# Acid-Catalyzed Rearrangement of N-Arylaminomethyl Aryl Sulfides

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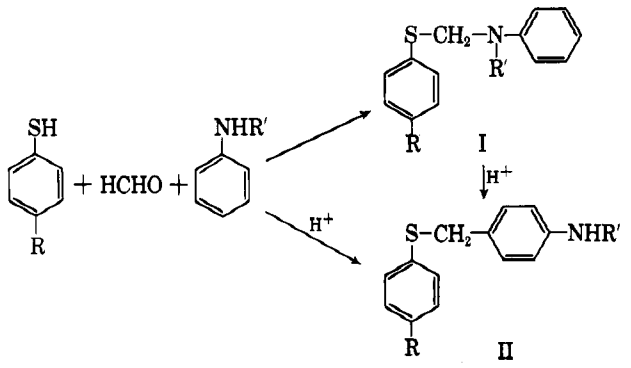
N-Arylaminomethyl aryl sulfides I are rearranged smoothly and in high yields to *p*-aminobenzyl aryl sulfides II when treated with strong acids. These sulfides II are similarly obtained when the corresponding aromatic thiols, formaldehyde, and aromatic amines are condensed in the presence of acid. The latter reaction has been found to be a general reaction, thus providing a useful one-step synthetic route to *p*-aminobenzyl aryl sulfides.

It is known generally that substituents attached to the nitrogen atom of the aromatic amine rearrange on treatment with acid under suitable conditions to give *ortho*- or *para*-substituted anilines.[2,3] In this paper we wish to report a similar type of reaction involving the acid-catalyzed rearrangement of N-arylaminomethyl aryl sulfides to *p*-aminobenzyl aryl sulfides.

Investigations at this laboratory show that when N-phenylaminomethyl phenyl sulfide[4] (Ia), prepared from thiophenol, formaldehyde, and aniline, is refluxed for half an hour in ethanol in the presence of an equimolar quantity of concentrated hydrochloric acid, a crystalline solid isomeric with the starting compound is obtained in over 80% yield. Its infrared spectrum shows two absorption bands in the 2.96- and 3.03-$\mu$ region which is characteristic of a free $NH_2$ group, and its melting and mixture melting points are identical with that of an authentic sample of *p*-aminobenzyl phenyl sulfide[5] (IIa) prepared by an unambiguous route.[6] Similarly, *p*-aminobenzyl *p*-chlorophenyl sulfide[7] (IIb), N-methyl-*p*-aminobenzyl phenyl sulfide (IIc), and N-methyl-*p*-aminobenzyl *p*-chlorophenyl sulfide (IId) are obtained in high yields when the corresponding Mannich bases (Ib, Ic, and Id) are treated with hydrochloric acid.

CHART I




a, R = H, R′ = H
b, R = Cl, R′ = H
c, R = H, R′ = $CH_3$
d, R = Cl, R′ = $CH_3$

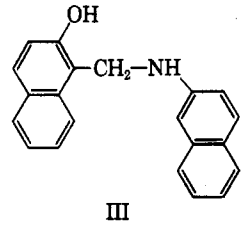
Although condensation of aromatic thiols, formaldehyde, and aromatic amines in refluxing ethanol gives exclusively the Mannich bases N-arylaminomethyl aryl sulfides,[4] these bases are not obtained when the reaction is carried out in the presence of hydrochloric acid. Instead, the *p*-aminobenzyl aryl sulfides are obtained in yields similar to those isolated from the rearrangement of the preformed Mannich bases.

This reaction of aromatic thiols with formaldehyde and aniline or N-methylaniline in hydrochloric acid has been found to be a general reaction, thus providing a useful one-step synthetic route to *p*-aminobenzyl aryl sulfides whose physical properties are summarized in Table I.

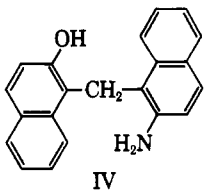
The structures of these compounds were identified by their physical constants, infrared spectra, and unambiguous syntheses.

No *ortho* rearrangement was observed in all the cases studied, even if the *para* position of the aromatic amine was blocked by an electron-donating group. For example, when the preformed N-methyl-N-(*p*-tolyl)aminomethyl *p*-chlorophenyl sulfide and N-methyl-N-(*p*-anisyl)aminomethyl *p*-chlorophenyl sulfide were refluxed in aqueous ethanol for two hours in the presence of concentrated hydrochloric acid, no *ortho* rearranged product was isolated. Instead, they were found to decompose into their individual components. On the other hand, if N-methyl-N-(*p*-tolyl)aminomethyl *p*-chlorophenyl sulfide was rearranged in the presence of an equimolar quantity of N-methylaniline, a high yield of N-methyl-*p*-aminobenzyl *p*-chlorophenyl sulfide was obtained, indicating that the arylthiomethyl radical, instead of migrating to its parent molecule, crosses over to the open *para* position of N-methylaniline.

Although all attempts to prepare *o*-aminobenzyl aryl sulfides were unsuccessful, $\beta$-naphthylamine was found to react smoothly with thiophenol and formaldehyde in concentrated hydrochloric acid to yield 65% of 1-phenylthiomethyl-2-naphthylamine. This observation was not unexpected since $\beta$-naphthylamine is known to be much more strongly activated than the amines of the benzene series.[8,9] Corley and Blout[10] have observed that when 2-naphthol, formaldehyde, and 2-naphthylamine are refluxed in benzene, 1-(2-naphthylaminomethyl)-2-naphthol (III) is not obtained as might be expected. Instead, the isomeric 1-(2-amino-1-naphthylmethyl)-2-naphthol (IV) is isolated.




III




IV

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TABLE I

*p*-AMINOBENZYL ARYL SULFIDES FROM AROMATIC THIOLS, FORMALDEHYDE, AROMATIC AMINES, AND HYDROCHLORIC ACID

*p*-NHRArCH$_2$SAr'

| Compound[a] | Thiols | Amines | Formula | M.p., °C. | Yield, % | | Analyses C | Analyses H |
|---|---|---|---|---|---|---|---|---|
| I | Thiophenol | Aniline | $C_{13}H_{13}NS$ | 74–75[b] | 88 | Calcd. | 72.51 | 6.08 |
| | | | | | | Found | 72.59 | 6.21 |
| II | Thiophenol | β-Naphthylamine | $C_{17}H_{15}NS$ | 121–122.5 | 66 | Calcd. | 76.93 | 5.69 |
| | | | | | | Found | 76.91 | 5.63 |
| III | *p*-Chlorothiophenol | Aniline | $C_{13}H_{12}ClNS$ | 100–101[c] | 90 | Calcd. | 62.49 | 4.85 |
| | | | | | | Found | 62.24 | 5.00 |
| IV | *p*-Chlorothiophenol | *m*-Chloroaniline | $C_{13}H_{11}Cl_2NS$ | 80.5–82 | 39 | Calcd. | 54.94 | 3.91 |
| | | | | | | Found | 55.03 | 3.87 |
| V | *p*-Chlorothiophenol | *p*-Toluidine | $C_{14}H_{14}ClNS$ | 85–86 | 70 | Calcd. | 63.74 | 5.35 |
| | | | | | | Found | 63.40 | 5.35 |
| VI | *p*-Toluenethiol | Aniline | $C_{14}H_{15}NS$ | 70–72 | 85 | Calcd. | 73.29 | 6.59 |
| | | | | | | Found | 71.60 | 6.49 |
| VII | Thiophenol | N-Methylaniline | $C_{14}H_{15}NS$ | 99–101.5 | 95 | Calcd. | 73.33 | 6.59 |
| | | | | | | Found | 73.37 | 6.52 |
| VIII | *p*-Chlorothiophenol | N-Methylaniline | $C_{14}H_{14}ClNS$ | 110–111 | 93 | Calcd. | 63.67 | 5.35 |
| | | | | | | Found | 63.61 | 5.56 |
| IX | *p*-Toluenethiol | N-Methylaniline | $C_{15}H_{17}NS$ | 66–68 | 82 | Calcd. | 74.01 | 7.04 |
| | | | | | | Found | 74.25 | 6.96 |
| X | *p*-Nitrothiophenol | N-Methylaniline | $C_{14}H_{14}N_2O_2S$ | 144–145.5 | 47 | Calcd. | 61.29 | 5.14 |
| | | | | | | Found | 61.17 | 5.45 |
| XI | Thiomesitol | N-Methylaniline | $C_{17}H_{21}NS$ | 53–55 | 45 | Calcd. | 75.21 | 7.79 |
| | | | | | | Found | 75.11 | 7.52 |

[a] Compounds I, III, V, VII, and VIII were recrystallized from ethanol; II from toluene; IV and IX from ligroin; VI and XI from ethanol–water; X from benzene–ligroin. [b] Ref. 5, m.p. 74–75.5°. [c] Ref. 7, m.p. 98–99.5°.

The reaction of aromatic thiols with formaldehyde and aromatic amines in acid has been found to yield several products depending upon the strength and amount of acid used in the reaction mixture. Table II shows that in the absence of acid or in the presence of one, or less than one equivalent of weak acid such as acetic and formic acid, the normal Mannich base N-methyl-N-phenylaminomethyl *p*-chlorophenyl sulfide (V) was obtained. Condensation is at a maximum, yielding 88–93% of N-methyl-*p*-aminobenzyl *p*-chlorophenyl sulfide (VI) with one equivalent of the strong acid in the mixture, and decreases with increasing amount of acid. When the reaction is run with less than one equivalent of strong acid or more than one equivalent of weak acid in refluxing ethanol, the predominate product isolated is N-(*p*-chlorophenylthiomethyl)-N-methyl-α-(*p*-chlorophenylthio)-*p*-toluidine (VII), accompanied by a small amount of N-methyl-*p*-aminobenzyl *p*-chlorophenyl sulfide.

CHART II

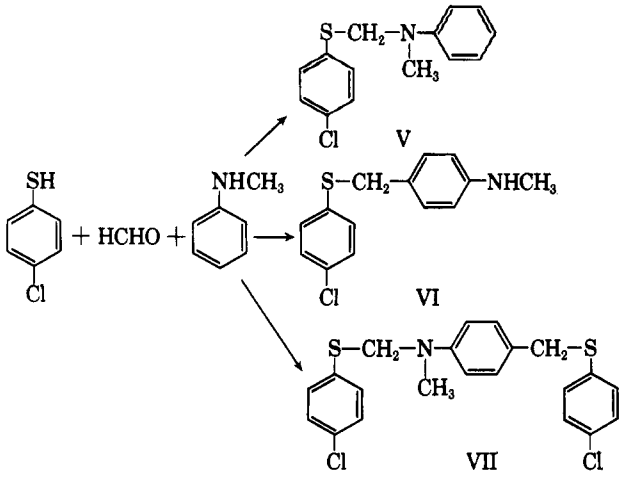


TABLE II

EFFECT OF ACIDITY ON THE CONDENSATION OF *p*-CHLOROTHIOPHENOL, FORMALDEHYDE, AND METHYLANILINE

| Acid | Acid equivalent | Time, min. | Product | Yield, % |
|---|---|---|---|---|
| None | ... | 120 | V[a] | 72 |
| HCl | 0.3 | 15 | VII[b] | 84 |
| HCl | 1.0 | 15 | VI[c] | 91 |
| HCl | 3.0 | 15 | VI | 65 |
| HCl | 5.0 | 15 | VI | 37 |
| $H_2SO_4$ | 1.0 | 15 | VI | 89 |
| HBr | 1.0 | 15 | VI | 93 |
| HOAc | 1.0 | 15 | V | 66 |
| HOAc | 5.0 | 15 | VII | 61 |
| HOAc | 5.0 | 60 | VII | 74 |
| $HCO_2H$ | 1.0 | 15 | V | 64 |
| $HCO_2H$ | 5.0 | 15 | VII | 70 |

[a] Ref. 4, m.p. 46–47°. [b] Recrystallized from benzene–ethanol, m.p. 103–104°. [c] Compound VIII, Table I.

Compound VII shows no –NH stretching bands in the infrared spectrum and has identical melting and mixture melting points with that of an authentic sample synthesized by reacting an equimolar mixture of N-methyl-*p*-aminobenzyl *p*-chlorophenyl sulfide, formaldehyde, and *p*-chlorothiophenol in refluxing ethanol.

## Experimental[11]

**Materials.**—Aromatic amines were obtained from commercial sources and were redistilled before use. Thiophenol, *p*-chlorothiophenol, and *p*-methylthiophenol (*p*-toluenethiol) were obtained from Eastman Kodak Co. and were used without further purification. *p*-Nitrothiophenol was prepared from the corresponding *p*-nitrochlorobenzene by the method employed by Price and Stacy.[12] 2,4,6-Trimethylbenzenethiol (thiomesitol) was prepared by reducing 2,4,6-trimethylbenzenesulfonyl chloride

(11) All melting points are uncorrected. Carbon and hydrogen analyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England.

(12) C. C. Price and G. W. Stacy, *J. Am. Chem. Soc.*, **68**, 499 (1946).

using the method of Adams and Marvel.[13] The Mannich bases, N-arylaminomethyl aryl sulfide (Chart I, a–d) and N-methyl-N-(*p*-anisyl)aminomethyl *p*-chlorophenyl sulfide were prepared according to the method of Grillot and Schaffrath.[4]

**Rearrangement of N-Arylaminomethyl Aryl Sulfides. General Procedure.**—(Table I, compounds I, III, VII, and VIII). To a solution of 0.1 mole of N-arylaminomethyl aryl sulfide in 50 ml. of ethanol was added slowly with stirring 8.6 ml. (0.1 mole) of concentrated hydrochloric acid. After 0.5 hr. of refluxing at 80°, the mixture was cooled in an ice bath and made strongly alkaline with 10% sodium hydroxide solution. The resulting solid product was collected by filtration and washed with water until the filtrate was neutral to litmus paper. The crude rearranged *p*-aminobenzyl aryl sulfides were then recrystallized from the appropriate solvents as listed in the footnotes of Table I. For melting points, yields, and analyses, see Table I.

***p*-Aminobenzyl Aryl Sulfides. General Procedure.**—To a stirred solution of 0.1 mole of aromatic thiol and 7.6 ml. (0.1 mole) of formaldehyde (37% formalin) in 50 ml. of ethanol was added slowly a solution of 0.1 mole of aromatic amine in 8.6 ml. (0.1 mole) of concentrated hydrochloric acid. The mixture was heated on a steam bath and refluxed with stirring for 0.5 hr. After cooling in an ice bath, the mixture was treated with an excess of 10% sodium hydroxide solution. The resulting solid was collected by suction, washed thoroughly with water, and recrystallized from the appropriate solvent. For data concerning these compounds, see Table I.

**Preparation of N-Methyl-N-(*p*-tolyl)aminomethyl *p*-Chlorophenyl Sulfide.**—To a mixture of 14.5 g. (0.1 mole) of *p*-chlorothiophenol and 7.6 ml. (0.1 mole) of 37% formaldehyde in 50 ml. of ethanol was added with stirring 12.1 g. (0.1 mole) of N-methyl-*p*-toluidine. The mixture was then refluxed for 2 hr., during which time the solution became cloudy and separated into two immiscible layers. Upon cooling to room temperature, the oil solidified into a white crystalline mass. The solid was collected by filtration and recrystallized from ethanol–ligroin, m.p. 46–47°. The yield was 73%.

**Attempted Rearrangement of N-Methyl-N-(*p*-anisyl)aminomethyl *p*-Chlorophenyl Sulfide.**—To a stirred solution of 13.9 g. (0.05 mole) of N-methyl-N-(*p*-tolyl)aminomethyl *p*-chlorophenyl sulfide in 50 ml. of ethanol was added portionwise 4.3 ml. (0.05 mole) of concentrated hydrochloric acid. After heating the stirred mixture on a steam bath for 2 hr., the mixture was cooled to 0° in an ice bath. When all attempts to induce crystallization failed, the oil was extracted with ether. The ether extract was washed with water and dried over anhydrous sodium sulfate. Recrystallization from ethanol yielded 5.5 g., equivalent to 75% recovery of *p*-chlorothiophenol, m.p. and m.m.p. 53–54°.

This aqueous portion was made alkaline with 10% sodium hydroxide solution. The resulting oil was extracted with ether, washed with water, and dried over anhydrous sodium sulfate. Filtration and removal of the ether by distillation gave an oil which could not be crystallized. The oil was distilled to give a slightly yellow oil, b.p. 194°. Its infrared spectrum is identical with that of N-methylaniline.

**Attempted Rearrangement of N-Methyl-N-(*p*-anisyl)aminomethyl *p*-Chlorophenyl Sulfide.**—To a stirred solution of 7.3 g. (0.025 mole) of N-methyl-N-(*p*-anisyl)aminomethyl *p*-chlorophenyl sulfide[4] in 25 ml. of ethanol was added 2.2 ml. (0.025 mole) of concentrated hydrochloric acid. After refluxing for 2 hr., the mixture was cooled to 0° in an ice bath. Working up in the previous usual manner resulted in the recovery of only the decomposition products *p*-chlorothiophenol and N-methyl-*p*-anisidine.

**Synthesis of 1-Phenylthiomethyl-2-naphthylamine.**—To 11 g. (0.1 mole) of thiophenol and 7.6 ml. of formaldehyde (37% formalin) in 20 ml. of ethanol was added slowly with stirring a solution of 14.3 g. (0.1 mole) of β-naphthylamine and 8.6 ml. of concentrated hydrochloric acid in 50 ml. of 95% ethanol. The reaction mixture was refluxed with stirring for 2 hr. After cooling to room temperature, a cold solution of 10% sodium hydroxide was added until it was distinctly alkaline. The solid product was collected by suction and washed with water. Yield of the crude product was 17.5 g. (66%). After several recrystallizations from toluene the white needles melted at 121–122.5°.

*Anal.* Calcd. for $C_{17}H_{15}NS$: C, 76.93; H, 5.69; S, 12.08. Found: C, 76.91; H, 5.63; S, 12.12.

**Synthesis of N-Formyl-N-methyl-*p*-aminobenzyl Phenyl Sulfide.**—To a mixture of 11 g. (0.1 mole) of thiophenol and 7.6 ml. (0.1 mole) of formaldehyde (37% formalin) was added with stirring a solution of 10.7 g. (0.1 mole) of N-methylaniline in 15.6 ml. (0.4 mole) of 97% formic acid. The reaction mixture was refluxed for 2 hr., after which time it was cooled in ice and made distinctly alkaline with 10% sodium hydroxide solution. The white solid (18.4 g., 72%) was removed by filtration and recrystallized from ethanol and then from ligroin. The melting point and mixture melting point with authentic sample prepared by the modified method of Morgan and Grist[14] was 98–99.5°. Its infrared spectrum showed the presence of a tertiary amide carbonyl band at the 6.0-μ region.[15]

*Anal.* Calcd. for $C_{15}H_{15}NSO$: C, 70.00; H, 5.88; S, 12.46. Found: C, 70.06; H, 5.76; S, 12.65.

**Effects of Acidity on the Condensation of *p*-Chlorothiophenol, Formaldehyde, and N-Methylaniline.**—To a stirred mixture of 14.5 g. (0.1 mole) of *p*-chlorothiophenol, 10.7 g. (0.1 mole) of N-methylaniline, and 7.6 ml. (0.1 mole) of formalin (37%) in 50 ml. of ethanol was added all in one portion the required acid. The mixture was heated on a steam bath and refluxed with stirring for 15 min. At the end of the reaction time, the mixture was cooled to 0° and treated with a slight excess of 10% sodium hydroxide solution. The resulting solid was collected by filtration and recrystallized from ethanol.

Depending upon the amount or type of acid used in the reaction mixture, three different products (V, VI, and VII of Chart II) were isolated. They were identified by comparing their melting point, mixture melting point, and infrared spectra with known samples. Compound VII was recrystallized from benzene–ethanol, m.p. 103–104°.

*Anal.* Calcd. for $C_{21}H_{19}Cl_2NS_2$: C, 59.99; H, 4.55. Found: C, 59.88; H, 4.45.

(13) R. Adams and C. S. Marvel, "Organic Synthesis," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1946, p. 504.

(14) L. F. Fieser and J. E. Jones, *ibid.*, Coll. Vol. III, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p. 950.

(15) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1959, p. 212.