cohol was partially dehydrated, yielding 1-phenylcyclobutene, a behavior in accord with previously observed behavior of the acetate[10]).

3. In Methanol.—1-Phenylcyclopropylcarbinyl *p*-toluenesulfonate (Ib, 1.2 g.) was solvolyzed in 25 ml. of absolute methanol at 25° for 20 half-lives. After the usual work-up, analysis by g.l.p.c. (Tide,[13b] 195°) revealed the presence of a single product peak with a retention time identical with that of authentic methyl 1-phenylcyclobutyl ether.

4. In Ethanol.—1-Phenylcyclopropylcarbinyl *p*-toluenesulfonate (Ib, 1.5 g.) was solvolyzed in 25 ml. of absolute ethanol at 35° for 15 half-lives. After the usual work-up, analysis by g.l.p.c. (Tide,[13b] 200°) revealed the presence of one large peak with a retention time identical with that of authentic 1-phenylcyclopropylcarbinyl ether and a smaller peak with a retention time identical with that of authentic ethyl 1-phenylcyclobutyl ether.

Preparation of Reference Materials. Allylcarbinol was prepared in 64% yield by lithium aluminum hydride reduction of 3-butenoic acid, b.p. 112–113° (760 mm.), lit.[14] b.p. 110–1111° (760 mm.).

Cyclobutanol was prepared by acid-catalyzed ring expansion of cyclopropylcarbinol,[2] b.p. 122–124° (760 mm.).

Methyl cyclopropylcarbinyl ether resulted when dimethyl sulfate (2.0 g., 16 mmoles) in dry *n*-butyl ether (10 ml.) was added dropwise to the sodium salt of cyclopropylcarbinol (prepared from 2.0 g., 28 mmoles, of alcohol and 2.0 g., 30 mmoles, of sodium hydride in mineral oil) stirred in dry *n*-butyl ether (30 ml.). After cooling, the material was poured onto ice and acidified with dilute hydrochloric acid, and the ether layer was separated. Drying over anhydrous sodium sulfate and distillation yielded the ether, 0.7 g., b.p. 80–81° (760 mm.).

Anal. Calcd. for $C_6H_{10}O$: C, 69.72; H, 11.70. Found: C, 68.95; H, 12.00.

Ethyl cyclopropylcarbinyl ether was prepared according to published procedure,[3] b.p. 99–100° (760 mm.).

1-Phenylcyclobutanol was prepared in 91% yield by the lithium aluminum hydride reduction of 1-phenylcyclobutyl acetate, m.p. 40–41°, lit.[10] m.p. 40–41°.

Methyl 1-phenylcyclobutyl ether resulted when dimethyl sulfate (0.5 g., 6 mmoles) in dry benzene (10 ml.) was added dropwise to the sodium salt of 1-phenylcyclobutanol (prepared from 1.5 g., 10 mmoles, of alcohol and 0.5 g., 11 mmoles, of sodium hydride in mineral oil) stirred in dry benzene (25 ml.). After cooling, the material was poured onto ice, and the benzene layer was separated. The aqueous layer was extracted with three 30-ml. portions of ether and the combined organic phases were dried over anhydrous sodium sulfate. Distillation yielded the ether, 0.8 g., b.p. 36° (0.02 mm.).

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.59; H, 8.71.

Ethyl 1-phenylcyclopropylcarbinyl ether resulted when the sodium salt of 1-phenylcyclopropylcarbinol (prepared from 4.0 g., 27 mmoles, of alcohol and 1.5 g., 30 mmoles, of sodium hydride in mineral oil) in dry benzene (40 ml.) and ethyl *p*-toluenesulfonate (5.4 g., 27 mmoles) were stirred together at reflux temperature for 24 hr. After cooling, and the usual work-up, distillation yielded the ether, 2.2 g., b.p. 60–62° (0.3 mm.).

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.71; H, 9.40.

A forecut was analyzed by g.l.p.c. and revealed in addition to ethyl 1-phenylcyclopropylcarbinyl ether an equivalent amount of ethyl 1-phenylcyclobutyl ether.

Acknowledgment.—The work was supported in part by a grant from the Research Corporation; grateful acknowledgment is made to the donors of this fund.

The Mechanism of the Acid-Catalyzed Rearrangement of N-Arylaminomethyl Aryl Sulfides

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Evidence is presented to indicate that the condensation of aromatic thiols, formaldehyde, and aromatic amines in the presence of strong acid results first in the formation of the intermediate products, N-arylaminomethyl aryl sulfides (I) which then rearrange intermolecularly to *p*-aminobenzyl aryl sulfides (II), a process resembling closely the acid-catalyzed rearrangement of diazoaminobenzenes to *p*-aminoazobenzenes. Two mechanisms consistent with the experimental data are indicated for the acid-catalyzed reaction of aromatic thiols and formaldehyde with primary and secondary amines, and also the mechanism of the condensation with tertiary amines. It is conjectured that a resonance-stabilized sulfonium–carbonium ion is the reactive species that migrates from the nitrogen atom to the *para* position of the aromatic amine.

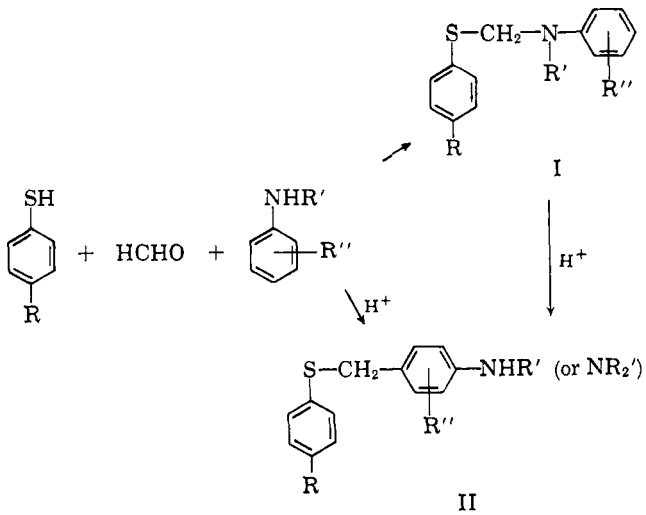
Recently Lau and Grillot[2] have found that N-arylaminomethyl aryl sulfides (I), prepared by the condensation of aromatic thiols, formaldehyde, and aromatic amines, rearrange smoothly and in good yield to *p*-aminobenzyl aryl sulfides (II) in the presence of acid. These benzyl sulfides can also be prepared in nearly the same yield by the condensation of the thiophenol, formaldehyde, and aromatic amine in an acid solution. The fact that the yields of the *p*-aminobenzyl aryl sulfides II are practically the same by either procedure suggests that N-arylaminomethyl aryl sulfides (I) are the intermediate products in the formation of *p*-aminobenzyl aryl sulfides (II) from thiophenols, formaldehyde, and aromatic amines. This is demonstrated by the isolation of over 40% of recrystallized N-methyl-N-phenylaminomethyl *p*-chlorophenyl sulfide (Ia) from the reaction mixture of *p*-chlorothiophenol, formaldehyde, N-methylaniline, and hydrochloric acid during the first 5 min. of the reaction carried out at 40°, while, with the less reactive *o*-chloroaniline, under similar conditions, over 80% of N-(*o*-chlorophenyl)-aminomethyl *p*-chlorophenyl sulfide (Ib) is isolated.

Furthermore, it is found that, if N,N-dimethylaniline, which cannot form an intermediate Mannich base, is refluxed with thiophenol or *p*-chlorothiophenol, formaldehyde, and hydrochloric acid in ethanol, a yield of only 15–33% of the N,N-dimethyl-*p*-aminobenzyl aryl sulfides (IIc and IId) are obtained. However, if the reaction is carried out in the presence of 0.5 *M* ratio of N-methyl-*p*-toluidine, the yield is increased to over 80%. Similarly β-naphthol, which does not react with thiophenol and formaldehyde in the presence of acid,[3] was found to react smoothly to give 65% of 1-phenylthiomethyl-2-naphthol (III) when a 0.5 *M* ratio of N-methyl-*p*-toluidine is added to the reaction mixture. Obviously, these reactions can only occur in such a manner that first the Mannich base N-methyl-N-

(1) Author to whom inquiries should be addressed.

(2) P. T. S. Lau and G. F. Grillot, *J. Org. Chem.*, **28**, 2763 (1963).

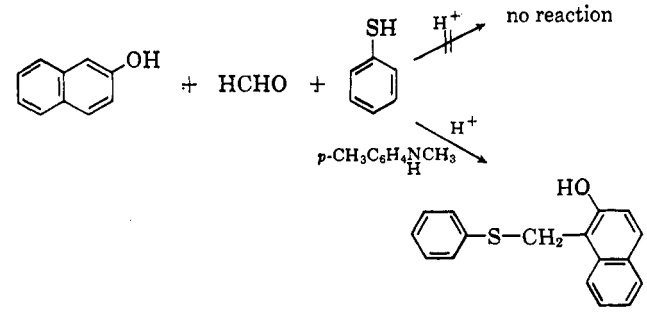
(3) F. Poppelsdorf and S. J. Holt, *J. Chem. Soc.*, 1124 (1954).



II

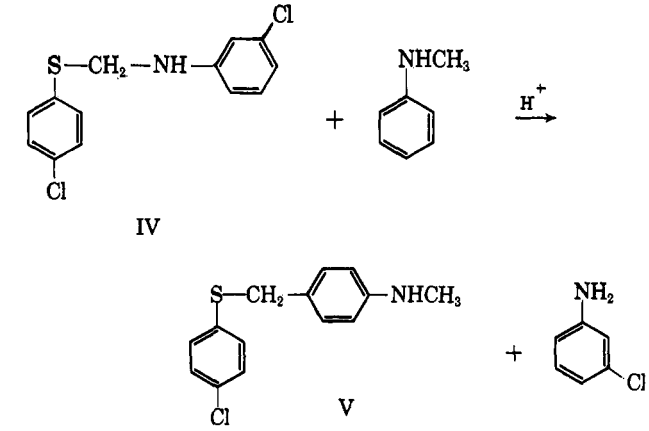
a, R = Cl; R′ = CH_3; R″ = H
b, R = Cl; R′ = H; R″ = *o*-Cl
c, R = H; R_2' = $(CH_3)_2$; R″ = H
d, R = Cl; R_2' = $(CH_3)_2$; R″ = H

(*p*-tolyl)aminomethyl phenyl sulfide[2] is formed from thiophenol, formaldehyde, and N-methyl-*p*-toluidine, which then in the presence of acid alkylates the dimethylaniline or β-naphthol by splitting off N-methyl-*p*-toluidine.



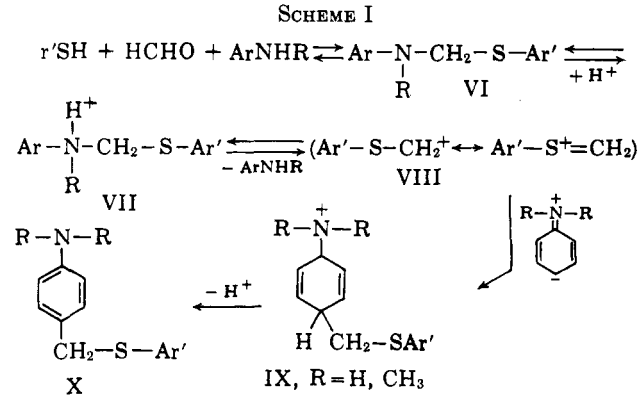
III

The fact that the migrating phenylthiomethyl group can be intercepted by N,N-dimethylaniline and β-naphthol is a clear indication that the acid-catalyzed rearrangement of N-arylaminomethyl aryl sulfides to *p*-aminobenzyl aryl sulfides is intermolecular. Other evidence that is consistent with this view is the rearrangement of N-(*m*-chlorophenyl)aminomethyl *p*-chlorophenyl sulfide (IV) in the presence of acid and N-methylaniline. Here the "labile" *p*-chlorophenylthiomethyl group, instead of migrating in its parent molecule, crosses over into the more activated and



IV V

SCHEME I



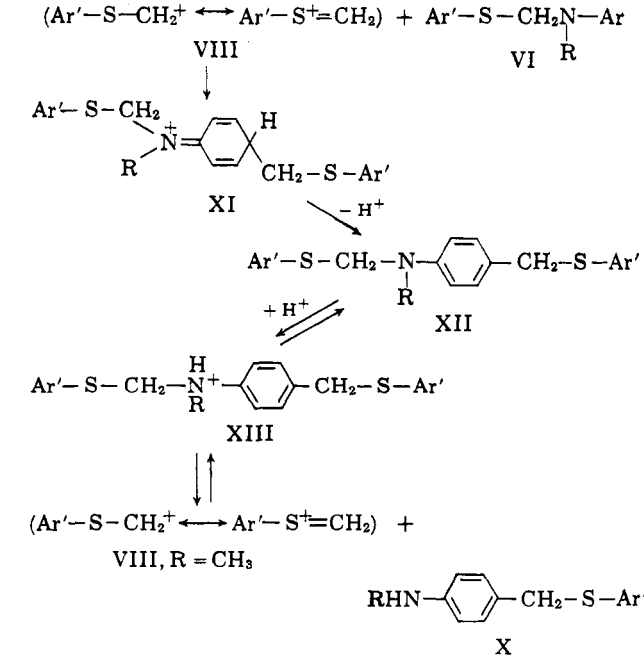
certainly less hindered N-methylaniline to give a yield of crude N-methyl-*p*-aminobenzyl *p*-chlorophenyl sulfide (V) in excess of 90%.

Two possible mechanisms for the reaction of aromatic thiols, formaldehyde, and primary or secondary aromatic amines in the presence of strong acid are schematically outlined. These mechanisms seem reasonable and are consistent with the evidence discussed above.

According to Scheme I, the Mannich base VI which is first formed by the condensation of thiophenol, formaldehyde, and aromatic amine is protonated and rearranges to the *p*-aminobenzyl compound X by way of the resonance-stabilized carbonium–sulfonium ion VIII. The last step in the reaction sequence is essentially irreversible. This is confirmed by the quantitative recovery of N-methyl-*p*-aminobenzyl *p*-chlorophenyl sulfide after being refluxed in concentrated hydrochloric acid with N,N-dimethylaniline for 2 hr.

In Scheme II, the arylthiocarbonium ion VIII is shown to attach to the Mannich base VI to yield first the intermediate product XII before decomposing in the presence of acids to the final product X and the arylthiocarbonium ion VIII. This postulation is supported by the isolation of the intermediate product XII in good yields from the reaction mixture of

SCHEME II



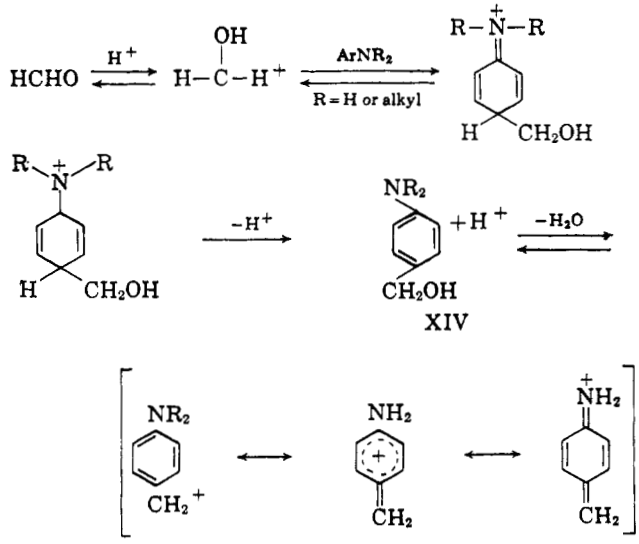
aromatic thiols, formaldehyde, N-methylaniline, and hydrochloric acid at 40°. Furthermore, these intermediates can be completely converted to the N-methyl-*p*-aminobenzyl aryl sulfides X by increasing the reaction temperature to 80°.

Indirect support can also be inferred from the experimental observations that no *ortho* (or *meta*) condensation products were obtained even when the *para* position of the aromatic amines is blocked[2] (except with β-naphthylamine). This observation can only be satisfactorily explained by the relatively large arylthiomethyl groups on the nitrogen atom which sterically interfer with the entering group in the *ortho* position.

At present, there is no conclusive evidence to indicate whether only the aromatic amine (Scheme I) or the Mannich base (Scheme II) or both are being attacked by the arylthiocarbonium ions. On the basis of the absence of *ortho* condensation products, as well as the isolation of N-methyl-N-arylthiomethyl-*p*-aminobenzyl aryl sulfides (XII) from the reaction mixture, Scheme II appears to be more attractive.

As far as the formation of the substituting carbonium ion is concerned, fundamentally there are two other possibilities. First, it is theoretically possible that *p*-aminobenzyl alcohol (XIV), formed by the condensation of aniline and formaldehyde, acts as the intermediate in the formation of *p*-aminobenzyl aryl sulfides (Scheme III).

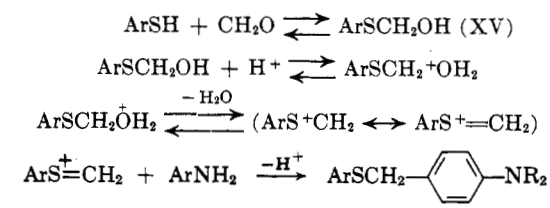
SCHEME III



If this hypothesis is correct, then it would be expected that under similar conditions N,N-dimethylaniline would react more rapidly with formaldehyde and aromatic thiols in acid, than aniline or N-methylaniline. In other words, N,N-dimethylaniline being more reactive should give higher yields. Experimental evidence indicates that the reverse is true, namely, very high yields of *p*-aminobenzyl compounds (80–90%) from aniline and N-methylaniline and low yields from dimethylaniline (15–33%).

The second possibility is the formation of hydroxymethyl aryl sulfides from aromatic thiols and formaldehyde, which in the presence of acid can produce the resonance-stabilized carbonium–sulfonium ion. This ion can then attack the nucleus of the amine according to the mechanism postulated in Scheme IV.

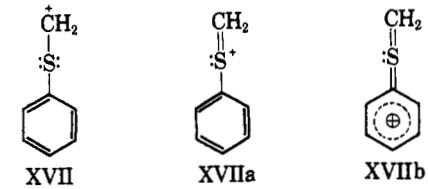
SCHEME IV



To test this hypothesis, hydroxymethyl *p*-chlorophenyl sulfide (XV) was prepared and allowed to react with N-methylaniline in hydrochloric acid under the same conditions as the acid-catalyzed rearrangement of N-methyl-N-phenylaminomethyl *p*-chlorophenyl sulfide. It was found that very nearly equal yields are obtained from either reaction path. However, this result does not necessarily prove that hydroxymethyl *p*-chlorophenyl sulfide is an authentic intermediate, since it, being in equilibrium with formaldehyde and *p*-chlorothiophenol, can also react with N-methylaniline to yield the Mannich base first before rearranging to the *p*-substituted product. That this may very well be the case is indicated by the isolation of over 60% of the crude Mannich base from the above reaction mixture during the first 5 min. of reaction. However, it is a different story with N,N-dimethylaniline. Being a tertiary amine, it cannot form a Mannich base intermediate like aniline or N-methylaniline. Therefore, it seems reasonable to assume that the formation of N,N-dimethyl-*p*-aminobenzyl aryl sulfides from N,N-dimethylaniline involves the hydroxymethyl aryl sulfides as intermediate products. This assumption is rendered more probable by the fact that N,N-dimethyl-*p*-aminobenzyl alcohol has been eliminated as a possible intermediate. The low yield of this reaction is probably a reflection of the higher energy required to form the arylthiocarbonium ion ($ArS^+{=}CH_2$) from hydroxymethyl aryl sulfides than from N-arylaminomethyl aryl sulfides since it is easier to protonate the nitrogen atom than the oxygen atom.

The importance of the participating effect of sulfur in the stabilization of the resulting carbonium ion is evident from the fact that the rate of hydrolysis of chloromethyl phenyl sulfide (XVI, $C_6H_5SCH_2Cl$) is ten times as fast as *t*-butyl chloride.[4] Further evidence is given by the data of Peters and Walker which indicates that the participating effect of sulfur to the release of halide ion is about five times as great in the α-position ($ClCH_2SCH_2Cl$) as in the β-position ($ClCH_2CH_2SCH_2CH_2Cl$).[5]

Since the sulfur can make use of its vacant d-orbitals to expand to eight or ten valence electrons[6] the question arises as to whether or not resonance structures of the type shown below are important or necessary for the stabilization of the arylthiocarbonium ion ($ArSC^+H_2$).



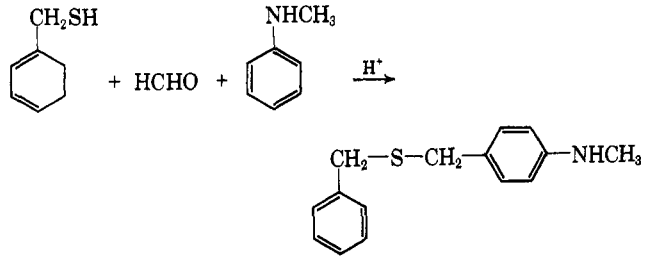
XVII XVIIa XVIIb

(4) F. G. Bordwell, G. D. Cooper, and H. Morita, *J. Am. Chem. Soc.*, **79**, 376 (1957).

(5) R. Peters and E. Walker, *Biochem. J.*, **17**, 260 (1923).

(6) G. Cilento, *Chem. Rev.*, **60**, 147 (1960).

To answer this question, α-toluenethiol was treated with formaldehyde, N-methylaniline, and concentrated hydrochloric acid under rearrangement conditions. The fact that over 70% of N-methyl-*p*-aminobenzyl benzyl sulfide (XVIII) was obtained from this reaction



XVIII

strongly suggests that resonance structure XVIIb is not important and probably not necessary for the stabilization of the carbonium ion XVII.

The failure of XVIIb to make a substantial contribution is surprising, since as pointed out above, it is theoretically feasible for sulfur to accommodate ten valence electrons. However, there is increasing evidence to show that the structures, in which sulfur is flanked by two double bonds, are not very important.[7,8]

Experimental

N-Methyl-N-phenylaminomethyl *p*-Chlorophenyl Sulfide (Ia).—In a 250-ml., three-necked, round-bottom flask, fitted with a thermometer and a stirrer, were placed 14.5 g. (0.1 mole) of *p*-chlorothiophenol, 7.6 ml. (0.1 mole) of 37% formalin, and 50 ml. of 95% ethanol. The flask was kept at 40 ± 1°. A solution of 10.7 g. (0.1 mole) of N-methylaniline and 8.6 ml. (0.1 mole) of concentrated hydrochloric acid was added with stirring. The mixture was stirred for 5 min. during which time an oil separated. The oil formed a solid crystalline mass upon chilling and scratching. The mixture was made alkaline with 10% sodium hydroxide solution. The product was collected and washed with water until neutral. After several recrystallizations from ligroin (b.p. 60–90°), a yield of 11 g. (42%) of a microcrystalline powder (m.p. 45–48°) was obtained, m.m.p. 45–48°.[9]

N-(*o*-Chlorophenyl)aminomethyl *p*-Chlorophenyl Sulfide (Ib).—Using a procedure similar to that described in the previous experiment, 14.5 g. (0.1 mole) of *p*-chlorothiophenol in 50 ml. of 95% ethanol was reacted with 7.6 ml. (0.1 mole) of formalin, a solution of 12.8 g. (0.1 mole) of *o*-chloroaniline in 30 ml. of 95% ethanol, and 8.6 ml. (0.1 mole) of concentrated hydrochloric acid at 40 ± 1° for 60 min. The yield of crude product was 25.4 g. (89%). On recrystallization first from ligroin and then from ethanol, 18 g. (63.4%) of white needles, m.p. 65–66°, m.m.p. 65–66°, was obtained.[9]

N,N-Dimethyl-*p*-aminobenzyl Phenyl Sulfide (IIc).—To a solution of 22 g. (0.2 mole) of thiophenol, 15.3 ml. (0.2 mole) of 37% formalin, and 30 ml. of 95% ethanol was added with stirring 24.2 g. (0.2 mole) of N,N-dimethylaniline and 17.2 ml. (0.2 mole) of concentrated hydrochloric acid. The reaction mixture was cooled in a water bath during the addition of the acid. It was then refluxed with stirring on a steam bath for 30 min.

The mixture was cooled in an ice bath and made alkaline with 10% sodium hydroxide solution. The white crystalline solid was collected and washed several times with water until neutral. The yield of crude product, m.p. 95–104°, was 16.0 g. (32.9%). The product was very soluble in benzene and toluene but could be recrystallized from ethanol and a small amount of benzene. After two recrystallizations from ethanol–benzene and recrystallization from ligroin and toluene, a constant melting point of 105–106.5° was obtained.

Anal. Calcd. for $C_{15}H_{17}NS$ (243.4): C, 74.02; H, 7.05. Found: C, 73.94; H, 7.14.

N,N-Dimethyl-*p*-aminobenzyl *p*-Chlorophenyl Sulfide (IId).—In a procedure similar to the one described in the previous experiment, 28.9 g. (0.2 mole) of *p*-chlorothiophenol and 15.3 ml. (0.2 mole) of formalin in 50 ml. of 95% ethanol were treated with 24.2 g. (0.2 mole) of N,N-dimethylaniline in 17.2 ml. (0.2 mole) of concentrated hydrochloric acid. The crude mass of crystals was washed three times with 30-ml. portions of water and twice with 30-ml. portions of cold ethanol. The yield of crude product was 13.9 g. (25%), m.p. 110–118°. After two recrystallizations from benzene and ethanol, 6.8 g. of shiny flakes, m.p. 122–123°, was obtained.

Anal. Calcd. for $C_{15}H_{16}ClNS$: C, 64.85; H, 5.91. Found: C, 64.64; H, 5.51.

The product gave no depression of the melting point when mixed with an authentic sample of N,N-dimethyl-*p*-aminobenzyl *p*-chlorophenyl sulfide as prepared below.

Unambiguous Synthesis of N,N-Dimethyl-*p*-aminobenzyl *p*-Chlorophenyl Sulfide (IId). A. From *p*-Aminobenzyl *p*-Chlorophenyl Sulfide.—*p*-Aminobenzyl *p*-chlorophenyl sulfide[2] (5 g.) was shaken for 2 hr. with 25 ml. of acetone and 17 ml. of methyl iodide. After standing at room temperature for 10 hr., the supernatant liquid was decanted from the partly crystalline and partly oily reaction product which was washed repeatedly with ether. The solid was then dissolved in 50% ethanol, filtered, and made alkaline with a cold solution of 10% sodium hydroxide. The precipitated solid was collected and was washed thoroughly with water. After drying in air, the solid was extracted with three 50-ml. portions of hot benzene. The combined benzene extracts were distilled under reduced pressure leaving a solid residue in the flask. Recrystallization of this solid from benzene and ethanol gave about 0.9 g. of N,N-dimethyl-*p*-aminobenzyl *p*-chlorophenyl sulfide, m.p. 121–123°.

B. From N-Methyl-*p*-aminobenzyl *p*-Chlorophenyl Sulfide.—N-Methyl *p*-aminobenzyl-*p*-chlorophenyl sulfide[2] (5 g.) was shaken for 2 hr. with 25 ml. of acetone and 10 ml. of methyl iodide. After standing at room temperature for 10 hr., the supernatant liquid was decanted from the crystalline product and washed repeatedly with ether. The solid mass was then dissolved in 95% ethanol, filtered, and made alkaline with a cold solution of 10% sodium hydroxide. The mass of white crystals which precipitated was collected and washed several times with water. The dried product was extracted with three 50-ml. portions of hot benzene. The combined extracts were distilled under reduced pressure. Recrystallization of the solid residue from benzene and ethanol gave 1.3 g. of N,N-dimethyl-*p*-aminobenzyl *p*-chlorophenyl sulfide melting at 121–123°.

Unambiguous Synthesis of N,N-Dimethyl-*p*-aminobenzyl Phenyl Sulfide from *p*-Aminobenzyl Phenyl Sulfide (IIc).—N,N-Dimethyl-*p*-aminobenzyl phenyl sulfide was prepared in the same manner as N,N-dimethyl-*p*-aminobenzyl *p*-chlorophenyl sulfide by the methylation of *p*-aminobenzyl phenyl sulfide.[2] Its melting point after recrystallization from benzene and ethanol was 105–106°.

Rearrangement of N-Methyl-N-(*p*-tolyl)aminomethyl *p*-Chlorophenyl Sulfide in the Presence of N,N-Dimethylaniline and Hydrochloric Acid.—In a 250-ml., three-necked, round-bottom flask, fitted with a stirrer, a reflux condenser, and a thermometer, were placed 13.9 g. (0.05 mole) of N-methyl-N-(*p*-tolyl)aminomethyl *p*-chlorophenyl sulfide,[2] 6.1 g. (0.05 mole) of N,N-dimethylaniline, and 50 ml. of 95% ethanol. With stirring 6.1 ml. (0.07 mole) of concentrated hydrochloric acid was added dropwise at such a rate as to maintain the reaction temperature below 30°. The reaction mixture was refluxed with stirring for 60 min. on a steam bath during which time a crystalline solid precipitated in the flask.

The mixture was cooled in an ice bath and was treated with a cold solution of 10% sodium hydroxide. The mass of crystals that formed was collected and was washed several times with water until neutral, and then once with cold ethanol. The product thus obtained was dried overnight in a vacuum desiccator over P_2O_5. After two recrystallizations from benzene and ethanol, a yield of 9.2 g. (66%) of shiny flakes, m.p. 122–123°, was obtained. It did not give a mixture melting point depression with an authentic sample of N,N-dimethyl-*p*-aminobenzyl *p*-chlorophenyl sulfide.

Effect of Added N-Methyl-*p*-toluidine on the Condensation of *p*-Chlorothiophenol, Formaldehyde, and N,N-Dimethylaniline in the Presence of Hydrochloric Acid.—To a solution of 14.5 g.

(7) F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **78**, 854 (1956).

(8) See A. Mangini and R. Passerini, *Experientia*, **12**, 49 (1956), and references cited therein for recent spectra evidence on this point.

(9) G. F. Grillot and R. E. Schaffrath, *J. Org. Chem.*, **24**, 1035 (1959).

(0.1 mole) of *p*-chlorothiophenol, 7.6 ml. (0.1 mole) of 37% formalin, and 50 ml. of 95% ethanol in a 250-ml., three-necked, round-bottom flask, fitted with a stirrer, a thermometer, and a reflux condenser, was added with stirring 6.1 g. (0.05 mole) of N-methyl-*p*-toluidine and a solution of 12.1 g. (0.1 mole) of N,N-dimethylaniline in 8.6 ml. of concentrated hydrochloric acid. The reaction mixture was refluxed for 60 min. on a steam bath during which time a white crystalline solid precipitated.

The reaction mixture was cooled to 0° in an ice bath and was then treated with an excess of 10% sodium hydroxide solution whereupon it solidified into a crystalline mass. The fine white crystals were collected and washed several times with water until neutral and then twice with cold ethanol. The yield of the dried crude N,N-dimethyl-*p*-aminobenzyl *p*-chlorophenyl sulfide was 22.2 g. (80%), m.p. 114–121°. After recrystallization from benzene and ethanol, a yield of 17.9 g. (64%), m.p. and m.m.p. 121–123°, was obtained.

Reaction of N-Methyl-*p*-aminobenzyl *p*-Chlorophenyl Sulfide (IIa) and N,N-Dimethylaniline with Hydrochloric Acid.—In a 250-ml., three-necked, round-bottom flask, fitted with a stirrer and a reflux condenser, were placed 13.2 g. (0.05 mole) of N-methyl-*p*-aminobenzyl *p*-chlorophenyl sulfide[2] and 50 ml. of 95% ethanol. With stirring, a solution of 6.1 g. (0.05 mole) of N,N-dimethylaniline in 4.3 ml. (0.05 mole) of concentrated hydrochloric acid was added all in one portion. The mixture was then refluxed with stirring for 2 hr. At the end of the reaction time, it was cooled in an ice bath and made basic with a 10% sodium hydroxide solution. The crystalline solid formed was collected and was washed several times with water and then with a 20-ml. portion of cold ethanol. The product was dried over P_2O_5. The yield of the almost-pure product was 12.7 g., corresponding to a recovery of 96% of the starting material, m.p. 106.5–109°.

Attempted Condensation of Thiophenol, Formaldehyde, and β-Naphthol in the Presence of Hydrochloric Acid.—In a 250-ml., three-necked, round-bottom flask, fitted with a stirrer, a dropping funnel, and a reflux condenser, were placed 11 g. (0.1 mole) of thiophenol, 7.6 ml. (0.1 mole) of 37% formalin, 14.4 g., (0.1 mole) of β-naphthol, and 50 ml. of ethanol (95%). To the mixture was added with stirring 8.6 ml. (0.1 mole) of concentrated hydrochloric acid. The mixture was refluxed for 60 min. with stirring. The resulting organic layer was separated and the aqueous layer was extracted twice with 50 ml. of ether. The combined oil and ether extracts were washed twice with water. After drying over anhydrous sodium sulfate, the ether was removed under reduced pressure, leaving a red-colored oil that solidified upon cooling. Recrystallizations using toluene and decolorizing charcoal, then benzene, gave a white crystalline product that melted at 200–203°. No sulfur was present in this product. It was identified as bis(2-hydroxy-1-naphthyl)methane by comparison of melting points (lit.[10] m.p. 198–200°) and infrared spectra with a sample prepared from β-naphthol, formaldehyde, and hydrochloric acid.[11]

Condensation of Thiophenol, Formaldehyde, and β-Naphthol in the Presence of Hydrochloric Acid and N-Methyl-*p*-toluidine.—To a solution of 11 g. (0.1 mole) of thiophenol, 7.6 ml. (0.1 mole) of 37% formaldehyde, 14.4 g. (0.1 mole) of β-naphthol, and 50 ml. of 95% ethanol was added with stirring all in one portion a solution of 6.1 g. (0.05 mole) of N-methyl-*p*-toluidine in 8.6 ml. (0.1 mole) of concentrated hydrochloric acid. The reaction mixture was refluxed on a steam bath for 60 min. with stirring, and was then cooled in an ice bath and made slightly alkaline with a 10% sodium hydroxide solution. The resulting oil soon solidified and after collection was washed with hot water and dried. The yield was 17.2 g. (65%). After two recrystallizations from toluene, it melted at 123–125° (lit.[3] m.p. 126–127°).

The compound was identified by comparing its melting point, mixture melting point, and infrared spectrum with those of a sample of 1-phenylthiomethyl-2-naphthol (III) prepared by the method of Poppelsdorf and Holt.[3]

Anal. Calcd. for $C_{17}H_{14}OS$ (266.4): C, 76.67; H, 5.29; S, 12.04. Found: C, 76.12; H, 5.22; S, 12.13.

Rearrangement of N-(*m*-Chlorophenyl)aminomethyl *p*-Chlorophenyl Sulfide (IV) in the Presence of N-Methylaniline and Hydrochloric Acid.—In a 250-ml., three-necked, round-bottom flask, fitted with a stirrer and a reflux condenser, were placed 14.2 g. (0.05 mole) of N-(*m*-chlorophenyl)aminomethyl *p*-chlorophenyl sulfide[2] and 50 ml. of 95% ethanol. With stirring a solution of 5.4 g. (0.05 mole) of N-methylaniline and 4.3 ml. (0.05 mole) of concentrated hydrochloric acid was added all in one portion. The mixture was refluxed with stirring for 30 min., after which time, it was cooled in an ice bath and made alkaline with a 10% sodium hydroxide solution. After collection, the mass of crystals was washed thoroughly with water and then once with a 30-ml. portion of ethanol. A yield of 12 g. (91%) of crude product was obtained. After several recrystallizations from ethanol, 7.8 g. (59%) of white crystals, N-methyl-*p*-aminobenzyl-*p*-chlorophenyl sulfide, m.p. 109–111°, m.m.p. 109–111°,[2] was obtained.

N-Methyl-N-(*p*-chlorophenylthiomethyl)-*p*-aminobenzyl *p*-Chlorophenyl Sulfide (XII).—To a solution of 14.5 g. (0.1 mole) of *p*-chlorothiophenol, 7.53 ml. (0.1 mole) of 37% formalin, and 50 ml. of 95% ethanol, was added with stirring a solution of 10.7 g. (0.1 mole) of N-methylaniline in 8.6 ml. (0.1 mole) of concentrated hydrochloric acid. The reaction mixture was stirred for 30 min. at 40°. A mass of crystals formed. After cooling to 0°, these were collected and then were washed with 10% sodium hydroxide solution followed by washings with water and cold ethanol. The yield of the crude product was 35.8 g. (88%). After recrystallization from benzene and ethanol, it melted at 103–104°.

The compound showed no N–H absorption band in the 2.86–3.03-μ region of the infrared spectra and exhibited identical melting point and mixture melting point as a sample of N-methyl-N-(*p*-chlorophenylthiomethyl)-*p*-aminobenzyl *p*-chlorobenzyl sulfide prepared from N-methyl-*p*-aminobenzyl *p*-chlorophenyl sulfide, formaldehyde, and *p*-chlorothiophenol by the method of Grillot and Schaffrath.[9] Treating this compound with an equimolar quantity of hydrochloric acid in refluxing ethanol for 60 min. was found to give N-methyl-*p*-aminobenzyl *p*-chlorophenyl sulfide[2] in over 80% yield.

Anal. Calcd. for $C_{21}H_{19}Cl_2NS_2$ (406.4): C, 59.99; H, 4.55. Found: C, 59.88; H, 4.45.

***p*-Aminobenzyl Alcohol (XIV).**[12,13]—A solution containing 9.1 g. (0.24 mole) of lithium aluminum hydride in 600 ml. of ether was placed in a 2-l., three-necked flask equipped with a Soxhlet extractor, a dropping funnel, and a stirrer. This was protected from moisture by a calcium chloride tube attached to the opening of the condenser. *p*-Aminobenzoic acid, 13.7 g. (0.1 mole), was placed in the extractor thimble. The solution was warmed until all of the *p*-aminobenzoic acid had been transferred to the reaction flask. The mixture was stirred for an additional 15 min. After cooling to room temperature, water was added cautiously to decompose excess hydride. To the mixture was then added 250 ml. of 10% sodium hydroxide solution. The ether layer was separated and the water layer was extracted twice with 200-ml. portions of ether. The ether extracts were dried over anhydrous Na_2SO_4, and the ether was removed under reduced pressure. After several recrystallizations from benzene 3.5 g. (28%) of *p*-aminobenzyl alcohol, m.p. 62–64°, was obtained.

Attempted Synthesis of *p*-Aminobenzyl *p*-Chlorophenyl Sulfide from *p*-Aminobenzyl Alcohol (XIV), *p*-Chlorothiophenol, and Hydrochloric Acid.—In a 250-ml. flask were placed 6.2 g. (0.05 mole) of *p*-aminobenzyl alcohol (XIV), 25 ml. of 95% ethanol, and 7.3 g. (0.05 mole) of *p*-chlorothiophenol. The mixture was stirred as 4.3 ml. (0.05 mole) of concentrated hydrochloric acid was added dropwise. Then the mixture was refluxed with stirring for 30 min. After cooling, the solution was made basic with 10% sodium hydroxide solution. The oil was separated, and the aqueous layer was extracted twice with 30-ml. portions of ether. The combined oil and ether extracts were dried over anhydrous sodium sulfate. Upon removal of ether under reduced pressure, a polymeric material melting above 200° remained in the flask.

Hydroxymethyl *p*-Chlorophenyl Sulfide (XV).—In a 250-ml. flask were placed 43.5 g. (0.3 mole) of *p*-chlorothiophenol and 100 ml. of 95% ethanol. The mixture was warmed on a steam bath until all of the *p*-chlorothiophenol had dissolved. To this solution was added slowly with stirring 22.8 ml. (0.3 mole) of 37% formalin. During the course of this addition, a crystalline mass was formed. The mixture was stirred at 40° for 30 min.

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after which it was cooled. The isolated product was recrystallized from ligroin (b.p. 60–90°), yielding 34 g. (67%) of white crystalline rods, m.p. 62.5–65°. This compound shows a strong O–H absorption band at 3.1 μ in the infrared spectra.

Anal. Calcd. for C_7H_7ClOS (174.7): C, 48.02; H, 4.04; S, 18.38. Found: C, 48.12; H, 3.97; S, 18.80.

N-Methyl-*p*-aminobenzyl *p*-Chlorophenyl Sulfide from Hydroxymethyl *p*-Chlorophenyl Sulfide (XV), N-Methylaniline, and Hydrochloric Acid.—To a solution of 8.8 g. (0.05 mole) of hydroxymethyl *p*-chlorophenyl sulfide (XV) and 25 ml. of 95% ethanol was added with stirring a solution of 5.4 g. (0.05 mole) of N-methylaniline in 4.3 ml. (0.05 mole) of concentrated hydrochloric acid. The reaction mixture was refluxed for 30 min., after which it was cooled and made basic with 10% sodium hydroxide solution. The white crystalline solid was collected and washed thoroughly with water until neutral and dried. The yield of crude product was 11.7 g. (88%) which was almost identical with the yield obtained from the rearrangement of N-methyl-N-phenylaminomethyl *p*-chlorophenyl sulfide.[2] Recrystallization from ethanol gave 10.2 g. of white crystals, m.p. 109–111°.[2]

N-Methyl-*p*-aminobenzyl Benzyl Sulfide (XVIII).—To a stirred mixture of 12.4 g. (0.1 mole) of α-toluenethiol (benzyl mercaptan), 7.6 ml. (0.1 mole) of 37% formalin, and 30 ml. of 95% ethanol was added slowly a solution of 10.7 g. (0.1 mole) of N-methylaniline in 8.6 ml. (0.1 mole) of concentrated hydrochloric acid. Following a procedure similar to that used to prepare N-methyl-*p*-aminobenzyl aryl sulfides,[2] 18 g. (74%) of a crude product was obtained. After two recrystallizations from isopropyl alcohol, white needles, m.p. 36–38°, were obtained.

The compound was identified by the appearance of a characteristic N–H absorption band in the 2.93-μ region of the infrared spectrum. *para* substitution was indicated by a strong absorption band in the 12.1-μ region which is characteristic of two adjacent hydrogens.

Anal. Calcd. for $C_{16}H_{17}NS$ (243.4): C, 74.02; H, 7.04; N, 5.76; S, 13.18. Found: C, 74.12; H, 6.84; N, 5.75; S, 13.24.

Organic Sulfur Compounds. III.[1] Synthesis of 2-(Substituted alkylamino)ethanethiols[2]

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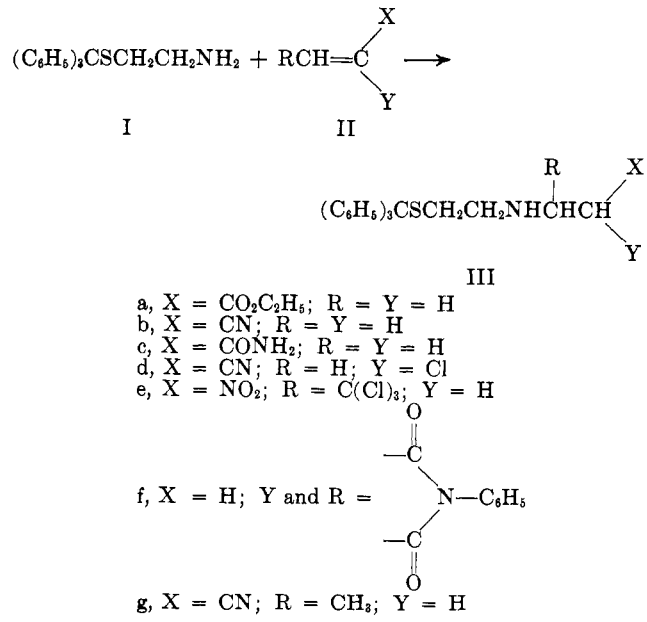
A two-step procedure for mercaptoethylation is described which can be used to prepare a number of 2-(alkylamino)ethanethiols containing additional functional groups. The N-(substituted alkyl)-N-2-tritylthioethylamines are obtained by adding 2-tritylthioethylamine to substrates containing activated double bonds. The addition products thus formed are converted by detritylation with mercuric acetate followed by treatment with hydrogen sulfide to 2-(substituted alkylamino)ethanethiols.

The potential use of 2-aminoethanethiols as antiradiation drugs[3] has created a recent interest in new methods for the synthesis of compounds in this class, particularly those containing additional functional groups.

A survey of the literature has indicated that the most general route for the preparation of 2-aminoethanethiols involves mercaptoethylation of amines with ethyl 2-mercaptoethylcarbonate or ethylene monothiocarbonate.[4] This procedure is an attractive route and has been used to prepare a number of 2-aminoethanethiols. However, except for one example the amines were simple alkyl or aryl amines containing no additional functional groups. Wineman and coworkers[5] have successfully prepared a few 2-aminoethanethiols containing hydroxyl or alkoxyl functions by prior preparation of ethylene sulfide followed by its treatment with an amine. The ease of polymerization of ethylene sulfide and its reactivity toward a number of functional groups limit the scope of this procedure.[6]

This paper describes our work on the preparation of 2-aminoethanethiols containing carbethoxy, cyano, carbamido, carboxy, carbohydrazido, and chloro groups. The reaction sequence used is shown in Charts I and II.

CHART I



2-Tritylthioethylamine (I), prepared from trityl mercaptan and 2-bromoethylamine hydrobromide, adds to compounds containing activated carbon–carbon double bonds to give crystalline addition products, III, in good yield (Table I). The addition reaction proceeds smoothly in ethanol at room temperature or lower in 1–8 hr. with the unsubstituted substrates, ethyl acrylate (IIa) and acrylonitrile (IIb); with substituted

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