usual manner afforded an oil which by vpc analysis (column H,[26] 180°, 60 ml of He/min) was shown (planimetry) to consist of 48.5% of **36** (t_r = 6.6 min) and 51.5% of unreacted **37** (t_r = 8.5 min).

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Azasulfonium Salts. Intermediates in a General Procedure for the Alkylation of Aromatic Amines[1]

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Abstract: A new, general process has been developed for the ortho alkylation of aromatic amines. Starting with anilines or N-alkylated anilines bearing ortho, meta, or para substituents with electronic character, varying from electron-donating groups such as methyl to electron-withdrawing groups such as nitro, ortho-alkylated anilines were prepared *via* the intermediacy of an *o*-alkyl-*α*-thioalkoxy substituent. The general procedure involved (a) mono-N-chlorination of the aniline with a suitable halogenating agent, (b) conversion of the *N*-chloroaniline into an azasulfonium salt through reaction with a dialkyl sulfide, (c) treatment of the azasulfonium salt with base to yield an azasulfonium ylide, (d) Sommelet–Hauser type rearrangement of the ylide to produce a substituted dienone imine, and (e) hydrogen transfer and accompanying rearomatization of the dienone imine to give the *o*-alkyl-*α*-thioalkoxy substituted aniline. Raney-nickel reduction then produced the ortho-alkylated aniline. Overall yields ranged from good to excellent. The scope and limitations of the process are discussed.

Alkylation of the aromatic nucleus is an old and extensively studied topic. Most attention has been directed toward the use of the Friedel–Crafts reaction,[2] which is undoubtedly the best known and most widely used method for the alkylation of aromatic rings. Major limitations of the Friedel–Crafts alkylation are associated with the introduction of *n*-alkyl groups, with the formation of isomers when substituted aromatics are used as starting materials, and with the substitution of aromatics bearing strong electron-withdrawing substituents. An additional limitation is associated with the inability of aromatic amines, such as anilines, to be readily used as substrates in Friedel–Crafts alkylations. We now wish to report the details of our process for the specific ortho-alkylation of aromatic amines. The application of our simple experimental procedure provides a superior method for the synthesis of a variety of isomerically pure polysubstituted aromatic compounds. In addition, it allows for the introduction of *n*-alkyl groups such as the *n*-pentyl and *n*-hexyl moieties.

In its simplest form, our procedure involves an intramolecular migration modeled after the classical Sommelet–Hauser rearrangement.[3,4] In principle, ylides of the general formula **1** should rearrange to give dienone imines, **2**, which on hydrogen transfer and accompanying rearomatization should produce the aniline derivative **3** with exclusive ortho substitution. Substantiation of this hypothesis was provided by Claus and coworkers, who demonstrated that sulfilimines, **4**, will rearrange in base to yield **3**, presumably *via* the intermediacy of **1** and **2**.[5] Unfortunately, the formation of sulfilimines is limited to anilines with an unsubstituted amino group, and the conditions used for sulfilimine formation (aniline, dimethyl sulfoxide, and phosphorous pentoxide) do not lend themselves to utilization in the presence of acid sensitive substituents. We reasoned that a more general procedure could be developed if an aniline, **5**, could be directly converted into the ylide **1** without the initial formation of a sulfilimine. Our investigation of the problem has led to the development of a procedure in which **5** is converted into **3** *via* the intermediacy of the azasulfonium salt **6**.

Initial efforts were devoted to the ortho substitution of a series of *N-tert*-butylanilines, **7**, which were available to us as a result of a prior study.[6] Treatment of **7**

(1) For preliminary reports of part of the study, see P. G. Gassman, G. Gruetzmacher, and R. H. Smith, *Tetrahedron Lett.*, 497 (1972); P. G. Gassman and G. Gruetzmacher, *J. Amer. Chem. Soc.*, **95**, 588 (1973).

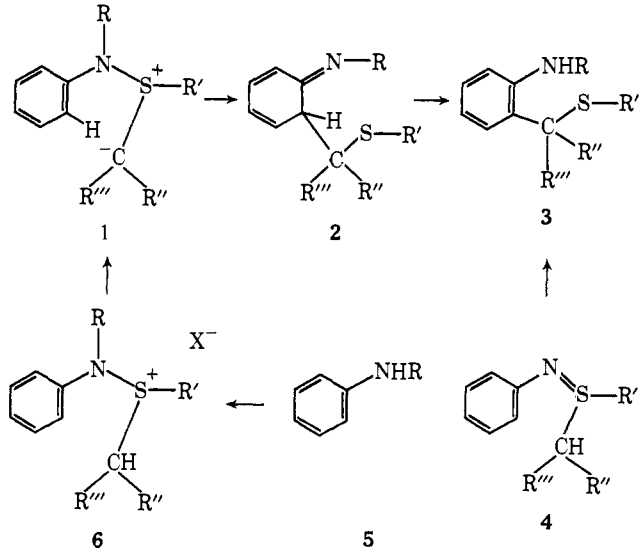
(2) C. Friedel and J. M. Crafts, *C. R. Acad. Sci.*, **84**, 1392, 1450 (1877). For a recent detailed account of the Friedel–Crafts reaction, see G. A. Olah, "Friedel-Crafts and Related Reactions," Interscience, New York, N. Y., 1963–1965.

(3) M. Sommelet, *C. R. Acad. Sci.*, **205**, 56 (1937); G. C. Jones and C. R. Hauser, *J. Org. Chem.*, 27, 3572 (1962); G. C. Jones, W. Q. Beard, and C. R. Hauser, *ibid.*, 28, 199 (1963); for a review, see H. J. Shine, "Aromatic Rearrangements," Elsevier, New York, N. Y., 1967, pp 316–326.

(4) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **85**, 3027 (1963); 87, 5661, 5670 (1965); M. G. Burdon and J. G. Moffatt, *ibid.*, 87, 4656 (1965); see also M. G. Burdon and J. G. Moffatt, *ibid.*, 88, 5855 (1966); *ibid.*, **89**, 4725 (1967); K. E. Pfitzner, J. P. Marino, and R. A. Olofson, *ibid.*, 87, 4658 (1965); J. P. Marino, K. E. Pfitzner, and R. A. Olofson, *Tetrahedron*, **27**, 4181 (1971); R. A. Olofson and J. P. Marino, *ibid.*, **27**, 4195 (1971); P. Claus, *Monatsh. Chem.*, **102**, 913 (1971); Y. Hayashi and R. Oda, *J. Org. Chem.*, 32, 457 (1967); G. R. Pettit and T. H. Brown, *Can. J. Chem.*, **45**, 1306 (1967); P. Claus, *Monatsh. Chem.*, **99**, 1034 (1968); P. Claus, N. Vavra, and P. Schilling, *ibid.*, **102**, 1072 (1972); see also J. Doucet and A. Robert, *C. R. Acad. Sci.*, **272**, 1562 (1971).

(5) (a) P. Claus and W. Vycudilik, *Tetrahedron Lett.*, 3607 (1968); (b) *Monatsh. Chem.*, **101**, 396, 405 (1970); (c) P. Claus, W. Vycudilik, and W. Rieder, *ibid.*, **102**, 1571 (1971); (d) P. Claus and W. Rieder, *ibid.*, **103**, 1163 (1972).

(6) P. G. Gassman and G. Campbell, *J. Amer. Chem. Soc.*, **94**, 3891 (1972).



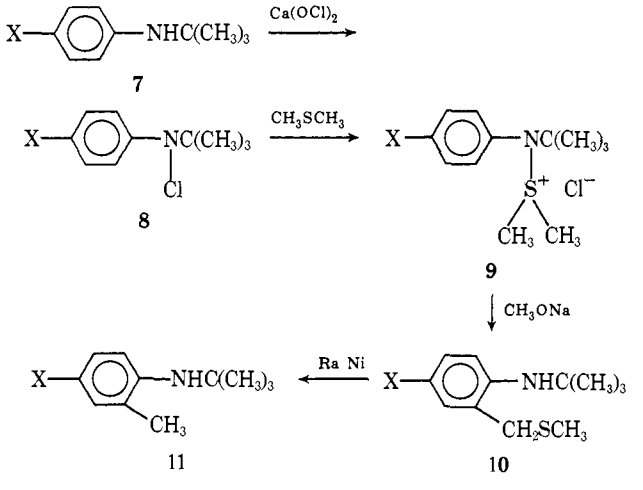
with calcium hypochlorite (HTH)[7] gave the mono-*N*-chloroaniline **8**, which reacted with dimethyl sulfide to give the azasulfonium salt **9**. Treatment of **9** with sodium methoxide gave the rearrangement product **10**, presumably *via* intermediate ylide formation and Sommelet–Hauser type rearrangement. Table I lists the

Table I. Yields Obtained in the Ortho Thiomethoxymethylation of *N-tert*-Butylanilines (**7**)

Compd	X	Anion	% yield of **9**	% yield of **10**	Overall % yield of **10** from **7**
7a	CH_3	Cl^-	76	92	70
7b	H	Cl^-	80	95	76
7c	F	Cl^-	81	88	71
7d	Cl	Cl^-	59	90	53
7e[a]	H	$CF_3CO_2^-$	76[a]	83	

[a] Compound **7e** was prepared from **7b** by anion exchange.

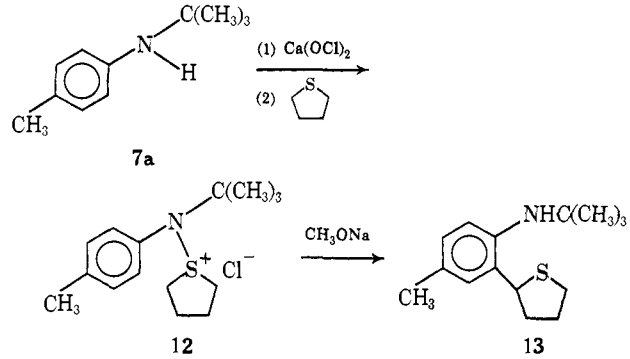
yields obtained in this series of reactions.[1,8] As can be noted from the table, the yields in the rearrangement step were all greater than 80%, and the overall yields of **10** from **7** were quite good. To illustrate the utility of



(7) In addition, *tert*-butyl hypochlorite, *N*-chlorosuccinimide, and other inorganic hypochlorites (*i.e.*, sodium hypochlorite) can be used as sources of chlorine in this reaction.

(8) For a related study, see C. R. Johnson, C. C. Bacon, and W. D. Kingsbury, *Tetrahedron Lett.*, 501 (1972).

the overall process in the ortho alkylation of anilines, **10a** and **10b** were reduced with Raney nickel to give **11a** and **11b** in 76 and 69% yields, respectively. The procedure was not restricted to dimethyl sulfide. Treatment of **7a** with calcium hypochlorite followed by tetrahydrothiophene gave **12** in 68% yield. Base promoted rearrangement of **12** gave 40% of **13**.



The success of this procedure in substituting the relatively hindered *N-tert*-butylanilines indicated that the process should have very general utility. Of particular importance was the question of whether the process could be used if the amino group of the aniline was unsubstituted. The requirements for such a process were (a) clean mono-N-chlorination of the aniline, (b) azasulfonium ion formation, and (c) competitive ylide formation in a situation where the nitrogen possessed a removable proton. These requirements were easily met. Sequential treatment of an aniline, **14**, with *tert*-butyl hypochlorite (one equivalent), dimethyl sulfide, and sodium methoxide in a one-pot reaction gave **15** in good to excellent yields. Table II gives the yields

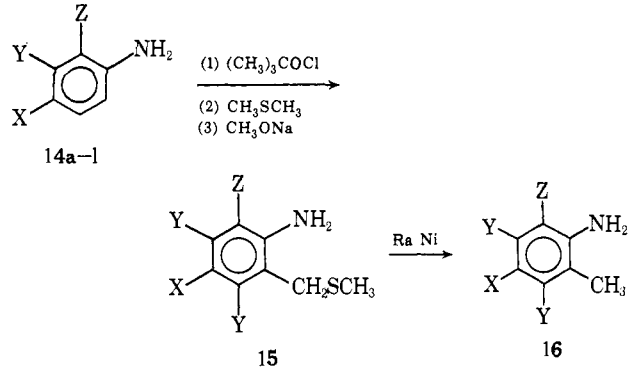


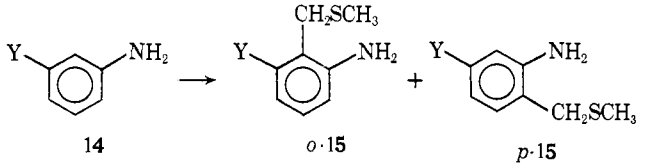
Table II. Conversion of Anilines into 2-Thiomethoxymethylanilines (**15**)

Aniline	X	Y	Z	% yield of **15**[a]	% conversion[b]
14a	H	H	H	90	82
14b	CH_3	H	H	54	74
14c	H	CH_3	H	86[c]	58
14d	H	H	CH_3	74	85
14e	Cl	H	H	83	75
14f	H	Cl	H	87[c]	49
14g	H	H	Cl	70	37
14h	$CO_2C_2H_5$	H	H	65	*d*
14i	H	H	C_6H_5	41	86
14j	NO_2	H	H	71	75
14k	OCH_3	H	H	3	97
14l	H	OCH_3	H	55[c]	87

[a] Per cent yield calculated on unrecovered starting material. [b] Per cent of unrecovered aniline. [c] Yields represent the combined percentages of the 3 and 5 isomers. [d] No attempt was made to recover starting material in this case.

and per cent conversion observed with a series of anilines. As can be noted from the data in the table, only **14k** gave a very poor yield. This was attributed to the instability of the mono-*N*-chloro derivative formed from **14k**. As we have previously shown,[6] *N*-chloroanilines solvolyze *via* heterolytic cleavage of the N–Cl bond to give nitrenium ions and chloride anion. The ρ for the reaction in acetate buffered ethanol was -6.35. Thus, it would be expected that the presence of a methoxyl function in the para position of the aniline should lead to an extremely unstable *N*-chloroaniline.

When meta-substituted anilines were used, intramolecular rearrangement could occur to the position ortho to the substituent to give *o*-**15** or to the position para to the substituent to yield *p*-**15**. In practice, both



14 *o*-**15** *p*-**15**

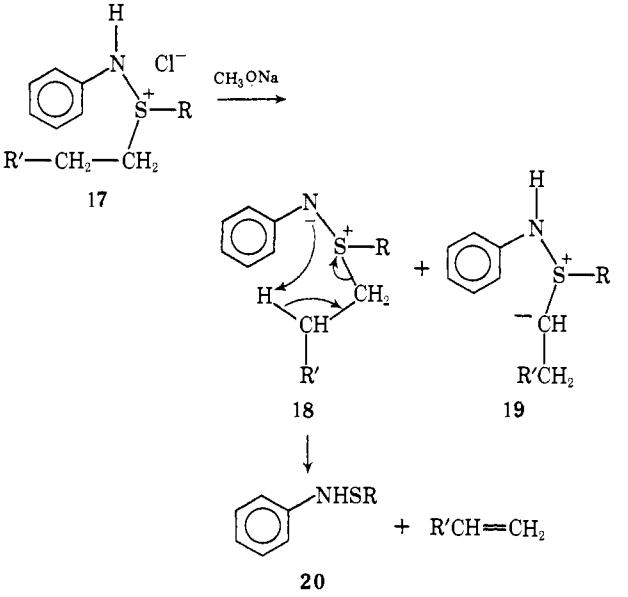
isomers were formed. Table III shows the ratio of

Table III. Ratios of 3- and 5-Substituted 2-(Thiomethoxymethyl)anilines from Meta-Substituted Anilines

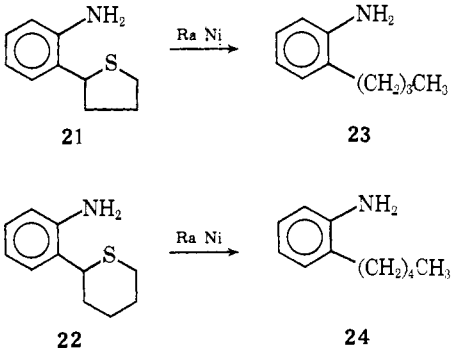
Starting material	Substituent	3-Substituted 2-(thiomethoxymethyl)aniline/ 5-substituted 2-(thiomethoxymethyl)aniline
14l	*m*-OCH_3	0.3
14c	*m*-CH_3	1.0
14f	*m*-Cl	1.5

o-**15** to *p*-**15** as determined by nmr analysis of the product mixtures. Since the steric bulks of the three substituents studied do not differ greatly, it would appear that the major factor involved in the determination of the product ratio was the electronic character of the substituent. The more electron-withdrawing groups would appear to favor substitution ortho to the meta substituent to give *o*-**15**, while electron-donating functions in the meta position apparently direct cyclization to the position para to the substituent. Undoubtedly, there is some steric effect, which cannot be evaluated on the basis of the data presently available, superimposed on this electronic effect.[9]

The use of other sulfides with anilines has been explored. When aniline (**14a**) was converted to *N*-chloroaniline and then treated with diethyl sulfide, di-*n*-propyl sulfide, or phenyl *n*-butyl sulfide, the desired azasulfonium salts, **17**, were obtained. Unfortunately, base treatment of these azasulfonium salts resulted in an elimination reaction, rather than the desired Sommelet–Hauser type rearrangement, as the major mode of reaction. Presumably, treatment of **17** with base resulted in the formation of an equilibrium mixture of **18** and **19**. Whereas **19** can undergo the desired intramolecular alkylation of the aromatic rings, **18** is ideally set up for an intramolecular elimination reaction. For example, with phenyl *n*-butyl sulfide (R = C_6H_5 and R′ = C_2H_5), **20** was obtained in 70% yield. In a similar manner, the use of phenyl isopropyl sulfide gave **20** (R = C_6H_5) in 76% yield.



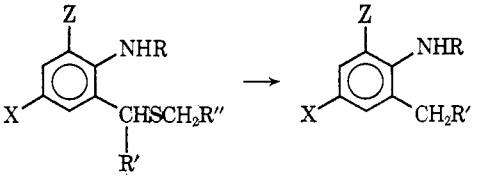
This major problem could be avoided in two ways. First, cyclic sulfides were much less prone to undergo the elimination reaction. When tetrahydrothiophene was used as the sulfide in our process, **21** was obtained in 31% yield (64% based on unrecovered starting material). Similarly, when tetrahydrothiopyran was the chosen sulfide, **22** was obtained in 41% yield. Apparently, when the β-carbon atoms are "tied back" as part of a ring, elimination is minimized and alkylation of the aromatic ring predominates. It is interesting to note at this point that reductive desulfurization of **21** and **22** with W-2 Raney nickel produced **23** and **24**, respectively. Thus, a relatively straightforward method for the introduction of the *n*-butyl and *n*-pentyl moiety has been developed.



When the aniline possesses an alkyl group on the amino function, formation of **18** is no longer possible and alkylation of the aromatic ring by our process should again be possible. In support of this idea, we found that *N*-methylaniline (**25**) could be readily used in our reaction sequence to give a variety of substituted anilines. Thus, reaction with dimethyl sulfide (R = H), diethyl sulfide (R = CH_3), or di-*n*-propyl sulfide (R = C_2H_5) and subsequent base treatment gave **26a** (R = H), **26b** (R = CH_3), and **26c** (R = C_2H_5) in 59, 45, and 24% yields, respectively.

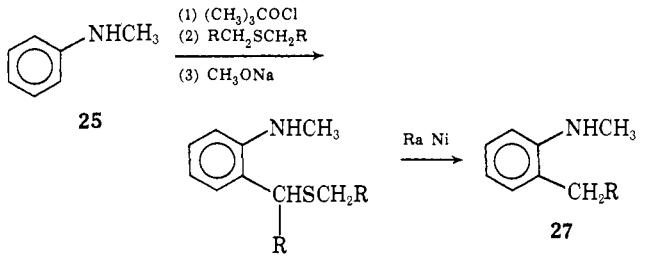
(9) For additional evidence concerning this electronic effect, see the following papers: P. G. Gassman and T. J. van Bergen, *J. Amer. Chem. Soc.*, **96**, 5508 (1974); P. G. Gassman, T. J. van Bergen, D. P. Gilbert, and B. W. Cue, Jr., *ibid.*, **96**, 5495 (1974); P. G. Gassman, G. Gruetzmacher, and T. J. van Bergen, *ibid.*, **96**, 5512 (1974).

Table IV. Yields Obtained in the Reductive Desulfurization of **10**, **15**, **21**, **22**, and **26** with W-2 Raney Nickel



2-(Thioalkoxy-alkyl)aniline	X	Z	R	R'	R''	Product	% yield
10a	CH_3	H	$C(CH_3)_3$	H	H	**11a**	76
10b	H	H	$C(CH_3)_3$	H	H	**11b**	69
15a	H	H	H	H	H	**16a**	63
15d	H	CH_3	H	H	H	**16d**	66
15e	Cl	H	H	H	H	**16e**	72[a]
15h	$CO_2C_2H_5$	H	H	H	H	**16h**	88
21	H	H	H	$-(CH_2)_2-$		**23**	62
22	H	H	H	$-(CH_2)_3-$		**24**	68
26a	H	H	CH_3	H	H	**27a**	72
26b	H	H	CH_3	CH_3	CH_3	**27b**	69

[a] In addition to 72% of **16e**, 10% of **16d** was obtained as a result of accompanying reductive dechlorination.



26a, R = H
b, R = CH_3
c, R = C_2H_5

The last aspect of this study which merits discussion is the reductive desulfurization with W-2 Raney nickel. In general, these reductions were very clean and simple to run. Table IV lists the yields obtained in selected reductive cleavages. As can be noted from the table the yields varied from *ca.* 60 to 90%.

In summary, our process provides a relatively simple method for the alkylation of aromatic amines. Since the key alkylation step occurs *via* a cyclic mechanism, little charge is developed on the aromatic ring. Thus, a wide variety of substituents can be tolerated. Through the use of sulfides such as tetrahydrothiophene and tetrahydrothiopyran, straight-chain alkyl groups can be readily introduced into the position ortho to the amino group. Since the primary amino group of anilines can be readily diazotized and replaced by a variety of other groups, our procedure provides a route into a large variety of specifically substituted aromatic compounds. Perhaps one of the most significant aspects of our overall process is that it can be readily used to introduce functionalized alkyl groups ortho to the amino function of anilines. Applications of this principle are described in the following papers in this series.

Experimental Section[10]

N-tert-**Butylanilines (7a–e).** The anilines 7a–e were prepared as described by Gassman, Campbell, and Frederick.[6,11]

N-tert-**Butyl-*p*-toluidinodimethylsulfonium Chloride (9a) (General Procedure).** In 250 ml of pentane under a nitrogen atmosphere in a three-necked, round-bottomed flask was placed 10.00 g (0.061 mol) of *N-tert*-butyl-*p*-toluidine. This solution was cooled to −10°, and 82 g (*ca.* 9 equiv) of calcium hypochlorite was added. After the reaction mixture was stirred for 1 hr at −10°, the excess calcium hypochlorite was removed by filtration, and the solution was concentrated by rotary evaporation. The *N*-chloroaniline was used in the next step without further purification.

The *N*-chloroaniline under a nitrogen atmosphere was placed in a three-necked, round-bottomed flask and cooled to −10°, and 100 ml of dimethyl sulfide was added slowly (about 5 min) with stirring. The flask was kept in the cooling bath for 5 min after completion of the addition of the sulfide. The reaction mixture was then stirred at room temperature for 4 hr. The salt formed was collected by filtration in a drybox to give 11.96 g (0.0461 mol, 76% yield) of **9a**. (This salt was extremely hygroscopic and had to be maintained under an anhydrous atmosphere.) An analytical sample was prepared by low-temperature recrystallization (three times from chloroform–ether). Between recrystallizations the salt was dissolved in chloroform and stirred over 3A molecular sieves. The purified sample had mp 153–154°: ir (KBr) 3.40, 6.67, 7.27, 8.47, 10.15, and 13.42 μ; nmr ($CDCl_3$) τ 8.58 (9 H, s), 7.53 (3 H, s), 6.72 (6 H, s), 2.45–2.88 (4 H, m).

Anal. Calcd for $C_{13}H_{22}ClNS$: C, 60.09; H, 8.53; N, 5.39; S, 12.34; Cl, 13.64. Found: C, 59.80; H, 8.37; N, 5.43; S, 12.04; Cl, 13.53.

N-tert-**Butylanilinodimethylsulfonium Chloride (9b).** In a generag procedure analogous to that used in the preparation of **9a**, 7.96 s (0.0534 mol) of *N-tert*-butylaniline was converted into **9b**. Changef involved the use of 8 equiv of calcium hypochlorite and 40 ml ol dimethyl sulfide. The white precipitate, which was formed, was collected by filtration to yield 10.39 g (0.0423 mol, 80% yield) of *N-tert*-butylanilinodimethylsulfonium chloride (**9b**). An analytical sample was prepared by low-temperature recrystallization (three times from methylene chloride–ether), mp 147–148°: ir (KBr) 3.39, 6.56, 8.33, 10.05, 12.66, 13.79 μ; nmr ($CDCl_3$) τ 2.30–2.85 (5 H, m), 6.72 (6 H, s), 8.56 (9 H, s).

Anal. Calcd for $C_{12}H_{20}ClNS$: C, 58.63; H, 8.20; N, 5.70; S, 13.04. Found: C, 58.63; H, 8.25; N, 5.67; S, 12.98.

N-tert-**Butyl-4-fluoroanllinodimethylsulfonium Chloride (9c).** In a general procedure analogous to that used for **9a**, 2.00 g (0.0120 mol) of *N-tert*-butyl-4-fluoroaniline was converted into **9c**. Changes involved the use of *ca.* 12 equiv of calcium hypochlorite and stirring for 2 hr at −10° instead of 1 hr and the use of 10 ml of dimethyl sulfide. A voluminous white precipitate formed within *ca.* 30 sec after the addition of dimethyl sulfide. After stirring for 5 min, 100 ml of dry ether was added and the mixture was stirred for 3 hr. The white precipitate was collected by filtration in a drybox to yield 2.52 g (0.0096 mol, 81%) of *N-tert*-butyl-4-fluoroanilinodimethylsulfonium chloride (**9c**); ir (KBr) 3.36, 6.29, 6.71, 8.17,

(10) Boiling points and melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 infracord. Nmr spectra were measured on Varian Associates A-60, A-60A, HA-100, or Joelco MH-100 nuclear magnetic resonance spectrometers. Mass spectral measurements were obtained on an MS-9 double-focusing mass spectrometer.

(11) P. G. Gassman, G. A. Campbell, and R. C. Frederick, *J. Amer. Chem. Soc.*, **94**, 3884 (1972).

10.18, 12.20 μ; nmr ($CDCl_3$) τ 8.54 (9 H, s), 6.68 (6 H, s), 2.51–2.95 (4 H, m). An analytical sample was prepared by drying a chloroform solution of **9c** over 4A molecular sieves, filtration and concentration of the solution, and recrystallization from chloroform–ether, mp 160–162°.

Anal. Calcd for $C_{12}H_{19}ClFNS$: C, 54.64; H, 7.26; N, 5.31; S, 12.15. Found: C, 54.06; H, 7.43; N, 5.31; S, 12.27.

***N-tert*-Butyl-4-chloroanilinodimethylsulfonium Chloride (9d).** In a general procedure analogous to that used for **9a**, 10.00 g (0.054 mol) of *N-tert*-butyl-4-chloroaniline in 250 ml of pentane was converted into **9d**. Changes involved the use of *ca.* 10 equiv of calcium hypochlorite and immediate stirring for 3 hr at room temperature, addition of 100 ml of dimethyl sulfide, and stirring the solution for 6 hr at room temperature. The salt, that was formed, was collected by filtration in the drybox and dried. The yield of **9d** was 9.04 g (0.0322 mol, 59%), mp 142–145°: ir (KBr) 3.45, 6.76, 8.47, 9.22, 13.79, 14.18 μ; nmr ($CDCl_3$) τ 8.62 (9 H, s), 6.75 (6 H, s), 2.02–2.83 (4 H, m). A satisfactory elemental analysis could not be obtained for 4-chloro-*N-tert*-butylanilinodimethylsulfonium chloride, presumably because it was extremely hygroscopic.

***N-tert*-Butylanilinodimethylsulfonium Trifluoroacetate (9e).** In 50 ml of dry methanol was placed 5.40 g (0.0220 mol) of *N-tert*-butylanilinodimethylsulfonium chloride. To this solution was added 4.86 g (0.0220 mol) of silver trifluoroacetate in 50 ml of dry methanol over a period of about 3 min. Upon commencement of the addition of the trifluoroacetate solution, a white precipitate formed. After 2 hr at room temperature, the silver chloride was filtered off and the solvent was removed by rotary evaporation. This procedure yielded a reddish-brown oil, which was triturated with dry ether to yield a white salt. This salt was dried to yield 5.43 g (0.0168 mol, 76%) of *N-tert*-butylanilinodimethylsulfonium trifluoroacetate. Three low-temperature recrystallizations from methylene chloride–ether gave an analytical sample, mp 149–150°; ir (KBr) 3.33, 5.92, 8.40, 8.97, 10.26, 12.20, 13.99, 14.18 μ; nmr ($CDCl_3$) τ 8.61 (9 H, s), 6.91 (6 H, s), 2.36–2.89 (5 H, m).

Anal. Calcd for $C_{14}H_{19}ClF_3NO_2S$: C, 52.00; H, 6.23; N, 4.33; S, 9.92. Found: C, 51.82; H, 6.24; N, 4.26; S, 10.10.

Sodium Methoxide Induced Rearrangement of *N-tert*-Butyl-*p*-toluidinodimethylsulfonium Chloride (9a) (General Procedure). In 5 ml of dry methanol, 1.00 g (3.61 mmol) of **9a** was dissolved, while 0.5 g (6 equiv) of sodium was allowed to react with 15 ml of dry methanol in a separate vessel. Both solutions were cooled to 0° and the sodium methoxide solution was added over a period of about 10 min to the azasulfonium salt solution. After the addition of the sodium methoxide solution, the ice bath was removed, and the solution was stirred for 4 hr at room temperature. At this time, 15 ml of water was added to the reaction mixture, and the solution was extracted three times with 25-ml portions of ether. The organic layer was washed with saturated sodium chloride solution, stirred over anhydrous magnesium sulfate, and filtered. Rotary evaporation removed the ether to yield a light yellow oil. Molecular distillation of the oil gave 0.75 g (3.36 mmol, 92%) of *N-tert*-butyl-2-(thiomethoxymethyl)-*p*-toluidine (**10a**); $n^{26.8}$D 1.5473; ir (neat) 3.33, 6.71, 7.41, 7.63, 12.42 μ; nmr (CCl_4) τ 8.69 (9 H, s), 8.20 (3 H, s), 7.87 (3 H, s), 6.52 (2 H, s), 5.79–5.98 (1 H, broad s), 3.03–3.42 (3 H, m).

Anal. Calcd for $C_{13}H_{21}NS$: C, 69.70; H, 9.48; N, 6.27; S, 14.35. Found: C, 70.00; H, 9.67; N, 6.23; S, 14.11.

Sodium Methoxide Induced Rearrangement of *N-tert*-Butylanilinodimethylsulfonium Chloride (9b). In a procedure analogous to that used in the rearrangement of **9a**, 1.00 g (4.06 mmol) of **9b** was rearranged. Changes involved stirring for 2 hr at room temperature after the ice bath was removed. Molecular distillation gave 0.81 g (3.87 mmol, 95%) of *N-tert*-butyl-2-(thiomethoxymethyl)aniline (**10b**); $n^{26.4}$D 1.5532; ir (neat) 3.28, 5.92, 6.76, 8.06, 12.66 μ; nmr (CCl_4) τ 8.64 (9 H, s), 8.15 (3 H, s), 6.46 (2 H, s), 5.56–5.85 (1 H, broad s), 2.84–3.64 (4 H, m).

Anal. Calcd for $C_{12}H_{19}NS$: C, 68.85; H, 9.15; N, 6.69; S, 15.31. Found: C, 68.86; H, 9.06; N, 6.58; S, 15.07.

Sodium Methoxide Rearrangement of *N-tert*-Butyl-4-chloroanilinodimethylsulfonium Chloride (9d). In an anhydrous atmosphere (or in a drybox), 1.47 g (5.25 mmol) of **9d** was placed in a tared, three-necked flask. The flask was removed from the drybox, nitrogen was passed through the flask, 25 ml of dry methanol was added, and the flask was cooled to 0°. Sodium methoxide (0.40 g, 1.4 equiv) was dissolved in 25 ml of methanol and cooled to 0°. The sodium methoxide solution was added over a period of about 15 min to the azasulfonium salt solution, after which time the reaction mixture was allowed to stir at room temperature for 2 hr and 25 ml of water was added. This solution was extracted three times with 25-ml portions of ether. The combined organic layers were washed with saturated sodium chloride solution, stirred over anhydrous magnesium sulfate, and filtered. Removal of the ether by rotary evaporation produced a light yellow oil. Molecular distillation of the oil gave 1.16 g (4.76 mmol, 90%) of *N-tert*-butyl-4-chloro-2-(thiomethoxymethyl)aniline (**10d**): $n^{24.2}$D 1.5649; ir (neat) 3.33, 6.62, 6.85, 8.26, 12.42 μ; nmr ($CDCl_3$) τ 8.61 (9 H, s), 8.03 (3 H, s), 6.40 (2 H, s), 5.85–5.97 (1 H, broad s), 2.69–3.43 (3 H, m).

Anal. Calcd for $C_{12}H_{18}ClNS$: C, 59.12; H, 7.44; N, 5.75; S, 13.15. Found: C, 59.19; H, 7.51; N, 5.50; S, 12.99.

Sodium Methoxide Induced Rearrangement of *N-tert*-Butyl-4-fluoroanilinodimethylsulfonium Chloride (9c). In a procedure identical with the one used in the sodium methoxide induced rearrangement of *N-tert*-butyl-4-chloroanilinodimethylsulfonium chloride, **9c** was rearranged in 88% yield to give *N-tert*-butyl-4-fluoro-2-(thiomethoxymethyl)aniline, **10c**, bp 85° (0.15 mm): $n^{23.7}$D 1.5363; ir (neat) 2.96, 3.33, 6.75, 8.14, 12.36, and 13.64 μ; nmr (CCl_4) τ 8.61 (9 H, s), 8.08 (3 H, s), 6.47 (2 H, s), 5.99 (1 H, broad s) and 3.12–3.47 (3 H, m).

Anal. Calcd for $C_{12}H_{18}FNS$: C, 63.40; H, 7.98; N, 6.16; S, 14.10. Found: C, 63.23; H, 8.03; N, 6.10; S, 14.17.

Sodium Methoxide Induced Rearrangement of *N-tert*-Butylanilinodimethylsulfonium Trifluoroacetate (9e). In a procedure analogous to that used for the rearrangement of **9a**, **9e** was rearranged. The reaction mixture was stirred for 1.5 hr at room temperature instead of 4 hr after the ice bath was removed. Molecular distillation of the oil produced 0.54 g (2.58 mmol, 83%) of *N-tert*-butyl-2-(thiomethoxymethyl)aniline (**10b**) identical in all respects with previously prepared samples.

***N-tert*-Butyl-*p*-toluidinotetramethylenesulfonium Chloride (12).** *N-tert*-Butyl-*N*-chloro-*p*-toluidine was prepared as described for the preparation of **9a**. To the dark red chloramine solution, cooled to −12° under nitrogen, was added dropwise 25 ml of tetrahydrothiophene. The resulting deep red solution was allowed to warm slowly to room temperature, during which time a large amount of precipitate formed. The reaction mixture was stirred at room temperature for 1 hr and the precipitated salt was collected by filtration in a drybox to give 5.97 g (0.021 mol, 68%) of a light purple solid. Purification was accomplished by stirring a chloroform solution of the salt over 4A molecular sieves for 12–16 hr, filtration, concentration of the solution *in vacuo*, and low-temperature recrystallization from chloroform–ether. This process was repeated twice to produce an analytically pure sample of **12**, mp 128.5–129.5°: ir ($CHCl_3$) 3.35, 6.63, 7.28, 8.0–8.3, 8.53, 9.00, 10.3 μ; nmr ($CDCl_3$) τ 8.62 (9 H, s), 8.20–8.75 (2 H, m), 7.61 (3 H, s), 7.49–8.06 (2 H, m), 6.31–6.93 (2 H, m), 5.37–5.99 (2 H, m), 2.56–2.98 (4 H, m).

Anal. Calcd for $C_{15}H_{24}ClNS$: C, 63.02; H, 8.46; Cl, 12.40; N, 4.90; S, 11.22. Found: C, 63.24; H, 8.35; Cl, 12.19; N, 4.93; S, 10.98.

Sodium Methoxide Induced Rearrangement of *N-tert*-Butyl-*p*-toluidinotetramethylenesulfonium Chloride (12). In a procedure analogous to the one used in the sodium methoxide induced rearrangement of **9a**, **12** gave, after column chromatography on silica gel (ether–hexane eluant), 29% of *N-tert*-butyl-2-(2-tetrahydrothionyl)-*p*-toluidine (**13**), mp 38.5–40.5°: ir (KBr) 2.91, 3.32, 6.60, 8.22, 12.35 μ; nmr (CCl_4) τ 8.62 (9 H, s), 7.52–8.00 (7 H, m), 6.73–7.12 (2 H, m), 6.06 (1 H, broad s), 5.40 (1 H, t), 3.03–3.24 (3 H, m).

Anal. Calcd for $C_{15}H_{23}NS$: C, 72.23; H, 9.29; N, 5.62; S, 12.86. Found: C, 72.32; H, 9.33; N, 5.59; S, 12.76.

The second compound eluted was 35% of *N-tert*-butyl-*p*-toluidine (**7a**).

The reaction was repeated and analyzed *via* gas phase chromatography on a 5% SE-30 on Chromsorb W column using diphenylmethane as an internal standard, which showed 56% of **7a** and 40% of **13**.

2-(Thiomethoxymethyl)aniline (15a) (General Procedure). A vigorously stirred solution of 10.0 g (0.1075 mol) of aniline in 250 ml of methylene chloride was cooled to −78° under nitrogen. From a jacketed, constant-pressure addition funnel, 11.68 g (0.1075 mol) of *tert*-butyl hypochlorite (also cooled to −78°) was added dropwise to the aniline solution over a 5-min period. The stirring was continued for 25 additional minutes, at which time the reaction mixture had turned dark green. The addition funnel was rinsed with 10 ml of methylene chloride, and 25 ml (*ca.* 3 equiv) of dimethyl sulfide was placed in the funnel and cooled to −78°. Upon addition of the dimethyl sulfide an exotherm was observed; this solution was stirred for 40 min. Methanol (50 ml) containing 7.0 g (0.13 mol, 1.2 equiv) of sodium methoxide was placed in the addi-

tion funnel, cooled to −78°, and added quickly to the reaction mixture. This solution was allowed to stir for 1 hr at −78°, at which time 100 ml of water was added and the heterogenous mixture was allowed to come to room temperature. The layers were separated, the aqueous layer was extracted with two 100-ml portions of methylene chloride, the combined organic extracts were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and filtered, and the solvent was removed *in vacuo* to leave a dark red oil. This oil was fractionally distilled to yield 1.84 g (0.02 mol) of aniline and 11.82 g (0.077 mol) of **15a**, bp 135–139° (10 mm), for a 72% yield based on starting material and a 90% yield based on unrecovered starting material; $n^{24.0}$D 1.6083 (lit.[5c] nD 1.6042).

4-Methyl-2-(thiomethoxymethyl)aniline (15b). A solution of 11.50 g (0.1075 mol) of *p*-toluidine (**14b**) in 400 ml of methylene chloride was vigorously stirred and cooled to −65° under nitrogen. To this solution was added dropwise 11.68 g (0.1075 mol) of *tert*-butyl hypochlorite in 20 ml of methylene chloride also at −65°. After the addition was complete, the solution was stirred for 15 min. The addition funnel was rinsed with 40 ml of methylene chloride and 25 ml (*ca.* 3 equiv) of dimethyl sulfide was placed in it and cooled to −65°. The dimethyl sulfide was added dropwise to the *N*-chloro-*p*-toluidine solution and the reaction mixture was stirred for 3.5 hr at −65°. In 50 ml of methanol, 7.0 g (0.1290 mol, 1.2 equiv) of sodium methoxide was cooled to −65°, and the solution was added dropwise to the reaction mixture. This reaction mixture was allowed to stir for 1 hr at −65° after which time the Dry Ice–acetone bath was removed and the reaction mixture was allowed to warm to room temperature. In order to remove the inorganic salts, 150 ml of water was added to the reaction mixture, the layers were separated, and the aqueous phase was washed twice with 100-ml portions of methylene chloride. The combined organic layers were dried over anhydrous magnesium sulfate and filtered. The solvents were removed *in vacuo* to yield a red oil. This oil was fractionally distilled to yield 3.04 g (0.028 mol, 26%) of *p*-toluidine, bp 85–90° (15 mm), and 7.50 g of **15b**, bp 90–92.5° (0.03 mm), which solidified and was recrystallized from pentane to yield 7.28 g (0.044 mol, 40%) of pure **15b**, mp 46.5–47.0° (lit.[5c] mp 42–45°). The yield of **15b** based on unrecovered *p*-toluidine was 55%.

3-Methyl-2-(thiomethoxymethyl)aniline (*o*-15c) and 5-Methyl-2-(thiomethoxymethyl)aniline (*p*-15c). The general procedure used for **15a** was used to convert 11.5 g (0.1075 mol) of *m*-toluidine (**14c**) in 400 ml of methylene chloride into a mixture of *o*-**15c** and *p*-**15c**. Changes involved stirring for 3 hr instead of 40 min after the addition of the dimethyl sulfide. Fractionation of the resultant oil gave 4.85 g (0.045 mol) of *m*-toluidine and 9.40 g (0.056 mol) of an approximately 1:1 mixture of the two named products (*o*-**15c** and *p*-**15c**) for a 50% yield (90% yield based upon unrecovered starting material), bp 87–90° (0.06 mm). All attempts to preparatively separate these two isomers failed.

6-Methyl-2-thiomethoxymethylaniline (15d). The general procedure used for **15a** was used to convert 11.5 g (0.1075 mol) of *o*-toluidine (**14d**) in 400 ml of methylene chloride into **15d**. After 1.5 hr following the addition of the dimethyl sulfide, a voluminous white precipitate had formed; the reaction mixture was stirred for an additional 30 min. Instead of stirring for 1 hr at −78°, the reaction mixture was allowed to warm to room temperature overnight. Fractionation of the resultant oil gave 1.80 g (0.017 mol) of *o*-toluidine and 11.38 g (0.068 mol, 63% yield based on starting material and a 74% yield based on unrecovered starting material) of **15d**, bp 82.5–84.5° (0.03 mm); $n^{24.0}$D 1.5963 (lit.[5c] nD 1.5998).

4-Chloro-2-thiomethoxymethylaniline (15e). In a procedure analogous to that used with **15a**, 5.50 g (0.043 mol) of *p*-chloroaniline (**14e**) was converted into **15e**. Changes involved the addition of *ca.* 5 equiv of dimethyl sulfide and subsequent stirring at −78° for 5.5 hr. After addition of the sodium methoxide solution, the resultant solution was stirred for 1 hr at −78°, the bath was removed, and the reaction mixture was allowed to warm to room temperature overnight. Chromatography of the red solid obtained as product on silica gel (25% ether–pentane solvent) separated the product from the starting material. The first compound eluted was **15e** (5.44 g, 0.029 mol), mp 79–80° (lit.[5c] mp 78–79°) (67%, 83% based on unrecovered starting material). The remaining 1.85 g of material eluted was a mixture of product and starting material.

3-Chloro-2-(thiomethoxymethyl)aniline (*o*-15f) and 5-Chloro-2-(thiomethoxymethyl)aniline (*p*-15f). A procedure analogous to that used for the conversion of **14e** was used to convert 13.7 g of **14f** into a mixture of *o*-**15f** and *p*-**15f**. After the dimethyl sulfide was added dropwise, the solution was stirred for 6 hr. The oil was fractionally distilled to yield 6.98 g (0.055 mol) of *m*-chloroaniline (**14f**) and 9.99 g (0.053 mol) of an approximately 60:40 mixture of *o*-**15f** and *p*-**15f** for a 50% yield (87% yield based on unrecovered starting material), bp 128–130° (0.08 mm). These two isomers could be separated by preparative gas phase chromatography on a 10% Carbowax 20M:KOH on 60–80 Chromosorb W column at 215°. The first compound eluted was *p*-**15f**: $n^{25.0}$D 1.6157; ir (neat) 3.00, 3.49, 6.24, 6.89, 10.25, 12.94 μ; nmr (CCl_4) τ 8.04 (3 H, s), 6.15 (2 H, s), 5.92 (2 H, broad s), 2.95–3.65 (3 H, m).

Anal. Calcd for $C_8H_{10}ClNS$: C, 51.19; H, 5.37; N, 7.46. Found: C, 51.10; H, 5.39; N, 7.40.

The second compound eluted was *o*-**15f**: $n^{25.0}$D 1.6153; ir (neat) 2.98, 3.45, 6.29, 6.75, 11.01 μ; nmr (CCl_4) τ 8.10 (3 H, s), 6.45 (2 H, s), 5.95 (2 H, broad s), 3.08–3.53 (3 H, m).

Anal. Calcd for $C_8H_{10}ClNS$: C, 51.19; H, 5.37; N, 7.46. Found: C, 51.13; H, 5.47; N, 7.36.

2-Chloro-6-(thiomethoxymethyl)aniline (15g). The procedure was identical with that used in the preparation of 3- and 5-chloro-2-(methylthiomethyl)aniline. In this manner, **15g** was synthesized from *o*-chloroaniline (**14g**) in 26% yield (5.25 g, 0.029 mol): $n^{23.7}$D 1.6160 (lit.[5c] nD 1.6730). Also recovered was 8.68 g (0.068 mol) of *o*-chloroaniline. The yield based on unrecovered starting material was 70%.

4-Carbomethoxy-2-(thiomethoxymethyl)aniline (15h). In a procedure analogous to that used for **15a**, 16.52 g (0.10 mol) of benzocaine (**14h**) was converted into **15h**. Changes involved stirring for 2 hr at −78° prior to the addition of dimethyl sulfide and 18 hr after the addition. At that time the reaction mixture was allowed to warm to room temperature prior to the addition of water. The inorganic salts that formed were dissolved by the addition of 100 ml of water, the layers were separated, and the aqueous phase was washed with two 150-ml portions of methylene chloride. The combined organic layers were dried over anhydrous magnesium sulfate and filtered, and the solvents were evaporated to produce a dark red oil, which solidified upon standing. This red solid was refluxed in 400 ml of toluene with 25 ml of triethylamine for 24 hr. The solvent was removed by rotary evaporation to produce again a red oil which solidified upon standing. The solid was recrystallized in two crops from absolute ethyl alcohol to yield 14.70 g (0.065 mol, 65%) of **15h**, mp 83–84.5°. An analytical sample was prepared by recrystallizing a small portion twice from pentane–ether, mp 84–85.5°: ir (KBr) 2.95, 3.32, 5.93, 6.13, 6.25, 7.81, 8.37, 8.75, 12.96 μ; nmr ($CDCl_3$) τ 8.66 (3 H, t), 8.04 (3 H, s), 6.33 (2 H, s), 5.68 (2 H, q), 5.60 (2 H, broad s), 2.78 (3 H, m).

Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 58.64; H, 6.71; N, 6.23. Found: C, 58.66; H, 6.66; N, 6.15.

2-Amino-3-(thiomethoxymethyl)biphenyl (15i). In a procedure analogous to that used for **15a**, 8.46 g (0.05 mol) of 2-aminobiphenyl (**14i**) was converted into **15i**. Changes involved stirring for 1 hr prior to the addition of the dimethyl sulfide and for 4 hr after the addition. After the addition of the methanolic sodium methoxide, the solution was stirred for 1 hr. The cooling bath was removed, the reaction mixture was allowed to warm to room temperature, 200 ml of water was added, the layers were separated, the aqueous phase was washed twice with 200 ml portions of methylene chloride, and the combined organic phases were dried with anhydrous magnesium sulfate. The solution was filtered, and the solvents were removed *in vacuo* to yield a dark oil. The oil was vacuum transferred to give 6.55 g of a yellow oil, which was chromatographed on silica gel with ether–pentane as eluant. This procedure yielded 1.25 g (0.0074 mol) of 2-aminobiphenyl (**14i**) and 4.02 g (0.0175 mol) of **15i** (35% yield, 41% based on unrecovered starting material): $n^{25.0}$D 1.6435; ir (neat) 2.94, 3.48, 6.25, 6.91, 13.20, 13.45, and 14.31 μ; nmr (CCl_4) τ 8.15 (3 H, s), 4.39 (2 H, s), 3.97 (2 H, broad s), 2.55–3.60 (8 H, m).

Anal. Calcd for $C_{14}H_{15}NS$: C, 73.32; H, 6.59; N, 6.11. Found: C, 73.34; H, 6.60; N, 6.23.

4-Nitro-2-(thiomethoxymethyl)aniline (15j). In a 1-l., three-necked flask, equipped with a mechanical stirrer, were placed 2.76 g (0.02 mol) of 4-nitroaniline, 300 ml of acetonitrile, and 100 ml of methylene chloride. This solution was cooled to *ca.* −45° by means of a Dry Ice–60% aqueous methanol bath. From an addition funnel, 2.17 g (0.02 mol) of *tert*-butyl hypochlorite in 5 ml of methylene chloride was added dropwise. This solution was stirred for 30 min at *ca.* −45°, 5 ml (*ca.* 3 equiv) of dimethyl sulfide was added dropwise, and the reaction mixture was stirred for 18 hr while maintaining the temperature at *ca.* −45°. At this time, 5 ml of triethylamine was added dropwise, and the solution was stirred for 1 hr. The cooling bath was removed, and the reaction mixture was refluxed for 48 hr. The solvents were removed by rotary evaporation. To the resultant red oil was added 100 ml of 10% aqueous

sodium hydroxide and 100 ml of methylene chloride. The layers were separated, the aqueous phase was extracted with two 100-ml portions of methylene chloride, the organic phases were combined, dried over anhydrous magnesium sulfate, and filtered, and the solvents were removed *in vacuo*. The resultant red-yellow solid was chromatographed on silica gel with hexane–ether to yield 2.10 g (10.6 mmol, 53%, 71% based on unrecovered starting material) of **15j**, mp 76–77° (lit.[5c] mp 75–77°). The second compound eluted was 4-nitroaniline (0.70 g, 5 mmol, 25%).

4-Methoxy-2-(thiomethoxymethyl)aniline (15k). In 150 ml of methylene chloride was placed 4.65 ml (3 equiv) of dimethyl sulfide, which was cooled to −78° under nitrogen. In a jacketed, constant-pressure addition funnel, 2.17 g (0.02 mol) of *tert*-butyl hypochlorite in 10 ml of methylene chloride was cooled to −78° and added dropwise to the dimethyl sulfide solution. The reaction mixture was stirred for 10 min. In a nonjacketed addition funnel was placed 2.46 g (0.02 mol) of *p*-anisidine (**14k**) in 20 ml of methylene chloride, and the solution was added dropwise to the reaction mixture. The reaction mixture was stirred for 2 hr at −78°. In 25 ml of absolute methanol was dissolved 2.28 g (2 equiv) of sodium methoxide. This solution was added dropwise to the reaction mixture which was then stirred for 15 min at −78°. At this time the Dry Ice–acetone bath was removed, and the reaction was allowed to warm to room temperature. The reaction was quenched with 50 ml of water, the layers were separated, and the aqueous phase was extracted two times with 50-ml portions of methylene chloride. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated to yield a dark oil. This oil was distilled to give a yellow oil (bp 80–120° (0.1 mm)) which solidified. Preparative gas chromatography on a 10% Carbowax 20M:KOH on 60–80° Chromosorb W column at 190° with a flow rate of 200 ml/min was used to separate product from starting material. The first compound eluted was *p*-anisidine (**14k**) (0.56 g, 4.6 mmol); the second compound eluted was 4-methoxy-2-(thiomethoxymethyl)aniline (**15k**) (82 mg, 0.45 mmol, 2.2%, 2.9% based on recovered starting material): $n^{24.4}$D 1.5965; ir (neat) 2.90, 3.38, 6.64, 8.03, 9.60, and 12.35 μ; nmr (CCl_4) τ 8.06 (3 H, s), 6.46 (2 H, s), 6.32 (3 H, s), 6.30 (2 H, broad s), 3.48 (3 H, s).

Anal. Calcd for $C_9H_{13}NOS$: exact mass mol wt, 183.0717. Found: exact mass mol wt, 183.0720.

3-Methoxy-2-(thiomethoxymethyl)aniline (*o*-15l) and 5-Methoxy-2-(thiomethoxymethyl)aniline (*p*-15l). Under nitrogen in a 1-l., three-necked flask equipped with a mechanical stirrer was placed 12.32 g (0.10 mol) of *m*-anisidine (**14l**) and 400 ml of methylene chloride. This solution was cooled to −78°. In a jacketed, constant-pressure addition funnel was placed 10.85 g (0.10 mol) of *tert*-butyl hypochlorite in 15 ml of methylene chloride. This solution was cooled to *ca.* −65° and added dropwise to the reaction mixture, and the solution was stirred for 5 min. The addition funnel was rinsed with 40 ml of methylene chloride, and 25 ml (*ca.* 3 equiv) of dimethyl sulfide was placed in the addition funnel (cooled to *ca.* −65°) and added dropwise to the reaction mixture. The solution was stirred for 30 min, during which time a white precipitate formed. Sodium methoxide (6.48 g, 0.12 mol) in 50 ml of anhydrous methanol was cooled and quickly added to the reaction mixture. The resultant solution was stirred for 15 min and the cooling bath was removed; the solution was allowed to warm to room temperature, 150 ml of water was added, the layers were separated, and the aqueous phase was washed with two 100-ml portions of methylene chloride. The combined organic phases were dried over anhydrous magnesium sulfate and filtered, and the solvents were removed to leave a red oil. This oil was taken up in 400 ml of *tert*-butyl alcohol and refluxed for 12 hr with 11.20 g (1 equiv) of potassium *tert*-butoxide. The *tert*-butyl alcohol was removed *in vacuo*. The residue was taken up in 100 ml of water and 100 ml of methylene chloride; the layers were separated, and the aqueous phase was washed with two 100-ml portions of methylene chloride. The combined organic phases were dried over anhydrous magnesium sulfate and filtered, and the solvents were removed by rotary evaporation to yield a dark oil. Distillation of this oil gave 1.62 g (0.013 mol, 13%) of *m*-anisidine (**14l**) and 8.77 g (0.048 mol, 48% (55% based on unrecovered starting material)) of a mixture (3:1 by nmr) of *p*-**15l** and *o*-**15l**, bp 141–145° (0.45 mm). By preparative gas phase chromatography, using a 10% Carbowax 20M:KOH on 60–80 Chromosorb W column, 10 ft × 1/4 in. at 220°, a pure sample of *p*-**15l** could be isolated: $n^{22.8}$D 1.6023; ir (neat) 2.96, 3.42, 6.17, 6.82, 7.93, 9.35, 12.80 μ; nmr (CCl_4) τ 8.10 (3 H, s), 6.32 (2 H, s), 6.28 (3 H, s), 6.03 (2 H, broad s), 3.81 (2 H, m), 3.18 (1 H, m).

Anal. Calcd for $C_9H_{13}NOS$: C, 58.98; H, 7.15; N, 7.64. Found: C, 59.27; H, 7.09; N, 7.74.

The sample of *o*-**15l** was contaminated with small amounts of the 5-methoxy isomer: nmr (CCl_4) τ 8.3 (3 H, s), 6.48 (2 H, s), 6.36 (3 H, s), 6.15 (2 H, broad s), 3.88 (2 H, m), and 3.25 (1 H, m).

Benzenesulfenanilide (20) from *n*-Butyl Phenyl Sulfide. In a vigorously stirred solution of 300 ml of acetonitrile and 100 ml of methylene chloride was placed 1.86 g (0.02 mol) of aniline and 4.98 g (0.03 mol) of *n*-butyl phenyl sulfide. This solution was cooled to −45 to −40°. A solution of 3.26 g (0.03 mol) of *t*-butyl hypochlorite in 10 ml of methylene chloride was added dropwise to the solution and stirred for 3 hr. A solution of 2.16 g (0.04 mol) of sodium methoxide in 20 ml of absolute methanol was added slowly to the solution and stirred for 30 min. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. The solvents were removed at reduced pressure, and 100 ml of water and 100 ml of methylene chloride were added to the residue. The layers were separated, the aqueous phase was washed twice with 100-ml portions of methylene chloride, and the combined organic extracts were dried over anhydrous magnesium sulfate. The solution was filtered, the solvents were removed on the rotary evaporator, and the resultant red oil was refluxed in 100 ml of anhydrous toluene with 5 ml of triethylamine for 2 hr. Upon removal of the solvents the dark red oil was chromatographed on silica gel with pentane–ether as eluant to yield 2.81 g (0.014 mol, 70%) of **20**, mp 57–59° (lit.[12] mp 53–55°). The ir and nmr spectra were consistent with the proposed structure.

Benzenesulfenanilide (20) from Phenyl Isopropyl Sulfide. Benzenesulfenanilide (**20**) was prepared in 76% yield using phenyl isopropyl sulfide in a manner similar to the one described using *n*-butyl phenyl sulfide except that the period of stirring at −40° was for 4.5 hr and the reflux period was for 4 hr. The ir and nmr spectra were identical with those of **20** prepared from *n*-butyl phenyl sulfide.

2-(2-Tetrahydrothienyl)aniline (21). In a general procedure analogous to that used in the preparation of **15a**, 10.0 g (0.1075 mol) of aniline in 200 ml of methylene chloride was converted into **21**. Changes involved stirring for 10 min after the addition of the hypohalite and the addition of 44 ml of tetrahydrothiophene instead of dimethyl sulfide. After the addition of the tetrahydrothiophene, the reaction mixture was stirred for 3 hr at −78° prior to the addition of the base. After the addition of base, the Dry Ice–acetone cooling bath was removed and the solution was stirred for 2 hr. Fractional distillation of the resulting oil gave 5.03 g (0.054 mol) of aniline and 6.11 g (0.034 mol) of **21** for a 31% yield based on starting material (64% yield based on unrecovered starting material), bp 130–134° (0.19 mm): $n^{26.8}$D 1.6258, ir (neat) 2.92, 3.36, 6.12, 6.70, and 13.40 μ; nmr (CCl_4) τ 7.82 (4 H, m), 6.99 (2 H, m), 6.06 (2 H, s), 5.52 (2 H, t), 3.20 (4 H, m).

Anal. Calcd for $C_{10}H_{13}NS$: C, 66.99; H, 7.31; N, 7.81. Found: C, 67.04; H, 7.29; N, 7.74.

2-(2-Tetrahydrothiopyranyl)aniline (22). In a 1-l., three-necked flask equipped with a mechanical stirrer was placed 9.30 g (0.10 mol) of aniline in 400 ml of methylene chloride. This solution was cooled to −70° by means of a Dry Ice–acetone bath. A solution of 10.85 g (0.10 mol) of *tert*-butyl hypochlorite in 25 ml of methylene chloride was added dropwise to the aniline solution. The resultant *N*-chloroaniline solution was stirred for 5 min and 25 ml (*ca.* 3 equiv) of tetrahydrothiopyran was added at such a rate as to maintain the exotherm to less than 10°. This dark solution was stirred for 4 hr, 25 ml of triethylamine was added dropwise, and the solution was stirred for 1 hr at −70 to −60°. The cooling bath was removed and the solvents were removed *in vacuo*. This yielded a dark residue which was refluxed overnight in 200 ml of acetonitrile containing 25 ml of triethylamine. The solvents were removed by rotary evaporation, 200 ml of 10% aqueous sodium hydroxide and 200 ml of methylene chloride were added, the layers were separated, and the aqueous phase was washed with two 200-ml portions of methylene chloride. The combined organic phases were dried over anhydrous magnesium sulfate and filtered, and the solvents were removed by rotary evaporation to produce a dark oil. Distillation of this oil yielded 0.56 g (0.006 mol) of aniline and 7.83 g (0.04 mol, 41%, 44% based on unrecovered starting material) of **22**, bp 139–140° (0.10 mm). An analytical sample was prepared by column chromatography on silica gel using hexane as an eluant: $n^{24.3}$D 1.6107; ir (neat) 2.92, 3.36, 6.12, 6.76, 7.94, 13.38 μ; nmr (CCl_4) τ 7.70–8.75 (6 H, m), 7.03–7.52 (2 H, m) 6.20

(12) H. Lercher, F. Holschneider, K. Koberle, W. Speer, and P. Stocklin, *Chem. Ber.*, **58**, 409 (1935).

(1 H, m), 6.04 (2 H, s), 2.80–3.59 (4 H, m). This sample solidified in the refrigerator, mp 65.5–67.0°; the original distillate also solidified.

Anal. Calcd for $C_{11}H_{15}NS$: C, 68.35; H, 7.82; N, 7.25. Found: C, 68.46; H, 7.93; N, 7.34.

N-Methyl-2-(thiomethoxymethyl)aniline (26a) (General Procedure). In a 1-l., three-necked flask, equipped with a mechanical stirrer, were placed 10.70 g (0.10 mol) of *N*-methylaniline (**25**) and 400 ml methylene chloride. This mixture was cooled to *ca.* −70° with a Dry Ice–acetone bath. To this solution was added dropwise 10.85 g (0.10 mol) of *tert*-butyl hypochlorite in 10 ml of methylene chloride. The resultant dark green solution was stirred for 5 min, 25 ml (*ca.* 3 equiv) of dimethyl sulfide was added dropwise while maintaining the exotherm to less than 10°, and the mixture was stirred for 3 hr. At this time 6.48 g (0.12 mol) of sodium methoxide in 50 ml of anhydrous methanol was added and the solution was stirred for 1 hr. The cooling bath was removed, the solution was allowed to warm to room temperature, and 200 ml of 10% aqueous sodium hydroxide was added to the reaction mixture. The layers were separated, and the aqueous phase was washed twice with 200-ml portions of methylene chloride. The organic phases were combined, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to yield a dark oil. This oil was distilled to yield 1.76 g (0.0164 mol, 16%) of *N*-methylaniline and 9.94 g (0.0594 mol, 59%, 72% based on unrecovered starting material) of **26a**, bp 86–89° (0.35 mm): $n^{23.4}$D 1.5994; ir (neat) 2.92, 3.41, 6.23, 6.63, 7.65, and 13.41 μ; nmr (CCl_4) τ 8.16 (3 H, s), 7.20 (3 H, s), 6.42 (2 H, s), 5.62 (1 H, broad s), 2.70–3.60 (4 H, broad m).

Anal. Calcd for $C_9H_{13}NS$: C, 64.62; H, 7.83; N, 8.37. Found: C, 64.64; H, 7.89; N, 8.36.

N-Methyl-2-(1-thioethoxyethyl)aniline (26b). In a procedure analogous to that used to prepare *N*-methyl-2-(thiomethoxymethyl)-aniline, **26b** was prepared from **25** and diethyl sulfide in 45% yield, bp 130–132° (6 mm): $n^{22.8}$D 1.5730; ir (neat) 2.90, 3.27, 6.16, 6.54, 7.60, and 13.40 μ; nmr (CCl_4) τ 8.90 (3 H, t), 8.41 (3 H, d), 7.73 (2 H, q), 7.17 (3 H, s), 6.02 (1 H, q), 5.21 (1 H, broad s), and 2.77–3.64 (4 H, m).

Anal. Calcd for $C_{11}H_{17}NS$: C, 67.64; H, 8.77; N, 7.17. Found: C, 67.32; H, 8.70; N, 7.05.

N-Methyl-2-(1-thiopropoxypropyl)aniline (26c). In a procedure analogous to that used in the preparation of **26a**, 5.35 g (0.05 mol) of *N*-methylaniline (**25**) was converted into **26e**. After the addition of the hypohalite and subsequent stirring for 5 min, a solution of 11.0 ml (0.075 mol) of di-*n*-propyl sulfide in 15 ml of dry methylene chloride was cooled to −70° and added dropwise to the reaction mixture while maintaining the exotherm to less than 10°. The resultant solution was stirred for 5 hr at *ca.* −70°. The base-promoted rearrangement was effected by addition of a solution of 5.40 g (0.10 mol) of sodium methoxide in 25 ml of absolute methanol. The reaction mixture was stirred for 1 hr at −70°, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. The reaction was worked up by addition of 200 ml of water, separation of the layers, and washing of the aqueous phase twice with 200-ml portions of methylene chloride. The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give a clear oil. Column chromatography on silica gel (ether–hexane eluant) gave 2.77 g (0.012 mol, 24%) of **26c** as a clear oil: $n^{23.8}$D 1.5549; ir (neat) 2.90, 3.28, 6.18, 6.55, 8.52, 13.39 μ; nmr (CCl_4) τ 7.60–9.30 (12 H, m), 7.14 (3 H, s), 6.21 (1 H, t), 5.10 (1 H, broad s), and 2.70–3.58 (4 H, m). The second compound eluted was *N*-methylaniline (0.012 mol, 24%). The yield of **26c** based on unrecovered starting material was 32%.

Anal. Calcd for $C_{13}H_{21}NS$: C, 69.90; H, 9.48; N, 6.27. Found: C, 69.57; H, 9.43; N, 6.17.

W-2 Raney Nickel. The W-2 Raney nickel used in these experiments was obtained from W. R. Grace and Co., Raney Catalyst Div., South Pittsburg, Tenn., as No. 28 Raney active nickel catalyst in water. A portion of this was placed in a beaker and washed with distilled water until neutral to pH paper and then several more times with distilled water, three times with 95% ethanol, and three times with absolute ethanol. The catalyst under absolute ethanol was stored in brown bottles until use. This material was identical in its reduction of sulfides with W-2 Raney nickel produced by the method of Mozingo.[13]

N-*tert*-Butyl-*o*-toluidine (11b). To a vigorously stirred solution of 0.504 g (2.41 mmol) of *N*-*tert*-butyl-2-(thiomethoxymethyl)-aniline (**10b**) in 20 ml of absolute ethanol was added 1.75 tsp (*ca.* 5 equiv) of W-2 Raney nickel[13] and about 40 ml of absolute ethanol was used to wash the spoon and powder funnel. This mixture was refluxed for 2 hr, 200 ml of water was added, and the *N*-*tert*-butyl-*o*-toluidine was azeotropically distilled with the water–ethanol. The distillate was extracted with three 100-ml portions of ether and the combined organic layers were washed with saturated sodium chloride, dried with anhydrous potassium carbonate, and filtered. The organic solvents were removed by distillation through a Vigreux column. Molecular distillation afforded 0.271 g (1.66 mmol, 69%) of *N*-*tert*-butyl-*o*-toluidine (**11b**); $n^{25.9}$D 1.5178 (lit.[11] $n^{25.9}$D 1.5178).

N-*tert*-Butyl-2,4-xylidine (11a). In a procedure identical with that used in the preparation of *N*-*tert*-butyl-*o*-toluidine (**11b**), **11a** was prepared in 76% yield from *N*-*tert*-butyl-2-(thiomethoxymethyl)-*p*-toluidine: $n^{25.2}$D 1.5136; ir (neat) 2.90, 3.34, 6.58, 6.86, 8.20, 12.42 μ; nmr (CCl_4) τ 8.69 (9 H, s), 7.94 (3 H, s), 7.82 (3 H, s), 3.22–3.37 (3 H, m). No N–H resonance was seen.

Anal. Calcd for $C_{12}H_{19}N$: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.08; H, 10.84; N, 8.03.

***o*-Toluidine (16a) (General Procedure).** To a vigorously stirred solution of 2.50 g (0.0163 mol) of 2-(thiomethoxymethyl)aniline (**15a**) in 100 ml of absolute ethanol was added *ca.* 30 g (10 level tsp) of W-2 Raney nickel. This solution was stirred for 30 min at room temperature. The Raney nickel was removed by filtration and washed five times with 100-ml portions of absolute ethanol. The ethanol was removed at reduced pressure. The resultant residue was taken up in 200 ml of methylene chloride and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solution was concentrated by rotary evaporation to yield a clear oil. Distillation of this oil gave 1.10 g (0.0103 mol, 63% yield), $n^{22.8}$D 1.5680 (lit.[14] n^{20}D 1.5688). The *o*-toluidine produced was identical in all respects with an authentic sample.

2,6-Xylidine (16d). 2,6-Xylidine, $n^{24.4}$D 1.5598 (lit.[15] $n^{14.75}$D 1.5616), was produced from 6-methyl-2-(thiomethoxymethyl)aniline (**15d**) in 66% yield in a fashion analogous to the procedure used to prepare 4-carboethoxy-2-methylaniline (see below).

4-Chloro-*o*-toluidine (16e). To a vigorously stirred solution of 1.10 g (0.0059 mol) of 4-chloro-2-(thiomethoxymethyl)aniline in 30 ml of absolute ethanol cooled to 0° was added *ca.* 9 g (3 tsp) of W-2 Raney nickel. After vigorously stirring this mixture for 10 min, the Raney nickel was removed by filtration and washed twice with 50-ml portions of methylene chloride. The solvents were removed by rotary evaporation. The resultant residue was taken up in 25 ml of methylene chloride and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and washed with two 50-ml portions of methylene chloride. The solvents were removed at reduced pressure to yield 0.66 g of a mixture of **16e** and *o*-toluidine (**16a**). This mixture was analyzed by vapor phase chromatography using a 10% Carbowax 20M:KOH on 60–80 Chromosorb W column at 150°, which showed the mixture to be 90% **16e** and 10% **16a**. The yield of **16e** (0.594 g, 0.0042 mol) was 72% and the yield of **16a** (0.066 g, 0.00062 mol) was 10%.

4-Carboethoxy-2-methylaniline (16h).[16] To a vigorously stirred solution of 3.67 g (0.0163 mol) of 4-carboethoxy-2-(thiomethoxymethyl)aniline (**15h**) in 100 ml of absolute ethanol was added *ca.* 30 g (10 tsp) of W-2 Raney nickel. This mixture was stirred for 30 min at room temperature. The Raney nickel was removed by filtration and washed twice with 100-ml portions of absolute ethanol and twice with 100-ml portions of methylene chloride. The combined washings were concentrated at reduced pressure to leave a clear oil. The oil was taken up in 100 ml of methylene chloride and dried over anhydrous magnesium sulfate. The magnesium sulfate was removed by filtration, and the solution was concentrated at reduced pressure to give a clear oil which solidified upon standing. This procedure gave 2.66 g (0.0143 mol, 88%) of **16h**, mp 76–77°: ir (KBr) 2.92, 5.90, 6.21, 7.72, 7.88, 8.36, 13.00 μ; nmr ($CDCl_3$) τ 8.67 (3 H, t), 7.85 (3 H, s), 5.96 (1 H, broad s), 5.69 (2 H, q), 2.12–3.50 (3 H, m).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.89; H, 7.24; N, 7.87.

2-*n*-Butylaniline (23). 2-*n*-Butylaniline (**23**) was produced from **21** in 62% yield in a manner analogous to the procedure used to

(13) R. Mozingo, "Organic Syntheses," Collect Vol. III, Wiley, New York, N. Y., 1955, p 181.

(14) H. G. Tanner and P. A. Lasselle, *J. Amer. Chem. Soc.*, 48, 2165 (1926).

(15) K. Auwers, *Justus Liebigs Ann. Chem.*, 422, 160 (1921).

(16) F. J. Viliani, U. S. Patent 2764519 (1956); *Chem. Abstr.*, 51, P 4443c (1957).

prepare *o*-toluidine; **23** gave nmr and ir spectral data consistent with the structure; $n^{23.4}$D 1.5362. The hydrochloride was prepared, mp 139–140° (lit.[17] mp 137°).

2-*n*-Pentylaniline (24). By a procedure identical with that used to prepare 4-carboethoxy-2-methylaniline, **24** was prepared from **22** in 68% yield, bp 80° (9 mm): $n^{22.4}$D 1.5292; ir (neat) 2.86, 3.35, 6.13, 6.64, 13.37 μ; nmr (CCl_4) τ 8.21–9.25 (9 H, m), 7.40–7.75 (2 H, m), 6.64 (2 H, s), 2.89–3.62 (4 H, m).

Anal. Calcd for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.50. Found: C, 80.86; H, 10.35; N, 8.62.

2,*N*-Dimethylaniline (27a). By a method similar to the one used to prepare 4-carboethoxy-2-methylaniline, **27a**, $n^{24.4}$D 1.5622 (lit.[18] n^{20}D 1.5649), was prepared from **26a** in 72% yield.

2-Ethyl-*N*-methylaniline (27b). 2-Ethyl-*N*-methylaniline, **(27b)**, $n^{25.1}$D 1.5538 (lit.[19] n^{20}D 1.5553), was prepared from **26b** in 69% yield by a procedure analogous to that used to prepare 4-carboethoxy-2-methylaniline.

Acknowledgment. We are indebted to the National Cancer Institute of the Public Health Services for a grant which supported this study.

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(18) H. Ley and G. Pfeiffer, *Chem. Ber.*, **54**, 363 (1921).

(19) G. G. Eche, J. P. Napolitano, A. H. Filbey, and A. J. Kolka, *J. Org. Chem.*, **22**, 639 (1957).

A General Method for the Synthesis of Indoles[1]

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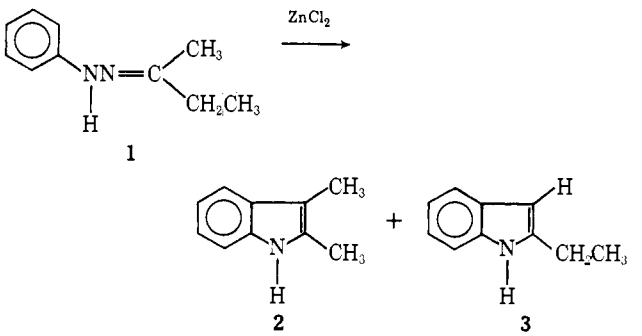
Abstract: A new, general method has been developed for the synthesis of indole and its derivatives from anilines and β-keto sulfides, α-formyl sulfides, or their derivatives. The method involves initial mono-N-chlorination of the aniline with *tert*-butyl hypochlorite or some other suitable halogenating agent. Addition of the sulfide to the *N*-chloroaniline gives an azasulfonium salt, which on treatment with mild base produces a sulfur ylide. These ylides spontaneously rearrange in a Sommelet–Hauser type rearrangement to give aniline derivatives which are substituted exclusively at the ortho position. Addition of the amino function to the carbonyl group produces 2-hydroxyindolines, which dehydrate under the reaction conditions to give indoles. The sulfide group, which occupied the 3 position of the indole system, was removed reductively by Raney nickel. The described procedure permitted the synthesis of a wide variety of indoles substituted in the 1, 2, 4, 5 and/or 7 positions in good to excellent overall yields. In a modification of this general indole synthesis, α-alkyl- or α-aryl-β-keto sulfides were used to produce the azasulfonium salts. Treatment of the azasulfonium salt with triethylamine produced an ylide which rearranged and intramolecularly condensed to form a 2,3-disubstituted 3-methylthioindolenine. Reductive desulfurization of these indolenines to the corresponding 2,3-disubstituted indoles could be accomplished with W-2 Raney nickel, lithium aluminum hydride, or sodium borohydride. The use of α-methylthio derivatives of cyclic ketones gave indole derivatives which were ring fused at the 2 and 3 positions. When α-methylthiocyclohexanone was used as the sulfide, tetrahydrocarbazoles were obtained as the end products. The potential utility of our modified synthesis in the preparation of complex indole derivatives is discussed.

For nearly a century, the classical Fischer method[3] has been a mainstay of those chemists involved in the synthesis of indole and its derivatives.[4,5] Its widespread use has resulted from its versatility, especially when coupled with the Japp–Klingemann reaction.[6] In its simplest form, the Fischer indole synthesis involves the rearrangement of a phenylhydrazone, such as **1**, in the presence of a Lewis acid, such as zinc chloride, into a mixture of **2** and **3**, with **2** predominating. We now wish to report the details of a new, simple



method for the synthesis of indoles, which we feel offers many advantages over the Fischer method. In its simplest form, our indole synthesis involves a one-pot reaction in which hypohalite, a β-carbonyl sulfide derivative, and base are added sequentially to an aniline to yield 3-thioalkoxyindoles in good to excellent yield. Raney-nickel reduction then produces the desulfurized indole.

Our studies of the ortho substitution of aromatic amines *via* intramolecular rearrangements of ylides derived from azasulfonium salts have been shown to offer a simple route to various ortho alkylated aromatic

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(4) For a recent review, see B. Robinson, *Chem. Rev.*, **69**, 227 (1969).

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