chloroform): ir 3250 (NH_2) and 1650 cm^{-1} (C=O); pmr ($CDCl_3$) τ 2.70–3.90 (6 H, m, NH_2, and aryl H), 5.39 (1 H, s, SCH), 5.66 (2 H, s, NH_2), 7.88 (3 H, s, SCH_3).

Anal. Calcd for $C_9H_{12}N_2OS$: C, 55.08; H, 6.16; N, 14.27; S, 16.33. Found: C, 54.79; H, 6.19; N, 14.19; S, 16.30.

Ring Closure of 17 to Oxindole 8a. The cyclization of **17** to **8a** was accomplished by stirring 1.70 g (8.7 mmol) of **17** for 24 hr in 60 ml of absolute ethanol containing 1 ml of concentrated hydrochloric acid. The solution was concentrated to *ca.* 15 ml and poured into 75 ml of water. The precipitate was collected by filtration and dried to give 1.22 g (6.8 mmol, 78%) of 3-methylthiooxindole (**8a**), mp 125–127°.

Ethyl α-(2-*N*-Acetaminophenyl)-α-methylthioacetate (18). Amide **18** was obtained following the procedure described above for the preparation of α-(2-aminophenyl)-α-methylthioacetate (**7**) with the following modification. Instead of purifying the residue by column chromatography, it was redissolved in 100 ml of dry ether and 20 ml of trimethylamine. While stirring it at 0°, a solution of 3.4 g (0.044 mol) of freshly distilled acetyl chloride in 25 ml of dry ether was added. After 2 hr of stirring, 50 ml of water was added and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was subjected to column chromatography (silica gel, methylene chloride–ether) giving 7.07 g (0.0265 mol, 60%) of **18**, mp 111–114° (recrystallization from methanol): ir (KBr) 3220 (NH), 1700 and 1640 cm^{-1} (C=O); pmr ($CDCl_3$) τ 1.27 (1 H, s, NH), 2.00–3.00 (4 H, m, aromatic H), 5.34 (1 H, s, SCH), 5.82 (2 H, q, OCH_2), 7.83 (3 H, s, CH_3), 7.98 (3 H, s, SCH_3), and 8.79 (3 H, t, CH_3).

Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.41; H, 6.41; N, 5.24; S, 11.99. Found: C, 58.24; H, 6.50; N, 5.23; S, 11.92.

Ethyl 2-Methylthiopropionate (19). Sulfide **19** was prepared according to a literature[21] procedure.

3-Methyl-3-methylthiooxindole (20). Oxindole **20** was obtained from aniline and **19** following the general procedure, which gave on concentration of the ethereal layer 5.45 g (0.028 mol, 64%) of **20**, mp 150–151° (recrystallization from benzene): ir (KBr) 3200 (NH) and 1680 cm^{-1} (C=O); pmr ($CDCl_3$) τ 0.40 (1 H, s, NH), 2.50–3.20 (4 H, m, aromatic H), 8.10 (3 H, s, SCH_3), and 8.31 (3 H, s, CH_3).

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25; S, 16.59. Found: C, 62.11; H, 5.70; N, 7.30; S, 16.57.

3-Methyloxindole (21). Oxindole **21** was obtained when 1.5 g (7.75 mmol) of **20** was desulfurized as described for **8b**. 3-Methyloxindole (**21**) was isolated in 70% yield, mp 122–124° (lit.[22] mp 123°).

3-Methylindole (22). Indole **22** was obtained when 1.0 g (5.0 mmol) of **20** was stirred for 16 hr with 0.9 g (26 mmol) of lithium aluminum hydride in 25 ml of dry tetrahydrofuran. The mixture was hydrolyzed at 0° by dropwise addition of 30 ml of 1 *N* aqueous hydrochloric acid and then extracted three times with 40-ml portions of ether. The extracts were washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and filtered. After evaporation of the solvent a solid residue remained, which was purified further by means of column chromatography over silica gel with methylene chloride as eluent giving 0.50 g (3.82 mmol, 76%) of **22**, mp 91.5–94° (lit.[23] mp 95°).

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

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Generation of Azasulfonium Salts from Halogen–Sulfide Complexes and Anilines. The Synthesis of Indoles, Oxindoles, and Alkylated Aromatic Amines Bearing Cation Stabilizing Substituents[1]

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Abstract: A new method for the synthesis of indoles, oxindoles, and ortho-substituted aromatic amines from anilines has been developed. It was found that dialkyl sulfides, β-keto sulfides, and α-carboalkoxy sulfides each reacted with chlorine at low temperatures to form stable complexes. These complexes reacted readily with anilines to form azasulfonium salts. Base treatment of these intermediate azasulfonium salts led to the formation of ylides, that, *via* Sommelet–Hauser type rearrangement, gave the specifically ortho-substituted anilines. In those cases where β-keto sulfides and α-carboalkoxy sulfides were used, the rearranged products were cyclized to give indoles and oxindoles, respectively. The procedures described are particularly useful in the synthesis of *o*-alkylanilines, indoles, and oxindoles, which are substituted with potential cation stabilizing groups such as *o*- and *p*-methoxyl functions.

In the preceding papers, we have described, in detail, our new methods for the synthesis of *o*-alkylated anilines,[3] indoles,[4] and oxindoles.[5] All of these procedures depend on the initial conversion of an aniline (**1**) into an *N*-chloroaniline (**2**), followed by conversion of **2** into an azasulfonium salt on treatment with an appropriate sulfide. Subsequent transformations of the azasulfonium salts gave the desired ortho-substituted anilines (*i.e.*, **3**), indoles **4**, and oxindoles **5**. Although these reaction sequences worked in high yield with a variety of substituents (X = CH_3, H, Cl, CO_2R, NO_2, etc.), they did not work well when powerful cation stabilizing groups were present. For instance, *p*-anisidine (**1**, X = *p*-OCH_3) gave *ca.* 2% of *o*-methylthiomethylanisidine (**3**, X = *p*-OCH_3) on treatment with

(1) For a preliminary report of part of this work, see P. G. Gassman, T. J. van Bergen, and G. Gruetzmacher, *J. Amer. Chem. Soc.*, **95**, 6508 (1973).
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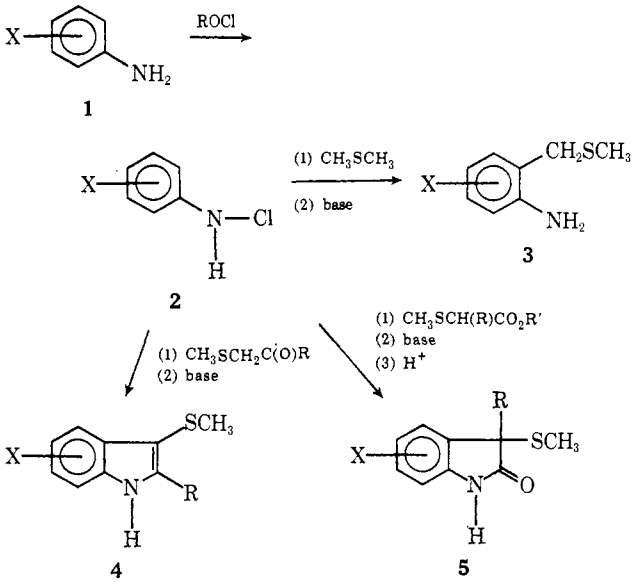
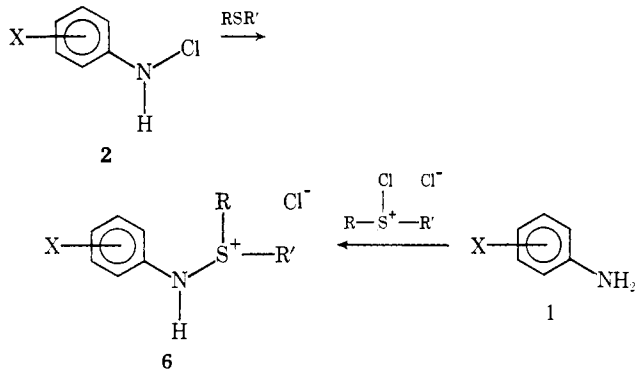


t-butyl hypochlorite and dimethyl sulfide, followed by base. The source of the poor yields obtained with the *p*-anisidine was found to be the extremely unstable nature of the *N*-chloroanilines (**2**), when X was a cation stabilizing group. As had been demonstrated by us previously,[6] *N*-chloroanilines ionize readily in polar solvents, such as buffered ethanol, to give aryl nitrenium ions and chloride anion. This heterocyclic cleavage was shown to be extremely dependent on substituent effects as demonstrated by the observed[6] ρ of -6.35, when a correlation with Brown's[7] σ^+ was made. Since numerous important indoles and oxindoles bear methoxyl functions in the 5, 6, and 7 positions of the indole and oxindole nuclei, the inability to effectively utilize the anisidines in our general synthetic procedures constituted a severe limitation to our process. We now wish to report the details of our modified synthesis of *o*-alkylated anilines, indoles, and oxindoles from anilines bearing cation stabilizing substituents, which circumvents the problems inherent in our general synthetic process as a result of the instability of certain *N*-chloroanilines.

Our original process for the ortho substitution of aromatic amines involved the conversion of anilines (**1**) to *N*-chloroanilines (**2**) and subsequent treatment of the *N*-chloroaniline with a sulfide to give an azasulfonium salt, **6**. Since **6** was the essential precursor of the



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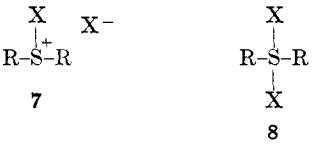
rearranged ortho-substituted anilines, the problem of the instability of **2** could be avoided if a method for the direct conversion of **1** into **6** could be developed. In principle, this goal should be attainable through the reaction of an aniline with the complex formed from halogens and sulfides.

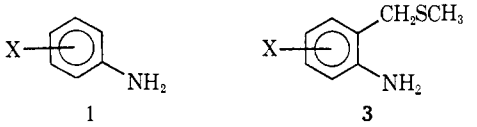
The complexes formed from halogens and sulfides at low temperatures have been long known.[8] They have been discussed both[9,10] in terms of the halosulfonium halide salt structure, **7**, and in terms of the sulfurane, **8**.



Although the exact structure of these complexes has not been rigorously determined in all cases, it would appear that the halosulfonium halide might be a better substrate than the sulfurane for halide displacement by a nucleophile.[10] In our studies this nucleophile would be the aniline, **1**.

In line with expectations, treatment of an appropriate sulfide with either chlorine or bromine in methylene chloride at $-70°$ gave a halogen–sulfide complex, which was used without isolation. Addition of aniline gave the azasulfonium salt which was treated directly with base to produce the desired Sommelet–Hauser like rearrangement product.[3-5,11,12] Many variations in sulfide and aniline were possible using this procedure. Table I lists the yields obtained with chlorine, dimethyl

Table I. Yields of 2-(Thiomethoxymethyl)anilines Obtained in the Reaction of Chlorodimethylsulfonium Chloride with Anilines, Followed by Treatment with Sodium Methoxide



Compd	X	Compd	% yield
1a	*p*-OCH_3	**3a**	62
1b	*p*-CH_3	**3b**	54
1c	H	**3c**	67
1d	*p*-Cl	**3d**	45
1e	*p*-$CO_2C_2H_5$	**3e**	35
1f	*p*-NO_2	**3f**	31

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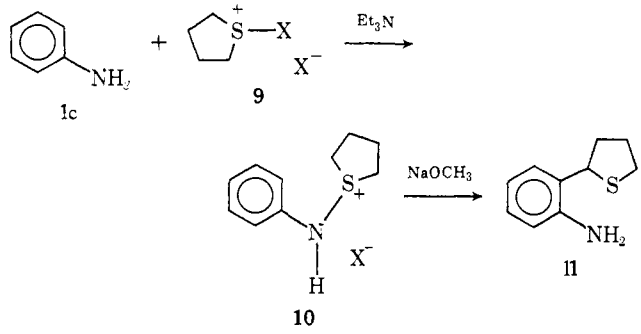
sulfide, and various anilines.[13] The reaction was quite good for the preparation of 2-(thiomethoxymethyl)-anilines bearing electron-donating groups as can be seen from Table I. As strong electron-withdrawing groups were placed on the aniline, the yields decreased. We believe this was probably due to the more electron-deficient amino group being less nucleophilic and hence poorer at displacing halogen from the halogen–sulfide complex. It is fortunate that our original procedure for the synthesis of ortho-alkylated anilines gave the best yields when the starting anilines were substituted with electron-withdrawing groups. Thus, the original ortho-alkylation procedure[3] and the new modification reported herein complement each other.

The procedure described above was found to be quite general. The use of bromine in place of chlorine to generate the halosulfonium halide made little difference as demonstrated by the 69% yield of **3c** obtained when bromine, dimethyl sulfide, and aniline were used as the prime reactants. Treatment of aniline with halotetramethylenesulfonium halide (**9**, X = Cl or Br) in the presence of triethylamine gave the azasulfonium salt **10**, which was not isolated. Addition of sodium methoxide to **10** gave the anticipated Sommelet–Hauser type rearrangement, resulting in the formation of 20% of **11**.



The most significant aspect of our new modification involved its application to the preparation of indoles and oxindoles. β-Keto sulfides were found to react readily with chlorine to give the corresponding chlorine–sulfide complexes. For instance, the complex **12** was readily formed from 1-methylthio-2-propanone and chlorine. Treatment of *p*-anisidine (**1a**, X = OCH_3, Y = H) with **12** followed by triethylamine, according to the general procedure, gave the 5-methoxyindole **13a** in 38% yield. Raney-nickel desulfurization of **13a** gave 2-methyl-5-methoxyindole (**14a**) in 72% yield. The procedure was also readily applied to *o*-anisidine (**1g**, X = H, Y = OCH_3). On treatment with **12** and triethylamine, **1g** gave **13g** in 45% yield. The 7-methoxyindole, **14g**, was obtained in 87% yield on Raney-nickel desulfurization of **13g**. As shown in Table II, this modified indole synthesis could be applied to a wide variety of substituted anilines. However, it should be stressed at this point that the most important application is in the synthesis of methoxylated indoles which are not readily prepared by our original indole synthesis.

Treatment of α-carboalkoxy sulfides with chlorine gave complexes similar to those formed with simple dialkyl sulfides and β-keto sulfides. On addition of

(13) An equivalent of triethylamine was also added with the aniline in order to neutralize the hydrochloric acid which was generated in the reaction of the halosulfonium halide with the aniline. In place of the aniline–triethylamine mixture, 2 equiv of aniline could be used, if desired.

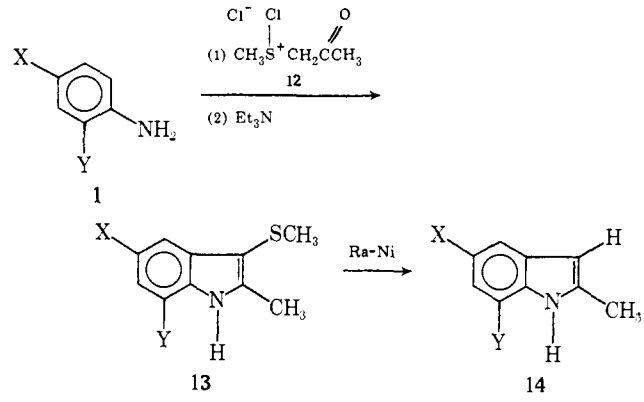
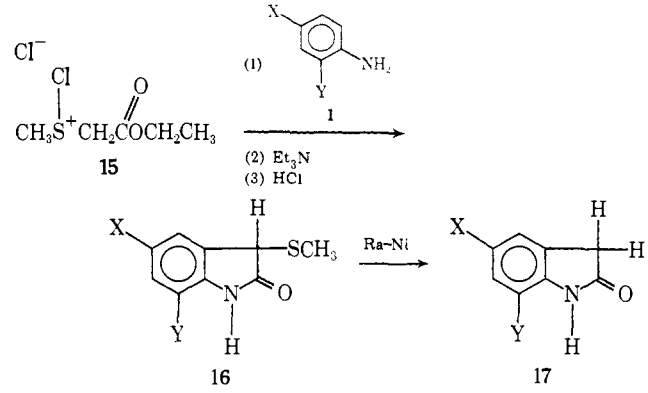


Table II. Synthesis of Indoles from Anilines and 1-Methylthio-2-propanone

Aniline	X	Y	Indole	% yield
1a	OCH_3	H	**13a**	38
1c	H	H	**13c**	68
1d	Cl	H	**13d**	45
1e	$CO_2C_2H_5$	H	**13e**	33
1g	H	OCH_3	**13g**	45

chlorine to ethyl methylthioacetate, we obtained the complex **15**. When *p*-anisidine (**1a**), triethylamine, and 2 *N* hydrochloric acid were added sequentially to **15**, we obtained **16a** (X = OCH_3, Y = H) in 53% yield. Raney-nickel desulfurization of **16a** gave **17a** (X =



OCH_3, Y = H) in 71% yield. As shown in Table III,

Table III. Synthesis of Oxindoles from Ethyl Methylthioacetate and Anilines

Aniline	X	Y	2-Methyl-3-methylthio-oxindole	% yield
1a	OCH_3	H	**16a**	53
1c	H	H	**16c**	65
1f	NO_2	H	**16f**	12
1h	H	CH_3	**16h**	62

this modified oxindole synthesis was applicable to the synthesis of various substituted oxindoles. Again, it can be seen that in the presence of electron-donating groups, the yields were quite good, while with strong electron-withdrawing groups present (**1f** for instance) the yield was low. This reemphasizes that the process described herein complements our previously described

procedure which utilized *N*-chloroanilines as crucial intermediates.

In summary, the use of halosulfonium halides with substituted anilines provides a simple process for the preparation of ortho-alkylated anilines, indoles, and oxindoles. The process is of particular importance in the synthesis of methoxylated indoles, which constitute a portion of numerous indole alkaloids, and in the synthesis of methoxylated oxindoles. Variation of the substitution patterns of the β-keto sulfides and β-carboalkoxy sulfides used in our prototype studies should provide a ready access to a wide variety of methoxylated indoles of value as key intermediates in the synthesis of certain natural products.

Experimental Section[14]

Preparation of 4-Methoxy-2-(thiomethoxymethyl)aniline (3a) from Chlorodimethylsulfonium Chloride and *p*-Anisidine (1a). General Procedure. In a graduated test tube was condensed 2.0 ml (0.044 mol) of chlorine at −78° (Dry Ice–acetone), 10 ml of dry methylene chloride was added to the chlorine, and the solution was allowed to warm slightly, stirred with a spatula, and poured into 100 ml of dry methylene chloride at −78° which was maintained under a static nitrogen pressure. The graduated test tube was washed with an additional 10 ml of methylene chloride which was added to the reaction mixture. The pale yellow solution was cooled back to *ca.* −70° and 3.90 ml (0.05 mol) of dimethyl sulfide in 10 ml of dry methylene chloride was added. The exotherm which occurred was kept to less than 5°, and the yellow color had dissipated upon completion of the addition of the dimethyl sulfide solution. The solution was stirred for 5 min, and a solution of 2.76 g (0.02 mol) of *p*-anisidine (1a) and 2.80 ml (0.02 mol) of triethylamine in 10 ml of dry methylene chloride was added dropwise. The resultant purple solution was stirred for 4 hr at −70°, and 3.24 g (0.06 mol) of sodium methoxide in 15 ml of absolute methanol was added dropwise to the reaction mixture. The cooling bath was allowed to warm to room temperature overnight (*ca.* 16 hr). The reaction mixture was diluted with 150 ml of 10% aqueous sodium hydroxide, the layers were separated, the aqueous phase was extracted twice with 100-ml portions of methylene chloride, and the organic layers were combined, dried with anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to yield a dark oil. Column chromatography on silica gel (ether–hexane) gave 2.24 g (0.0124 mol, 62%) of 3a, bp 95–100° (0.16 mm), $n^{23.6}$D 1.5998 (*vs.* $n^{23.4}$D 1.6011 for an analytical sample).[3] The ir and nmr spectra were identical with those of a previously prepared sample.[3]

Preparation of 2-(Thiomethoxymethyl)aniline (3c) from Chlorodimethylsulfonium Chloride and Aniline (1a). Chlorodimethylsulfonium chloride was prepared as described above for the preparation of 4-methoxy-2-(thiomethoxymethyl)aniline. A solution of 1.86 g (0.02 mol) of aniline (1a) and 2.80 ml (0.02 mol) of triethylamine in 10 ml of dry methylene chloride was added dropwise to the clear solution of chlorodimethylsulfonium chloride. A white precipitate formed after *ca.* 1 hr and the reaction mixture was stirred for a total of 6 hr at −70°. The cooling bath was allowed to warm to room temperature overnight (*ca.* 16 hr). A work-up procedure identical with that used in the preparation of 4-methoxy-2-(thiomethoxymethyl)aniline gave a dark oil. This oil was refluxed in 100 ml of acetonitrile containing 5 ml of triethylamine for 5 hr. The solvent was removed *in vacuo;* the resultant oil was chromatographed on silica gel (ether-hexane) to produce 2.04 g (0.0133 mol, 67%) of 2-(thiomethoxymethyl)aniline, bp 80–82° (0.08 mm), $n^{21.8}$D 1.6094 (*vs.* $n^{24.0}$D 1.6083 for a previously prepared sample[3]). The ir and nmr spectra were identical with those of a previously prepared sample.[3]

Preparation of 4-Methyl-2-(thiomethoxymethyl)aniline (3b) from Chlorodimethylsulfonium Chloride and *p*-Toluidine (1b). 4-Methyl-2-(thiomethoxymethyl)aniline was prepared in 54% yield after purification by column chromatography on silica gel (ether–hexane eluant) and distillation [bp 90–95° (0.03 mm)] in a procedure identical with that used in the preparation of 2-(thiomethoxymethyl)-aniline. The distillate solidified upon standing, mp 45–47° (lit.[15] mp 42–45°). The ir and nmr spectra were identical with those of a previously prepared sample.[3]

Preparation of 4-Chloro-2-(thiomethoxymethyl)aniline (3d) from Chlorodimethylsulfonium Chloride and 4-Chloroaniline (1d). In a procedure analogous to that used in the preparation of 3a, 2.55 g (0.02 mol) of 4-chloroaniline (1d) was converted into 3d. Changes in the general procedure involved stirring for 8 hr at *ca.* −70° prior to the addition of the sodium methoxide and quenching with 100 ml of 10% aqueous sodium hydroxide. The red oil obtained as a crude product was taken up in 100 ml of acetonitrile containing 5 ml of triethylamine and refluxed for 18 hr. The solvents were removed *in vacuo* to yield a red oil which solidified upon standing. Column chromatography on silica gel (ether–hexane eluant) gave 1.68 g (0.009 mol, 45%) of 4-chloro-2-(thiomethoxymethyl)aniline (3d), mp 76–78° (lit.[3] mp 78–80°). The ir and nmr spectra were identical with those of a previously prepared sample.[3]

Preparation of 4-Nitro-2-(thiomethoxymethyl)aniline (3f) from Chlorodimethylsulfonium Chloride and 4-Nitroaniline (1f). In a graduated test tube was condensed 2.0 ml (0.044 mol) of chlorine at −78° (dry ice-acetone), 10 ml of dry methylene chloride was added to the chlorine, and the solution was allowed to warm slightly, stirred with a spatula, and poured into a solution of 75 ml of acetonitrile and 25 ml of methylene chloride at −50 to −40° (40% aqueous methanol bath), which was maintained under a static nitrogen pressure. The graduated test tube was washed with an additional 10 ml of methylene chloride, which was added to the solution. A solution of 3.90 ml (0.05 mol) of dimethyl sulfide in 10 ml of dry methylene chloride was added while the exotherm was kept to less than 5° by dropwise addition. The yellow color had dissipated upon completion of the addition of the dimethyl sulfide solution. This solution was stirred for 5 min, and a solution of 2.76 g (0.02 mol) of *p*-nitroaniline and 2.80 ml (0.02 mol) of triethylamine in 20 ml of acetonitrile and 20 ml of methylene chloride was added dropwise while maintaining the temperature to −40° or less. A voluminous precipitate formed and the reaction mixture was stirred for 9 hr while maintaining the temperature from −50 to −40°. A solution of 3.24 g (0.06 mol) of sodium methoxide in 15 ml of methanol was added, the cooling bath was removed, and the solution was stirred overnight. The reaction was quenched by addition of 100 ml of 10% aqueous sodium hydroxide, the layers were separated, and the aqueous phase was extracted twice with 100-ml portions of methylene chloride. The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to produce a yellow solid. This solid was taken up in 150 ml of dry toluene containing 5 ml of triethylamine and refluxed for 48 hr. The solvents were again removed *in vacuo* to yield a yellow solid. Column chromatography on silica gel (ether–hexane eluant) gave 1.24 g (0.0063 mol, 31%) of 4-nitro-2-(thiomethoxymethyl)aniline (3f), mp 73–75° (lit.[15] mp 75–77°). The ir and nmr spectra were identical with those of a previously prepared sample.[3] In addition, 1.30 g (0.0094 mol, 42%) of 4-nitroaniline was recovered.

Preparation of 4-Carboethoxy-2-(thiomethoxymethyl)aniline (3e) from Chlorodimethylsulfonium Chloride and Benzocaine (1e). Chlorodimethylsulfonium chloride was prepared as described for the preparation of 4-nitro-2-(thiomethoxymethyl)aniline. A solution of 3.30 g (0.02 mol) of benzocaine and 2.80 ml (0.02 mol) of triethylamine in 10 ml of dry methylene chloride was added dropwise to the clear solution of chlorodimethylsulfonium chloride. A voluminous white precipitate formed and this was stirred for 6.5 hr. At this time, 8.40 ml (0.06 mol) of triethylamine was added to the reaction mixture, the cooling bath was removed, and the solution was stirred overnight. A work-up procedure identical with that used in the preparation of 4-nitro-2-(thiomethoxymethyl)-aniline gave a dark red oil which solidified upon standing. This oil was taken up in 100 ml of acetonitrile containing 5 ml of triethylamine and the solution was refluxed for 48 hr. The solvents were removed *in vacuo* to leave a red solid. Recrystallization from absolute ethanol gave 1.60 g (0.0071 mol, 35%) of 4-carboethoxy-2-(thiomethoxymethyl)aniline (3e), mp 83–84° (lit.[3] mp 84.5–85.5°). The ir and nmr spectra were identical with those of a previously prepared sample.[3]

Preparation of 2-(Thiomethoxymethyl)aniline (3c) from Bromodimethylsulfonium Bromide and Aniline (1c). A solution of 3.20

(14) Melting points and boiling points are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 137 infrared spectrophotometer. Nmr spectra were obtained using Varian Associates A-60, A-60A, and HA-100 nuclear magnetic resonance spectrometers or a Joelco MH-100 nmr spectrometer.

(15) P. Claus, W. Vycudilik, and W. Reider, *Monatsh. Chem.*, 102, 1571 (1971).

g (0.02 mol) of bromine in 100 ml of dry methylene chloride was cooled to −70° (Dry Ice–acetone) under a static nitrogen pressure. To this dark red solution was added 1.55 ml (0.02 mol) of dimethyl sulfide in 10 ml of methylene chloride, resulting in the immediate formation of a yellow precipitate. Note: the yellow color persists even if another equivalent of dimethyl sulfide is added. The resultant solution was stirred for 30 min. A solution of 1.86 g (0.02 mol) of aniline (**1c**) was added and the procedure described above for the preparation of **3c** was then followed. The resultant oil was chromatographed on silica gel (ether-hexane eluent) to produce 2.10 g (0.0137 mol, 69%) of 2-(thiomethoxymethyl)aniline (**3c**), bp 88–90° (0.12 mm), $n^{24.8}$D 1.6093 (lit.[15,3] nD 1.6042, $n^{24.0}$D 1.6083). The ir and nmr spectra were identical with those of a previously prepared sample.[3]

Preparation of 2-(2-Tetrahydrothienyl)aniline (11) from Chlorotetramethylenesulfonium Chloride (9, X = Cl) and Aniline (1c). Chlorotetramethylenesulfonium chloride was prepared from tetrahydrothiophene and chlorine in a procedure identical with that used in the preparation of chlorodimethylsulfonium chloride. 2-(2-Tetrahydrothienyl)aniline was prepared in a procedure identical with that used in the preparation of 2-(thiomethoxymethyl)-aniline from chlorodimethylsulfonium chloride except that the acetonitrile–triethylamine reflux time was overnight (*ca.* 16 hr). After column chromatography on silica gel (ether–hexane eluant) and distillation, a 20% yield of **11** was obtained, bp 102–105° (0.08 mm), $n^{22.2}$D 1.6251 (lit.[3] $n^{26.8}$D 1.6258). The ir and nmr spectra were identical with those of a previously prepared sample.[3]

Preparation of 2-(2-Tetrahydrothienyl)aniline (11) from Bromotetramethylenesulfonium Bromide (9, X = Br) and Aniline (1c). Bromotetramethylenesulfonium bromide was prepared from tetrahydrothiophene and bromine in a procedure identical with that used in the preparation of bromodimethylsulfonium bromide. 2-(2-Tetrahydrothienyl)aniline was prepared in a procedure identical with that used in the preparation of 2-(thiomethoxymethyl)aniline from bromodimethylsulfonium bromide except that the acetonitrile–triethylamine reflux time was overnight (*ca.* 16 hr). The yield of purified **11** was 19%.

General Procedure for the Synthesis of Indoles from Anilines and a Chlorine–Sulfide Complex. To a mechanically stirred solution of 2.0 ml (0.044 mol) of chlorine in 100 ml of methylene chloride, cooled to −70°, was added dropwise, over a 20-min period, 4.6 g (0.044 mol) of methylthio-2-propanone dissolved in 15 ml of methylene chloride, while the temperature was maintained below −60°. The yellow solution decolorized and the chlorine–sulfide complex precipitated. Stirring was continued for 5 min and then 2 equiv (0.088 mol) of the aniline, dissolved in 30 ml of methylene chloride, was added over a 30–60-min period, while maintaining the temperature below −60°. After another 30 min at −70°, 10 ml (0.069 mol) of triethylamine was added. The mixture was stirred for another 15 min at −70°, and the cooling bath was removed. To the clear solution which resulted at room temperature, 50 ml of water was added to remove the amine hydrochloride. After separation of the layers, the organic solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The indole derivative was isolated by column chromatography of the residue.

5-Methoxy-2-methyl-3-methylthioindole (13a). The indole, **13a**, was synthesized from 4-methoxyaniline (**1a**) following the above procedure. Column chromatography (silica gel and a 2:5 petroleum ether–methylene chloride mixture) gave 3.44 g (0.017 mol, 38%) of **13a**, mp 109–111° (recr. from cyclohexane): ir (KBr) 3350 cm^{-1} (NH); pmr (CCl_4) τ 2.17 (1 H, br s, NH), 2.91 (1 H, br s, 4-aryl H), 3.00 (1 H, d, J = 8.0 Hz, 7-aryl H), 3.27 (1 H, dd, J = 8.0 and 2.0 Hz, 6-aryl H), 6.18 (3 H, s, OCH_3), 7.60 and 7.81 (3 H each, s, SCH_3, and s, CH_3).

Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.76; S, 15.47. Found: C, 63.61; H, 6.30; N, 6.64; S, 15.41.

5-Methoxy-2-methylindole (14a). Desulfurization of 5-methoxy-2-methyl-3-methylthioindole (1.4 g, 6.75 mmol) with W-2 Raney nickel gave 5-methoxy-2-methylindole in a 72% yield, mp 55.0–56.5°. This solid was melted, cooled to −70°, and slowly allowed to warm to room temperature. In this way a solid material was obtained melting at 82.0–84.5° (lit.[16] mp 85–86°).

2-Methyl-3-methylthioindole (13c). The indole, **13c**, was synthesized from aniline (**1c**) following the above procedure. Column chromatography (silica gel and a 1:2 petroleum ether–methylene chloride mixture) of the residual mixture gave 5.28 g (0.030 mol, 68%) of 2-methyl-3-methylthioindole as a viscous oil, that solidified on standing, mp 56.5–58.3° (lit.[4] mp 58–59°).

5-Chloro-2-methyl-3-methylthioindole (13d). The indole **13d** was synthesized from 4-chloroaniline (**1d**) following the above procedure. To complete the formation of the azasulfonium salt the mixture was stirred for 3 hr at −70° after the solution of **1d** had been added and before the triethylamine was added. Further work-up and column chromatography (silica gel and a 1:1 petroleum ether–methylene chloride mixture) gave 4.14 g (0.020 mol, 45%) of 5-chloro-2-methyl-3-methylthioindole, mp 62–63.5° (lit.[4] mp 64.0–65.5°).

5-Carboethoxy-2-methyl-3-methylthioindole (13e). The indole, **13e**, was synthesized from 4-carboethoxyaniline (**1e**) following essentially the above procedure. In this case a solvent mixture of 75 ml of methylene chloride and 75 ml of acetonitrile was used for the 2.0 ml of chlorine, and the 0.088 mol of 4-carboethoxyaniline was added in 50 ml of acetonitrile to increase its solubility at low temperature. Before the triethylamine was added, the mixture was stirred for 4 hr at −70° to maximize the azasulfonium salt formation. After warming to ambient temperature, a 50-ml portion of water was added and the layers were separated. The organic layer was extracted thoroughly with 2 *N* aqueous hydrochloric acid (to remove all unreacted **1e**) and subsequently treated with saturated sodium bicarbonate. Drying of the organic solution over anhydrous magnesium sulfate followed by filtration and evaporation of the solvent gave a residue that was subjected to column chromatography (silica gel and methylene chloride). There was obtained 3.82 g (0.015 mol, 35%) of 5-carboethoxy-2-methyl-3-methylthioindole (**13e**), mp 127–130° (lit.[4] mp 126–127°).

2-Methyl-3-methylthio-7-methoxyindole (13g). To a mechanically stirred solution of 4.0 ml (0.088 mol) of chlorine in 200 ml of methylene chloride, cooled to −70°, was added over a 1-hr period 9.2 g (0.088 mol) of methylthio-2-propanone in 20 ml of methylene chloride, while maintaining the temperature below −60°. After 15 min, 21.70 g (0.176 mol) of *o*-anisidine (**1g**) dissolved in 50 ml of methylene chloride was added over a 1-hr period and stirring was continued at −70° for 3 hr. Subsequently, 20 ml (0.138 mol) of triethylamine was added dropwise and the cooling bath was removed to allow warming to room temperature. A 100-ml portion of water was added, the layers were separated, and the organic solvent was evaporated. The residue was redissolved in 150 ml of ether and then extracted three times with 50-ml portions of 2 *N* aqueous hydrochloric acid. The ethereal solution was washed with saturated sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by column chromatography (silica gel and methylene chloride) to give 11.33 g of a viscous oil, that on recrystallization from a 6:1 cyclohexane–*n*-hexane mixture gave 8.2 g (0.0397 mol, 45%) of 2-methyl-3-methylthio-7-methoxyindole (**13g**), mp 58–59° (recrystallization from cyclohexane): ir (KBr) 3400 cm^{-1} (NH); pmr (CCl_4) τ 1.80 (1 H, br s, NH), 2.78 and 3.53 (1 H each, d, J = 7.0 Hz, 4- and 6-aryl H), 7.09 (1 H, t, J = 7.0 Hz, 5-aryl H), 6.17 (3 H, s, OCH_3), and 7.67 and 7.83 (3 H each, s, CH_3, and s, SCH_3).

Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.76; S, 15.47. Found: C, 63.72; H, 6.46; N, 6.69; S, 15.36.

2-Methyl-7-methoxyindole (14g). The indole, **14g**, was prepared by stirring 5.0 g (0.0241 mol) of 2-methyl-3-methylthio-7-methoxyindole (**13g**) with 10 tsp of W-2 Raney nickel for 1 hr. Following the general work-up procedure,[4] there was obtained 3.40 g (0.0211 mol, 87%) of 2-methyl-7-methoxyindole (**14g**), mp 79–81° (lit.[17] mp 83–85°).

General Procedure for the Synthesis of Oxindoles from Anilines and a Chlorine–Sulfide Complex. To a mechanically stirred solution of 2.0 ml (0.044 mol) of chlorine in 100 ml of methylene chloride, cooled to −70°, was added dropwise, over a 15-min period, 5.9 g (0.044 mol) of ethyl methylthioacetate dissolved in 15 ml of methylene chloride, while maintaining the temperature below −60°. The yellow solution decolorized. After 5 min, a solution of 2 equiv (0.088 mol) of the aniline dissolved in 30 ml of methylene chloride was added over a 30-min period, while the temperature was maintained below −60°. Usually, a precipitate was formed at this stage. Subsequently, the mixture was stirred for another hr at −70°, after which 10 ml (0.069 mol) of triethylamine was added. After another 30 min, the cooling bath was removed to allow the reaction mixture to warm to room temperature, at which time a clear solution resulted. A 50-ml portion of water was added to remove the amine hydrochloride salt and the layers were separated.

(16) E. Späth and O. Brunner, *Chem. Ber.*, 58, 520 (1925).

(17) J. Blair and G. T. Newbold, *J. Chem. Soc., London*, 2871 (1955).

The organic solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was redissolved in 150 ml of ether and stirred overnight with 20 ml of 2 *N* aqueous hydrochloric acid. Usually, the oxindole had precipitated and could be collected by filtration. In case no precipitate was formed, the two layers were separated and the ethereal solution was concentrated causing the oxindole to crystallize. This latter procedure also allowed the isolation of a second fraction in those cases where the oxindole had precipitated initially.

5-Methoxy-3-methylthio-2-oxindole (16a). The oxindole, **16a**, was synthesized from 4-methoxyaniline (**1a**) *via* the above procedure. This allowed the isolation of 6.16 g of crude material that was recrystallized from methanol to give 4.90 g (0.023 mol, 53%) of pure 5-methoxy-3-methylthio-2-oxindole, mp 149.0–150.5°: ir (KBr) 3400 and 3100 (NH), 1670 cm^{-1} (C=O); pmr (DMSO-d_6) τ −0.34 (1 H, br s, NH), 3.00–3.22 (3 H, m, aryl H), 5.50 (1 H, s, CH), 6.26 (3 H, s, OCH_3), and 8.00 (3 H, s, SCH_3).

Anal. Calcd for $C_{10}H_{11}NO_2S$: C, 57.40; H, 5.30; N, 6.69; S, 15.32. Found: C, 57.28; H, 5.36; N, 6.71; S, 15.20.

5-Methoxy-2-oxindole (17a). Desulfurization of 1.5 g (7.17 mmol) of 5-methoxy-3-methylthio-2-oxindole (**16a**) dissolved in 100 ml of absolute ethanol with W-2 Raney nickel gave, in 71% yield, 5-methoxy-2-oxindole, mp 148.5–150.5° (lit.[18] mp 152–154°).

3-Methylthio-2-oxindole (16c). 3-Methylthio-2-oxindole was synthesized from aniline (**1c**) *via* the above procedure. In this case the ethereal solution, containing the oxindole, was worked up by extracting the reaction mixture twice with 2 *N* aqueous hydrochloric acid, drying the organic phase over anhydrous magnesium sulfate, filtration, and evaporation. The solid residue was dissolved in 30 ml of refluxing ethanol, which was poured into 125 ml of hot water. On standing, 5.10 g (0.029 mol, 65%) of 3-methylthio-2-oxindole crystallized and was collected by filtration, mp 126–127° (lit.[5] mp 126–127°).

7-Methyl-3-methylthio-2-oxindole (16h). The oxindole, **16h**, was synthesized from 2-methylaniline (**1h**) *via* the above procedure. There was obtained 5.30 g (0.028 mol, 62%) of **16h**, mp 190.5–193.0° (lit.[5] mp 194.0–195.5°).

3-Methylthio-5-nitro-2-oxindole (16f). The oxindole, **16f**, was synthesized from 4-nitroaniline (**1f**) *via* essentially the above procedure with the following modifications. A mechanically stirred solution of 0.044 mol of the chlorine–sulfide complex was prepared in the usual manner in 420 ml of methylene chloride. Through an addition funnel was added, as fast as possible, a solution of 13.1 g (0.088 mol) of 4-nitroaniline in a solution of 200 ml of methylene chloride and 25 ml of acetonitrile (to prevent premature crystallization of the nitro compound) with an accompanying temperature rise to −40°. The mixture was stirred for an additional 5 hr at −70° before the triethylamine was added. After warming to room temperature, a 200-ml portion of water was added and the layers were separated. Cyclization to the oxindole was accomplished with acid as described above, after which the layers were separated and the organic layer was extracted thoroughly with 2 *N* aqueous hydrochloric acid. After washing with saturated sodium bicarbonate solution, the organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated, leading to the crystallization of the product. There was obtained 1.15 g (0.5 mmol, 12%) of 3-methylthio-5-nitro-2-oxindole, mp 190.0–193.5° (lit.[5] mp 196–197°).

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Oxidation of Hydrocarbons. IV. Kinetics and Mechanism of the Oxidative Cleavage of Cinnamic Acid by Acidic Permanganate[1]

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Abstract: Permanganate ion reacts rapidly with *trans*-cinnamic acid in aqueous perchloric acid to form an intermediate which subsequently decomposes in a slightly slower reaction to give benzaldehyde and Mn^{III}. Inverse secondary deuterium kinetic isotope effects (k_D/k_H = 1.3) which are obtained for the oxidation of *trans*-cinnamic acid-α-*d* and *trans*-cinnamic acid-β-*d* are taken as evidence that the initial reaction involves addition of permanganate ion to the carbon–carbon double bond to form an intermediate hypomanganate ester. Normal secondary deuterium kinetic isotope effects (k_H/k_D = 1.09) are observed for the decomposition of the intermediate into products. The first step of the reaction (ester formation) is characterized by a small enthalpy of activation (4.2 kcal/mol) and a large negative entropy of activation (−30 eu), whereas the second step (ester decomposition) exhibits a larger enthalpy of activation (11.9 kcal/mol) and an entropy of activation of similar magnitude (−27 eu). The rate of formation of the intermediate is rather insensitive to the presence of substituents on the aromatic nucleus; however, the rate of decomposition of the intermediate exhibited a Hammett ρ value of −1.1. An attempt has been made to propose a unified mechanism which is consistent with all of the known physical data concerning the reaction and which also satisfactorily accounts for the array of products that can be obtained under various conditions.

The oxidation of carbon–carbon bonds by permanganate ion is an important and well-known reaction in organic chemistry. Under alkaline conditions olefins are converted to the corresponding diols in good yields,[2,3] while in neutral or only slightly basic solutions α-hydroxy ketones are produced.[3,4] These reactions are always accompanied by a certain amount of carbon–carbon bond cleavage[5] and under acidic conditions cleavage products predominate.[6,7]

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