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A series of *N*-phenyl-3-methylthiopropylamine hydrochlorides were prepared by reacting a series of anilines with methional and sodium cyanoborohydride. These were cyclized upon oxidation by *N*-chlorosuccinimide to the corresponding *N*-phenyl-*S*-methylisothiazolidinium derivatives which were isolated as the tetraphenylborate salts. Compounds successfully prepared included the *m*-methyl, *p*-methyl, *m*-methoxy, and *p*-methoxyphenyl derivatives.

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We previously reported the iodine-induced cyclization of a series of *N*-benzyl-3-methylthiopropylamine salts to form the corresponding *N*-benzyl-*S*-methylisothiazolidinium salts [1]. The cyclization reactions proceeded smoothly at room temperature and neutral pH. We also reported that these isothiazolidinium salts were labile to hydrolysis in aqueous media, and under acidic conditions, were quantitatively hydrolyzed to the corresponding *N*-benzyl-3-methylsulfenylpropylamines.

phenyl-3-methylthiopropylamines **1-5** were formed by using sodium cyanoborohydride to reduce the imine resulting from the reaction of the appropriate aniline with methional [3,4]. The products were isolated and purified *via* fractional crystallization. The progress of these and other reactions reported in this paper were easily followed utilizing hplc and an ultraviolet monitor.

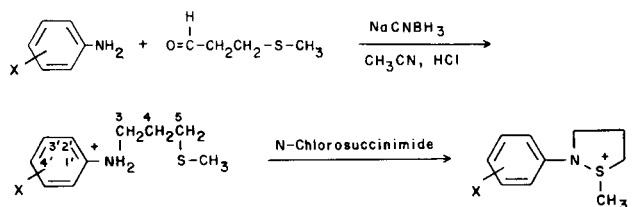
Syntheses of the *m*-trifluoro, *m*- and *p*-chloro, and *m*- and *p*-nitrophenyl derivatives of methylthiopropylamine were also attempted. Complete reaction of the appropriate aniline was achieved only by much longer reaction times and several fold excesses of methional and sodium cyanoborohydride. Under these conditions, reduction of methional was presumably a competing reaction. Attempts to isolate the products by fractional crystallization were unsuccessful.

As judged by examination of product mixtures on hplc, cyclization of the *N*-phenyl-3-methylthiopropylamines to form the isothiazolidinium salts proceeded quantitatively within five minutes at  $-70^{\circ}$ . Silver tetrafluoroborate was added in order to precipitate chloride as silver chloride. The *N*-phenyl-*S*-methylisothiazolidinium tetraphenylborate salts were then obtained by addition of sodium tetraphenylborate. Similar procedures were used by Johnson *et al.* [5] and Claus *et al.* [6] for the preparation of sulfiminines.

Here, we report the results of our efforts to cyclize *N*-phenyl-3-methylthiopropylamines. When iodine was used to induce cyclization, equilibrium mixtures resulted which favored reactants. Efforts to drive the reactions to completion by precipitating iodide with silver ions [2] did not meet with satisfactory results. Success was achieved by using *N*-chlorosuccinimide. The requirement for a more powerful oxidizing agent is not surprising in view of the less basic and nucleophilic nitrogen of the *N*-phenyl derivatives in comparison with the corresponding *N*-benzyl derivatives.

The general route for the synthesis of the *N*-phenyl-3-methylthiopropylamines and their subsequent cyclization by *N*-chlorosuccinimide is illustrated in Scheme I. The *N*-

SCHEME I



X	<i>N</i> -Phenyl-3-methylthiopropylamine	<i>N</i> -Phenyl- <i>S</i> -methylisothiazolidinium Tetraphenylborate
H	<b>1</b>	<b>6</b>
<i>p</i> -OCH <sub>3</sub>	<b>2</b>	<b>7</b>
<i>m</i> -OCH <sub>3</sub>	<b>3</b>	<b>8</b>
<i>p</i> -CH <sub>3</sub>	<b>4</b>	<b>9</b>
<i>m</i> -CH <sub>3</sub>	<b>5</b>	<b>10</b>

In order to provide additional evidence that the products of oxidation by *N*-chlorosuccinimide were the isothiazolidinium salts rather than the sulfenyl derivatives, we isolated and characterized *N*-*p*-methoxyphenyl-3-methylsulfenylpropylamine hydrochloride following acid hydrolysis [1] of the putative isothiazolidinium salt. Under the conditions listed for hplc in the Experimental Section, *N*-*p*-methoxyphenyl-3-methylthiopropylamine and its isothiazolidinium and sulfenyl salts were found to elute at 2.35, 4.70 and 7.40 ml, respectively. Satisfactory elemental analyses were obtained for each of the three derivatives, and <sup>1</sup>H nmr spectra are consistent with the proposed structures.

Comparison of the  $^1\text{H}$  nmr spectra showed that oxidative cyclization resulted in a downfield shift of the hydrogens in both the *S*-methyl and C-5 moieties. These shifts are consistent with the deshielding effect of the positively-charged azasulfonium center present within the isothiazolidinium salts. Similar downfield shifts were observed for these same moieties when the nmr spectra of *N*-*p*-methoxyphenyl-3-methylsulfenylpropylamine are compared with its methylthiopropylamine derivative. This is consistent with the deshielding effect of the electron-withdrawing oxygen of the methylsulfenyl group. Finally, the  $^1\text{H}$  nmr signals of the C-3, C-4, and C-5 hydrogens were extremely split as expected for a ring system in which none of the ring hydrogens are equivalent. Similar findings were obtained for isothiazolidinium salts previously synthesized [1,2].

We have previously shown that *N*-benzyl-3-methylthiopropylamines and a variety of *S*-substituted-thiopropylamines could be cyclized to their respective isothiazolidinium salts by oxidation with iodine. The use of iodine to synthesize sulfilmines is unusual and was presumably successful in these cases because of the intramolecular attack by the favorably located amine nitrogen on the iodo-sulfonium intermediate. In the case of the *N*-phenyl derivatives reported in this paper, however, the nitrogen is much less nucleophilic and cyclization was obtained only through the use of a more reactive reagent of the active-halogen type.

## EXPERIMENTAL

Sodium cyanoborohydride, silver tetrafluoroborate, sodium tetraphenylborate, *N*-chlorosuccinimide and all aniline derivatives were obtained from Aldrich and used without further purification. Deuteriochloroform (99.8 atom %) and  $d_6$ -dimethylsulfoxide (99.9 atom %), each containing 1% tetramethylsilane, were obtained from Aldrich. Methional was obtained from Sigma Chemical Company.

Elemental analyses were conducted by Galbraith Laboratories, Inc., Knoxville, Tennessee. Melting points were taken on a Fisher-Johns melting point apparatus. Proton nmr spectra were obtained on a Varian EM-390 90 MHz nmr spectrometer. The compounds analyzed were dissolved in deuteriochloroform or  $d_6$ -dimethylsulfoxide at concentrations of 15-20 mg/ml for proton nmr. Chemical shifts were determined relative to the methyl substituents of tetramethylsilane.

High pressure liquid chromatography was performed in the reversed phase mode on a 25 cm  $\times$  4.6 mm ultrasphere - ODS silica column, as described previously [1], except the solvent for chromatography was 70:30 (v/v) acetonitrile:5mM ammonium phosphate in water.

General Procedure for Synthesis of the *N*-Phenyl-3-methylthiopropylamine Hydrochlorides.

The molar quantities of aniline derivative, methional, and sodium cyanoborohydride reacted were 0.10, 0.15 and 0.15, respectively. The reactions were carried out in 150 ml of acetonitrile. The pH was maintained between 6 and 8 with concentrated formic acid. The reactions went to completion within 2-4 hours as evidenced by the disappearance of the peak for aniline on hplc, and the concomitant appearance of the *N*-phenyl-3-methylthiopropylamine. The product mixture was then treated with 100 ml of 1M potassium hydroxide and the acetonitrile was removed by rotary evaporation leaving a basic, aqueous mixture which,

in turn, was extracted with three, 100 ml portions of ether. The ether fractions were combined, dried with anhydrous magnesium sulfate, and filtered. Anhydrous hydrogen chloride gas was bubbled through the ether mixture resulting in the separating out of a colored oil. This oil was dissolved in hot ethanol, treated with charcoal, filtered, and the chloride salt was precipitated with ether. Yields were approximately 35%. The product was repeatedly crystallized from a suitable solvent to constant melting point. Crystals were routinely collected by vacuum filtration and dried under vacuum.

General Procedure for the Synthesis of the *N*-Phenyl-*S*-methylisothiazolidinium Salts.

To 2.0 mmoles of the respective *N*-phenyl-3-methylthiopropylamine hydrochloride was added 1.5 ml of 2M potassium hydroxide. After thorough mixing the neutral amine was extracted from the aqueous mixture by thorough vortexing with 2.0 ml methylene chloride followed by separation of the aqueous and organic layers. The combined methylene chloride fractions from three extractions were dried with anhydrous magnesium sulfate and filtered gravimetrically. Methylene chloride was then added to the solution to give a final volume of 25 ml in a round-bottom flask equipped with a calcium chloride drying tube. The temperature of this solution was decreased to  $-70^\circ$  by a dry ice-acetone bath.

To the cold methylene chloride solution, 2.1 mmoles of 95% *N*-chlorosuccinimide dissolved in 5-10 ml methylene chloride at room temperature was added with stirring. The reaction was complete within five minutes as monitored by hplc. The dry ice-acetone bath was removed. After further stirring for five minutes, 2.0 mmoles silver tetrafluoroborate was added to the reaction mixture and stirred for 20 minutes. After removing the silver chloride by filtering through a Millipore filter under vacuum, all methylene chloride was removed by rotary evaporation leaving an almost colorless oil. The oil was dissolved in 50 ml methanol, after which 2.0 mmoles sodium tetraphenylborate was added in 20 mg quantities with stirring. Precipitation of the isothiazolidinium salt in 80% yield followed. Recrystallization was carried out by dissolving the isothiazolidinium salt with heating in a minimal volume of acetone followed by cooling at  $-20^\circ$  for 4-5 days. Recrystallizations were carried out until purity was obtained as evidenced by hplc and constant melting point.

*N*-Phenyl-3-methylthiopropylamine Hydrochloride.

Compound **1** was crystallized from ethanol-ether and had melting point of  $131.5^\circ$ ;  $^1\text{H}$  nmr ( $d_6$ -dimethylsulfoxide):  $\delta$  2.01 (s, 3H), 1.8-2.2 (quin, 2H), 2.4-2.7 (t, 2H), 3.1-3.4 (t, 2H), 7.3-7.7 (m, 5H).

Anal. Calcd. for  $\text{C}_{10}\text{H}_{14}\text{ClNS}$ : C, 55.16; H, 7.41; N, 6.43; S, 14.72. Found: C, 55.15; H, 7.61; N, 6.40; S, 14.58.

*N*-*p*-Methoxyphenyl-3-methylthiopropylamine Hydrochloride.

Compound **2** was crystallized from ethyl acetate and had a melting point of  $131.0^\circ$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.9-2.4 (quin, 2H), 2.01 (s, 3H), 2.4-2.7 (t, 2H), 3.2-3.5 (t, 2H), 3.79 (s, 3H), 6.8-7.0 (d, 2H), 7.4-7.7 (d, 2H).

Anal. Calcd. for  $\text{C}_{11}\text{H}_{18}\text{ClNOS}$ : C, 53.32; H, 7.32; N, 5.65; S, 12.94. Found: C, 53.43; H, 7.30; N, 5.67; S, 13.20.

*N*-*m*-Methoxyphenyl-3-methylthiopropylamine Hydrochloride.

Compound **3** was crystallized from ethyl acetate and had mp  $94.0^\circ$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  2.0-2.4 (quin, 2H), 2.0 (s, 3H), 2.4-2.7 (t, 2H), 3.3-3.7 (t, 2H), 3.79 (s, 3H), 6.8-7.4 (m, 4H).

Anal. Calcd. for  $\text{C}_{11}\text{H}_{18}\text{ClNOS}$ : C, 53.32; H, 7.32; N, 5.65; S, 12.94. Found: C, 53.65; H, 7.26; N, 5.66; S, 13.11.

*N*-*p*-Methylphenyl-3-methylthiopropylamine Hydrochloride.

Compound **4** was crystallized from acetonitrile and had mp  $120.5^\circ$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.9-2.4 (m, 2H), 2.01 (s, 3H), 2.35 (s, 3H), 2.4-2.7 (t, 2H), 3.2-3.6 (t, 2H), 7.0-7.3 (d, 2H), 7.4-7.7 (d, 2H).

Anal. Calcd. for  $\text{C}_{11}\text{H}_{18}\text{ClNS}$ : C, 57.00; H, 7.83; N, 6.04; S, 13.83. Found: C, 56.96; H, 7.89; N, 5.97; S, 14.00.

*N-m*-Methylphenyl-3-methylthiopropylamine Hydrochloride.

Compound **5** was crystallized from acetonitrile and had mp 132.0°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.9-2.4 (quin, 2H), 2.01 (s, 3H), 2.35 (s, 3H), 2.4-2.7 (t, 2H), 3.3-3.6 (t, 2H), 7.1-7.6 (m, 4H).

*Anal.* Calcd. for C<sub>11</sub>H<sub>16</sub>ClNS: C, 57.00; H, 7.83; N, 6.04; S, 13.83. Found: C, 57.10; H, 7.91; N, 6.04; S, 13.90.

*N*-Phenyl-*S*-methylisothiazolidinium Tetraphenylborate.

Compound **6** had mp 176°; <sup>1</sup>H nmr (d<sub>6</sub>-dimethylsulfoxide): δ 2.4-2.9 (m, 2H), 2.95 (s, 3H), 3.5-4.3 (m, 4H), 6.6-7.5 (m, aromatic H).

*Anal.* Calcd. for C<sub>34</sub>H<sub>34</sub>BNS: C, 81.75; H, 6.86; N, 2.80; S, 6.42. Found: C, 81.88; H, 7.10; N, 2.81; S, 6.65.

*N-p*-Methoxyphenyl-*S*-methylisothiazolidinium Tetraphenylborate.

Compound **7** had mp 120°; <sup>1</sup>H nmr (d<sub>6</sub>-dimethylsulfoxide): δ 2.3-2.9 (m, 2H), 2.9 (s, 3H), 3.7 (s, 3H), 3.5-4.2 (m, 4H), 6.6-7.3 (m, aromatic H).

*Anal.* Calcd. for C<sub>35</sub>H<sub>36</sub>BNOS: C, 79.39; H, 6.85; N, 2.65; S, 6.05. Found: C, 79.51; H, 7.06; N, 2.59; S, 5.99.

*N-m*-Methoxyphenyl-*S*-methylisothiazolidinium Tetraphenylborate.

Compound **8** had mp 170°; <sup>1</sup>H nmr (d<sub>6</sub>-dimethylsulfoxide): δ 2.3-2.9 (m, 2H), 2.95 (s, 3H), 3.75 (s, 3H), 3.5-4.2 (m, 4H), 6.5-7.4 (m, aromatic H).

*Anal.* Calcd. for C<sub>35</sub>H<sub>36</sub>BNOS: C, 79.38; H, 6.85; N, 2.65; S, 6.05. Found: C, 79.29; H, 7.01; N, 2.52; S, 5.92.

*N-p*-Methylphenyl-*S*-methylisothiazolidinium Tetraphenylborate.

Compound **9** had mp 161.5°; <sup>1</sup>H nmr (d<sub>6</sub>-dimethylsulfoxide): δ 2.2 (s, 3H), 2.2-2.7 (m, 2H), 2.86 (s, 3H), 3.5-4.2 (m, 4H), 6.6-7.4 (m, aromatic H).

*Anal.* Calcd. for C<sub>35</sub>H<sub>36</sub>BNS: C, 81.86; H, 7.07; N, 2.73; S, 6.24. Found: C, 81.67; H, 7.30; N, 2.67; S, 6.32.

*N-m*-Methylphenyl-*S*-methylisothiazolidinium Tetraphenylborate.

Compound **10** had mp 172.5°; <sup>1</sup>H nmr (d<sub>6</sub>-dimethylsulfoxide): δ 2.3 (s, 3H), 2.35-2.8 (m, 2H), 2.91 (s, 3H), 3.5-4.2 (m, 4H), 6.5-7.4 (m, aromatic H).

*Anal.* Calcd. for C<sub>35</sub>H<sub>36</sub>BNS: C, 81.86; H, 7.07; N, 2.73; S, 6.24. Found: C, 81.66; H, 7.13; N, 2.70; S, 6.16.

*N-p*-Methoxyphenyl-3-methylsulfenylpropylamine Hydrochloride (**11**).

Compound **11** was synthesized from compound **7** according to the following procedures. Compound **7** was formed in methylene chloride solution as described above. The solution containing **7** was treated with two, 25 ml portions of 1*M* potassium hydroxide. The waste potassium hydroxide fractions were combined and extracted once with 15 ml of methylene chloride. The combined methylene chloride fractions containing **7** were dried with anhydrous magnesium chloride and filtered. An equal volume of 6*M* hydrochloric acid was added and then all solvent was removed by rotary evaporation. The resultant oil was dissolved in minimal acetone with heating. Upon cooling and adding ether to the cloud point, crystallization of an ivory-colored product in 80% yield was achieved. Recrystallization in acetone-methanol was carried out until a constant melting point of 136.5 was obtained. The <sup>1</sup>H nmr (d<sub>6</sub>-dimethyl sulfoxide) showed δ 1.9-2.4 (quin, 2H), 2.55 (s, 3H), 2.6-3.1 (m, 2H), 3.2-3.5 (t, 2H), 3.78 (s, 3H), 7.0-7.2 (d, 2H), 7.5-7.7 (d, 2H).

*Anal.* Calcd. for C<sub>11</sub>H<sub>18</sub>ClNO<sub>2</sub>S: C, 50.08; H, 6.88; N, 5.31. S, 12.16. Found: C, 50.70; H, 7.19; N, 5.32; S, 12.53.

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