with ether. The insoluble material was dissolved in 50 ml. of concentrated sulfuric acid and the evolved hydrogen chloride was eliminated under reduced pressure (Cl absent with the silver nitrate test). The solution was added dropwise to 300 ml. of acetone allowing the temperature to rise. After cooling, the precipitate was collected and dried, yield 45.5 g. (75%), m.p. 145-150° dec. An analytical sample was recrystallized from methanol, m.p. 161-162° dec.; ir: $\nu$ 3100 (NH), 2700 shoulder, 2300 ($\overset{+}{N}H$), 1620 (C=$\overset{+}{N}$); $\delta$, 1580 ($\overset{+}{N}H$, NH), $\nu$ 1190 ($HSO_4^-$) other bands, 1280, 1030, 870, 725 $cm^{-1}$; nmr (DMSO-$d_6$) (19) $\delta$: 3.97 [s, 4H, $(CH_2)_2$], 11.21 (s, 3H, mobil protons); (deuteriotrifluoroacetic acid) $\delta$: 4.3 [s, 4H, $(CH_2)_2$].

*Anal.* Calcd. for $C_3H_7ClN_2O_4S$: C, 17.88; H, 3.48; N, 13.82; Cl, 17.50; S, 15.82. Found: C, 17.86; H, 3.59; N, 13.69; Cl, 17.42; S, 16.00.

1-(2′-Imidazolin-2′-yl)-2-imidazolidinethione Dihydrochloride (IX).

The mixture of acetone and ether, used to wash compound VIIIa, was concentrated *in vacuo*. The solid residue was crystallized from methanol, yield 5 g., m.p. 270°, mass spectrum: m/e 170 ($M^+$), for parent base.

*Anal.* Calcd. for $C_6H_{12}Cl_2N_4S$: C, 29.63; H, 4.97; N, 23.03; Cl, 29.15. Found: C, 29.54; H, 4.97; N, 21.98; Cl, 28.86.

2-Chloro-2-imidazoline Hydrochloride (VIIIb).

Five g. of VIIIa was triturated with cold 5% sodium hydroxide solution and extracted with 4 x 20 ml. portions of methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate. After filtration, ethereal hydrogen chloride was added. The precipitate was washed with hot ethanol and dried, yield 3 g., m.p. 189-190° dec.; ir (Nujol): 3150 shoulder (NH), 2800 broad, 2600 ($\overset{+}{N}H$), 1610 (C=$\overset{+}{N}$), $\delta$, 1550 ($\overset{+}{N}H$, NH); other bands 1300, 1265, 1240, 1035, 993, 910, 750 (broad) $cm^{-1}$.

*Anal.* Calcd. for $C_3H_6Cl_2N_2$: C, 25.52; H, 4.28; N, 19.86; Cl, 50.28. Found: C, 25.70; H, 4.41; N, 19.94; Cl, 50.26.

1-(2′-Imidazolin-2′-yl)imidazolidin-2-one (XI).

Five g. of VIIIa was triturated with cold 5% sodium hydroxide solution and extracted with 4 x 20 ml. portions of methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate. After filtration the solvent was evaporated *in vacuo* at 10°. When the methylene chloride was completely evaporated, a rapid decomposition was observed in the flask, the product was no more soluble in methylene chloride but soluble in water. Crystallization from methanol gave 0.5 g. of XI, m.p. 295-296°; ir (Nujol): $\nu$ 3300, 3100 (NH), 1750 (C=O), 1660 (C=$\overset{+}{N}$H), $\delta$ 1620, 1590 (NH); nmr (DMSO-$d_6$) $\delta$: 3.25-3.65 and 3.85-4.25 [2 m sim, 4H, $(CH_2)_2$ position 4,5)] 3.70 [s, 4H, $(CH_2)_2$ position 4′,5′], 8.2 and 9.2 (2 s broad, 3H, mobil protons].

*Anal.* Calcd. for $C_6H_{11}ClN_4O$: C, 37.78; H, 5.28; N, 29.38; Cl, 18.59. Found: C, 37.59; H, 6.13; N, 29.46; Cl, 18.70.

2-Arylamino-2-imidazolines (XIII) (X = NH).

General Procedure A.

Example: 2-Phenylamino-2-imidazoline Hydrochloride (No. **1**, Table I).

Compound VIIIa (9.8 g.) was treated with 5% sodium hydroxide and extracted with 4 x 30 ml. portions of ether. The combined extracts, dried over sodium sulfate and concentrated to 50 ml., were treated with 3 g. of aniline in ether. After 3 hours at room temperature, the precipitate was filtered, washed with ether and crystallized twice from absolute ethanol, yield 4.38 g. (67%), m.p. 214° [lit. (17) m.p. 212°].

2,3,6,7,10,11-Hexahydrotriimidazo[1,2-*a*:1′,2′-*c*:1″,2″-*e*]-*s*-triazine (XII).

Compound VIIIa (10.1 g.) was treated with 5% sodium hydroxide and extracted with 3 x 50 ml. of methylene chloride. The combined extracts, dried over sodium sulfate, were put into a flask with 5.1 g. of triethylamine. Then 6.4 ml. of trimethylsilyl-chloride were dropped into the stirred solution at 0°. The solution was refluxed for 1 hour and then the solvent was removed *in vacuo*. The residue was dissolved in 5 ml. of water and made basic with 10% sodium hydroxide. The precipitate was collected and crystallized from absolute ethanol, yield 1.2 g., m.p. 320° [lit. (16) m.p. 320-321°], mass spectrum: m/e 204 ($M^+$).

2-Arylthio and 2-aryloxy-2-imidazolines (XIII: X = S and X = O).

General Procedure B.

Example: 2-(2,6-Dichlorophenylthio)-2-imidazoline Hydrochloride (No. **5**, Table I).

To a stirred solution of 10 g. of 2,6-dichlorothiophenol in 100 ml. of cold 1*N* sodium hydroxide at 10°, 10 g. of VIIIa in 20 ml. of water were added. The solution was allowed to warm to room temperature. After 2 hours, ammonium sulfate was added down to *p*H 9. Stirring was continued until *p*H 8. The precipitate was collected, washed with cold water, and dried *in vacuo* at room temperature, yield 8.2 g., m.p. 108°. The analytical sample

(crystallized from benzene) showed m.p. 112°. The base with 108° was dissolved in chloroform and then added to an ethereal hydrogen chloride solution. The oil obtained solidified upon treatment with a mixture of absolute ethanol and ether. The precipitate was collected and crystallized from ethanol-ether, yield 6.8 g., m.p. 218-219°, mass spectrum: m/e 247 ($M^+$) for parent base; ir (Nujol): $\nu$ 3200-2400 ($C=\overset{+}{N}H$), 3100 (NH), 1575 (C=N), 1540 (aromatic C=C) 1195, $\delta$ 790 (aromatic CH), $\nu$ 710 (C-S) $cm^{-1}$.

Example: 2-(*O*-Tolyloxy)-2-imidazoline Hydrochloride (No. **10**, Table I).

A solution of 2-chloro-2-imidazoline sulfate (20 g., 0.1 mole) in 50 ml. of water was added dropwise to a stirred solution of *o*-methylphenol (10.8 g., 0.1 mole) in 150 ml. of 2*N* sodium hydroxide. After two days at room temperature, the precipitate was collected, washed with water and dried under reduced pressure. After crystallization from acetone, the base of 10 was collected, m.p. 116-119°. The salt was obtained by dissolving the base in ethanolic hydrogen chloride solution. After evaporation of the solvent the salt was crystallized from 2-propanol/isopropyl ether: 2/1., yield 7.8 g., m.p. 192-194°; ir: 3200-2200 ($\nu$ $C=\overset{+}{N}H$, $\overset{+}{N}H_2$), 1610 ($\nu$ $C=\overset{+}{N}$; $\nu$ $\overset{+}{N}H_2$), 1575, 1480 ($\nu$ C=C aromatic), 1280 ($\nu$ asim. C-O-C) 1020 ($\nu$ asim. C-O-C), 1170 ($\nu$ CH aromatic) 725 ($\nu$ CH aromatic) $cm^{-1}$; nmr (deuteriochloroform) $\delta$: 2.25 (s, 3H, $CH_3$), 3.84 [s, 4H, $(CH_2)_2$], 7-7.4 (m, 4H, aromatic), 10.0 (broad, 2H, mobil protons).

General Procedure C.

2-Phenylthio-2-imidazoline Maleate, (No. **3**, Table I).

2-Chloro-2-imidazoline sulfate (VIIIa) (78 g., 0.386 mole) was treated at 0° with a cold solution of 800 ml. of 1*N* sodium hydroxide saturated with sodium chloride. The solution was extracted with 4 x 500 ml. portions of ether, the organic extracts were combined, dried over anhydrous sodium sulfate and filtered in the reaction flask containing sodium thiophenate (0.319 mole) in 900 ml. of 2-propanol. The ether was evaporated, and the remaining alcoholic solution was refluxed for 3.5 hours. The mixture was cooled and diluted with 4 l. of anhydrous ether, filtered on Celite and added to 55 g. of oxalic acid in ether. The oxalate was allowed to stand overnight, collected and dried, yield 29 g. This crude salt was basified with 10% sodium hydroxide and extracted with ether. The organic layer, dried over anhydrous sodium sulfate, was again dropped into an ethereal solution of oxalic acid (15 g.). After standing overnight, the precipitate was collected, yield 16 g., m.p. 171-173°. An analytical sample was crystallized from absolute ethanol, m.p. 176-178°.

*Anal.* Calcd. for $C_9H_{10}N_2S{\cdot}C_2H_2O_4$: C, 49.42; H, 4.52; N, 10.47; S, 11.98. Found: C, 49.36; H, 4.51; N, 10.57; S, 11.85.

The maleate from 2-propanol had m.p. 91-92°; ir (Nujol); $\nu$ 3400-2300 ($C=\overset{+}{N}H$), 3100 (NH); 1600 asim. ($COO^-$), 1575 (C=N), 1540 (aromatic C=C), $\delta$ 1195; $\delta$ 763, 704 (aromatic CH) $cm^{-1}$; nmr (deuteriochloroform/DMSO-$d_6$) $\delta$: 3.97 [s, 4H, $(CH_2)_2$] 6.19 (s, 2H, CH=CH), 7.3-7.9 (broad 5H, aromatic protons), 10.5-12.9 (broad, 3H, mobil protons).

Compounds XIV.

General Procedure D.

Example: 1-(2′-Imidazolin-2′-yl)-2-(2,6-dichlorophenylthio)-2-imidazoline (No. **6**, Table I).

Product XIII-5 was dissolved in methylene chloride or in benzene at room temperature; after several days a precipitate formed. The ir and nmr data are consistent with formula XIV, m.p. 175°; ir (Nujol): $\nu$ 3100 (NH), 1630 (N-C=N), 1590 (N-C=N), 1570, 1500 (aromatic CH), $\nu$ 708 (C-S) $cm^{-1}$; nmr (deuteriochloroform-DMSO-$d_6$) $\delta$: 3.62 (s, 4H, 4′,5′-$CH_2$-$CH_2$), 3.80 (m., 4H; 4,5-$CH_2$-$CH_2$), 4.83 (s, broad, 1H, NH), 7.1-7.6 (m, 3H, aromatic protons).

2,6-Dichlorothiophenol.

A solution of 10 g. of 2,6-dichloro-benzenesulfochloride (22) in 110 ml. of anhydrous ether was dropped into a suspension of 2.35 g. of lithium aluminum hydride in 150 ml. of ether at 0°. After boiling for four hours, the solution was cooled to 0°, 3 g. of lithium aluminum hydride was added and the mixture was refluxed for 4 more hours. The complex was destroyed with 35 ml. of water saturated with ammonium chloride and then 20 ml. of 10% hydrochloric acid was added, the organic layer was separated, dried over sodium sulfate and evaporated. The crude product was distilled under reduced pressure (b.p. 95-100/3 mm. Hg), yield 5.95 g., m.p. 45-48°. An analytical sample was obtained by crystallization from petroleum ether at -40°, m.p. 48-50°; ir (Nujol); $\nu$ 3060 (aromatic CH), 2580 (SH), 1560 (aromatic C=C), 1195, 1150, $\nu$ 770 (aromatic CH), $\nu$ 728 (C-S) $cm^{-1}$; nmr (deuteriochloroform) $\delta$: 4.65 (s, 1H, SH), 6.8-7.5 (m, 3H, aromatic protons).

*Anal.* Calcd. for $C_6H_4Cl_2S$: C, 40.24; H, 2.25; Cl, 39.59; S, 17.90. Found: C, 40.11; H, 2.27; Cl, 38.75; S, 17.02.

Acknowledgement.

We wish to thank Professor R. Fusco for his useful advice and Mr. E. Fazio for the technical work.

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