and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was evaporated to give 10.50 g (84% yield) of **61** as a light yellow oil: ir (neat) 3380 (enamine NH), 3050–2850 (CH), 1735 (ester C=O), 1670 (C=N), and 1615 (C=C) cm^{-1}; pmr (CCl_4) 2.80–3.50 (4 H, m, aromatic protons), 5.85 (2 H, q, $CO_2CH_2CH_3$), 7.40–8.60 (7 H, m, cyclohexyl protons), 8.35 (3 H, s, SCH_3), and 8.75 (3 H, t, $CO_2CH_2CH_3$).

1-Carbethoxy-1,2,3,4-tetrahydrocarbazole (57). A solution of 10.00 g (0.035 mol) of **61** in 200 ml of absolute ethanol was stirred with 15 teaspoonsful of W-2 Raney nickel at room temperature for 6 hr. The catalyst was removed by filtration and washed thoroughly with ethanol (care should be taken to keep the catalyst moist with solvent since the dry catalyst is highly pyrophoric). The combined ethanol solutions were evaporated *in vacuo* to give an oil which was chromatographed on silica gel (elution with methylene chloride) to give 7.30 g (88%) of **57**, bp 125–130° (0.2 mm) [lit.[29] bp 125–135° (0.15 mm)]; ir (neat) 3400 (indole NH) and 1730 cm^{-1} (ester C=O); nmr (CCl_4), τ 1.73 (1 H, br s, NH, exchanges with deuterium oxide), 2.70–3.20 (4 H, m, aromatic protons), 5.90 (2 H, q, $CO_2CH_2CH_3$), 6.30 (1 H, m, $CHCO_2Et$), 7.35 (2 H, m, C-4 protons), 7.70–8.50 (4 H, m, C-2 and C-3 protons), and 8.75 (3 H, t, $CO_2CH_2CH_3$).

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Oxindoles. A New, General Method of Synthesis[1]

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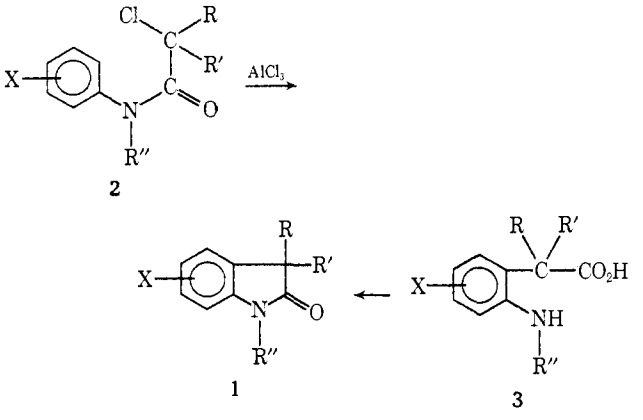
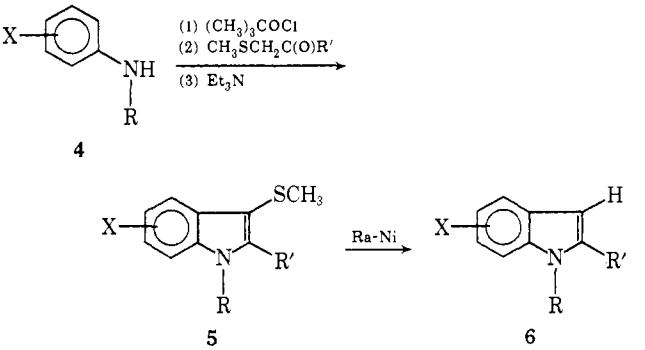
Abstract: A new general method has been developed for the synthesis of oxindoles. The procedure involves sequential treatment of an aniline derivative with (a) *tert*-butyl hypochlorite, (b) an α-carboalkoxy sulfide, (c) triethylamine, and (d) acid to produce a 3-methylthiooxindole derivative. Reductive desulfurization of the 3-methylthiooxindole derivative then produced the corresponding oxindole. In the overall process the α-carboalkoxy sulfide can be replaced by α-carbamoyl sulfides. The mechanistic steps involved in the formation of the 3-methylthiooxindoles are (a) formation of a mono-*N*-chloroaniline, (b) formation of an azasulfonium salt, (c) ylide formation, (d) Sommelet–Hauser type rearrangement, and (e) intramolecular attack of the free amino group on the appropriately situated carbonyl group. The evidence for the mechanistic hypothesis and the overall scope of the reaction is discussed.

Of the various routes to oxindoles (**1**) which have appeared in the literature,[3] the most commonly



encountered are variations of the Lewis acid catalyzed cyclization of α-haloacetanilides (**2**)[4,5] and the cyclization of *o*-aminophenylacetic acid derivatives.[5-7] However, these processes are limited in scope, the first by the rather strongly acidic conditions required, and the second by the availability of the starting materials. This paper presents the details of our new synthesis of oxindoles from aniline derivatives and α-carboalkoxy sulfides *via* the intermediacy of azasulfonium salts.

In the preceding papers, we have described the sequential reaction of aniline derivatives, **4**, with (a) *tert*-



butyl hypohalite, (b) β-keto sulfides, and (c) base in a process which produced good to excellent yields of indole derivatives, **5**.[8] Reductive desulfurization of **5** then provided a simple access to the indoles, **6**, where R could be hydrogen or alkyl and R′ could be hydrogen, alkyl, or aryl. The ease with which this synthesis could be carried out, and the versatility of the process, prompted us to extend our general concept to the synthesis of oxindoles. In principle, the replacement of the β-keto sulfide used in the indole synthesis with an

(1) For a preliminary report of part of this work, see P. G. Gassman and T. J. van Bergen, *J. Amer. Chem. Soc.*, **95**, 2718 (1973).

(2) Fellow of the Netherlands Organization for the Advancement of Pure Research (Z. W. O.), 1972–1973.

(3) For a review of oxindole syntheses, see R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N. Y., 1970.

(4) W. C. Sumpter, *Chem. Rev.*, **37**, 443 (1945).

(5) A. H. Beckett, R. W. Daisley, and J. Walker, *Tetrahedron*, **24**, 6093 (1968).

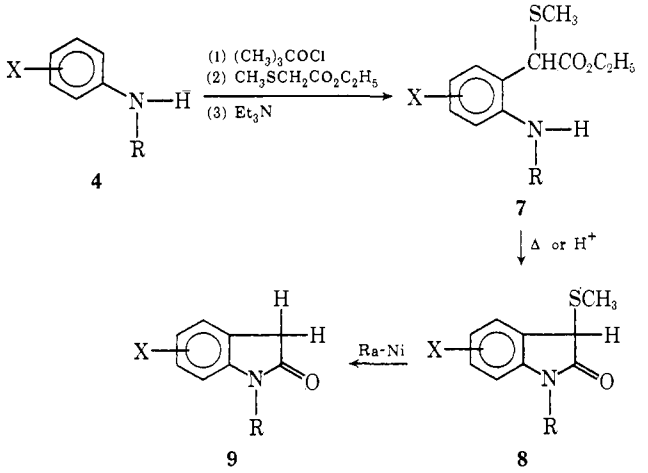
(6) E. Hardegger and H. Corrodi, *Helv. Chim. Acta*, **39**, 514 (1956).

(7) H. Romeo, H. Corrodi, and E. Hardegger, *Helv. Chim. Acta*, **38**, 463 (1955).

(8) P. G. Gassman, T. J. van Bergen, D. P. Gilbert, and B. W. Cue, Jr., *J. Amer. Chem. Soc.*, **96**, 5495 (1974).

α-carboalkoxy sulfide should produce an oxindole, rather than an indole.

In a typical procedure, 1 equiv of an aniline (**4**) in methylene chloride at $-65°$ was treated with 1 equiv of *tert*-butyl hypochlorite. After 5–10 min, 1 equiv of an appropriate ethyl methylthioacetate was added (slight exotherm) and the reaction mixture was stirred at $-65°$ for 1 hr. One equivalent of triethylamine was then added and the stirred reaction mixture was allowed to warm to room temperature. Careful work-up of the reaction mixture at this point gave a 62% yield of the relatively unstable amino ester **7** (X = R = H). In



contrast to the behavior of the analogous intermediate in our indole synthesis,[8] **7** does not spontaneously cyclize at low temperatures. On heating, or prolonged standing at room temperature, **7** was converted into **8**. In a very efficient process, treatment of **7** with dilute acid rapidly gave **8** in 84% yield. When the crude reaction mixture derived from **4** (X = R = H) was treated directly with acid, the overall yield of **8** was 84%. Raney-nickel reduction of **8** gave the oxindole **9** (X = R = H) in 76% yield.

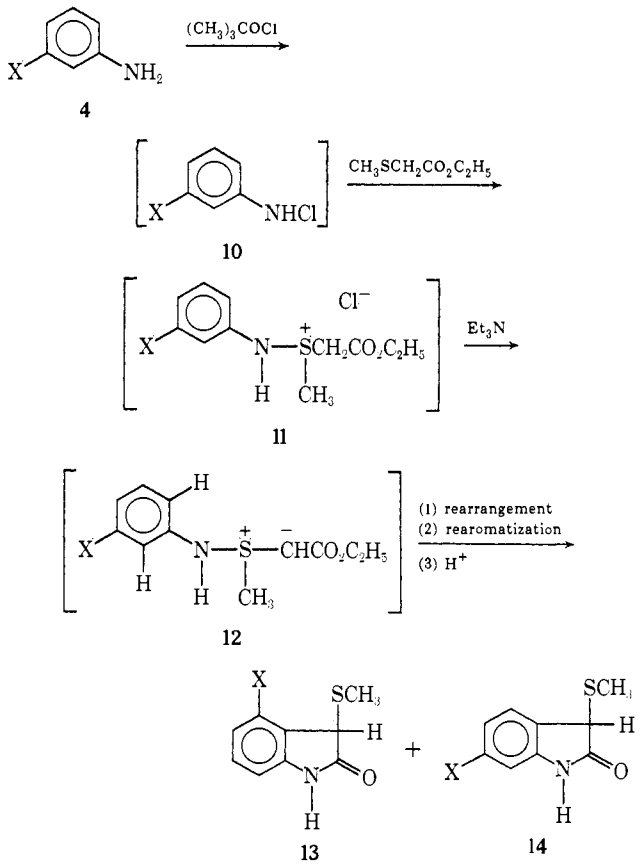
The procedure described above was quite general. Table I lists the yields of **8** obtained in the utilization of

Table I. Yields Obtained in the Conversion of Anilines (**4**) to Oxindoles (**8**) with Ethyl Methylthioacetate

Aniline	X	R	Methylthiooxindole	Yield of 8, %	Oxindole	Yield of 9, %
4a	H	H	**8a**	84	**9a**	76
4b	*p*-CH_3	H	**8b**	34	**9b**	55
4c	*o*-CH_3	H	**8c**	67	**9c**	72
4d	H	CH_3	**8d**	46	**9d**	77
4e	*p*-$CO_2C_2H_5$, *o*-CH_3	H	**8e**	66	**9e**	67
4f	*p*-NO_2	H	**8f**	51	*a*	

[a] No attempt was made to carry out a Raney-nickel desulfurization of **8f**.

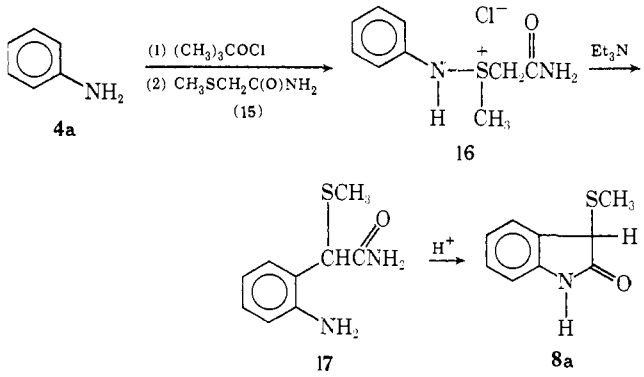
our process with a variety of anilines. As can be seen from Table I, the yields of oxindoles range from good to excellent. In addition, a broad range of substituents, which extends from mildly electron donating to strongly electron withdrawing, can be tolerated. When ortho- and para-substituted anilines are used in our indole synthesis the reaction is quite straightforward, insofar as the para substituent always is found at the 5 position of the oxindole, while the ortho substituent can only reside at the 7 position of the resulting oxindole. Meta-substituted anilines present a more complex problem. In order to fully understand the nature of this complication, we need to explore some aspects of the mechanism of our oxindole synthesis. As shown below, the first step of the synthesis involved the conversion of the aniline **4** into a mono-*N*-chloroaniline (**10**) which was used without further purification. On



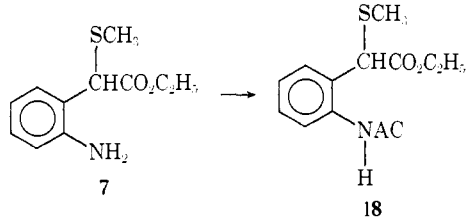
addition of the sulfide, **10** was converted into the azasulfonium salt **11**. Treatment of **11** with base gave the ylide **12**, which underwent a Sommelet–Hauser type rearrangement to give **7** after rearomatization of the intermediate cyclohexadienone imine. When the substituent was in the meta position the intramolecular attack of the ylide could occur at either the position ortho or para to the X function. Our studies indicate that when X is a strong electron-withdrawing group, attack occurs adjacent to the X group to give the 4-substituted oxindole **13**. Thus, when *m*-nitroaniline was used in our process, we obtained 61% of **13** (X = NO_2). None of the isomer corresponding to **14** was detected. In analogy to our findings associated with our indole synthesis[8] relative to this question, we found that the presence of electron-donating groups in the meta position resulted in the formation of the 6-substituted oxindole, **14**, as the major product.[9]

In a variation of our process, we used methylthioacetamide (**15**) as the sulfide. This led to a much more stable intermediate, which could be readily isolated and characterized. Treatment of aniline (**4a**) with *tert*-butyl hypochlorite, followed by addition of **15**, gave 89% of the crystalline azasulfonium salt, **16**. Base-

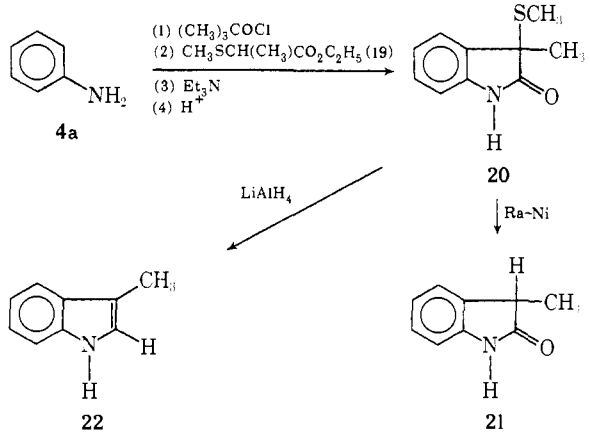
(9) P. G. Gassman and B. W. Cue, Jr., unpublished work. A detailed study of these inductive effects is in progress.



promoted rearrangement of **16** with triethylamine gave an 84% yield of **17**, which was quite stable. Conversion of **17** to **8a** could be accomplished in 78% yield in the presence of hydrochloric acid. The isolation and purification of **17** illustrate that our general synthetic process can be used to prepare stable derivatives of *o*-aminophenylacetic acid. An alternate approach to preparing such compounds involved the acetylation of **7** (X = R = H) with acetyl chloride to give the amide **18**, which was also quite stable.



When the nature of the sulfide was changed by substitution of the active methylene group, a route to 3-substituted oxindoles was provided. When **4a** was allowed to react sequentially with (a) *tert*-butyl hypochlorite, (b) ethyl 2-methylthiopropionate (**19**), (c) tri-



ethylamine, and (d) acid, we obtained **20** in 64% yield. Raney-nickel reductive desulfurization of **20** gave 3-methyloxindole (**21**) in 70% yield. The ease with which 3-substituted oxindoles, such as **20** and **21**, can be prepared should lead to the use of these materials in a variety of synthetic endeavors. Of particular importance in this regard is the facile, high-yield reduction of 3-substituted 3-alkylthiooxindoles to indoles.[10] Treatment of **20** with lithium aluminum hydride gave a 76% yield of **22**. This provides a simple two-step synthesis of 3-substituted indoles, which compliments our other indole synthesis.[8]

(10) T. Wieland and D. Grimm, *Chem. Ber.*, **98**, 1727 (1965).

In summary, we have developed a new method for oxindole synthesis which is very versatile. The ease of carrying out these procedures, the normally good yields obtained, and the readily available nature of the starting materials make our method superior to many of the procedures which are currently available. The mild conditions used in our oxindole synthesis should permit the construction of this ring system in the presence of various rather sensitive substituent groups.

Experimental Section[11]

Ethyl Methylthioacetate. Ethyl methylthioacetate was prepared according to the procedure of Schoenberg and Pfaecke.[12]

General Procedure for the Synthesis of Oxindoles (8) from Anilines and Ethyl Methylthioacetate. To a vigorously stirred solution of 0.044 mol of the aniline in 150 ml of methylene chloride at −65° was added dropwise a solution of 0.044 mol of *t*-butyl hypochlorite in 20 ml of the same solvent. After 5–10 min, 0.044 mol of ethyl methylthioacetate dissolved in 20 ml of methylene chloride was added causing an exotherm, and stirring at −65° was continued for 1 hr. Usually the azasulfonium salt did not precipitate. Subsequently, 0.044 mol of triethylamine in 20 ml of methylene chloride was added. After the addition was completed the cooling bath was removed and the solution was allowed to warm to room temperature. A 50-ml portion of water was added and the organic layer was separated and evaporated. The residue was redissolved in 150 ml of ether and stirred overnight with 20 ml of 2 *N* aqueous hydrochloric acid. In general, the 2-oxindole (**8**) had precipitated and was collected by filtration. A second fraction could be obtained from the ether layer by concentrating it after it had been dried over anhydrous magnesium sulfate and filtered.

Ethyl α-(2-Aminophenyl)-α-methylthioacetate (7). Compound **7** was obtained from aniline and ethyl methylthioacetate following the general procedure without the acid treatment. After addition of triethylamine and warming to room temperature, 50 ml of water was added. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue, when subjected to column chromatography (silica gel and chloroform), gave 6.12 g (0.027 mol, 62%) of **7** as a yellow oil (undistilled): ir (neat) 3350 (NH_2) and 1700 cm^{-1} (C=O); pmr (CCl_4) τ 2.80–3.55 (4 H, m, aromatic H), 5.48 (1 H, s, CHS), 5.85 (2 H, q, OCH_2), 6.02 (2 H, s, NH_2), 8.05 (3 H, s, SCH_3), 8.80 (3 H, t, CH_3). In view of the very unstable nature of **7**, it was used in subsequent reactions without further purification.

Cyclization of Ethyl α-(2-Aminophenyl)-α-methylthioacetate (7) to 3-Methylthiooxindole (8a). The cyclization was accomplished by stirring 2.00 g (8.9 mmol) of **7** in 20 ml of ether for 4 hr with 10 ml of 2 *N* hydrochloric acid. The ethereal layer was dried over anhydrous sodium sulfate, filtered, and evaporated, giving 1.340 g (7.5 mmol, 84%) of **8a**, mp 126–127° (recrystallization from ether): ir (KBr) 1700 (C=O) and 3350 cm^{-1} (NH); pmr (CCl_4) τ −0.08 (1 H, s, NH), 2.70–3.20 (4 H, m, aromatic H), 5.88 (1 H, s, SCH), 7.84 (3 H, s, SCH_3).

Anal. Calcd for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.82; S, 17.89. Found: C, 60.16; H, 5.19; N, 7.71; S, 17.70.

Oxindole (9a). A solution of 2.00 g (0.011 mol) of **8a** in 50 ml of absolute ethanol was stirred and refluxed with 4 tsp of W-2 Raney nickel[13] for 2 hr. Stirring was stopped and the supernatant liquid was decanted. The residue was washed twice with 25-ml portions of absolute ethanol. The alcoholic solutions were evaporated to dryness, and the residue was redissolved in 50 ml of methylene chloride, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 1.13 g (0.008 mol, 76%) of **9a**, mp 116–117° (lit.[14] mp 126°). This material was identical with an authentic sample purchased from the Aldrich Chemical Co.

3-Methylthiooxindole (8a). Oxindole **8a** was prepared from **4a**

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

(12) A. Schoenberg and K. Pfaecke, *Chem. Ber.*, **99**, 2321 (1966).

(13) A teaspoonful of W-2 Raney nickel is *ca.* 3 g. For the details of Raney-nickel preparation, see R. Mozingo, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 181. The W-2 Raney nickel used here was purchased from W. R. Grace and Co.

(14) A. Reissert, *Chem. Ber.*, **41**, 3926 (1908).

on a 0.4 mol scale by adding to a vigorously mechanically stirred solution of 37.2 g (0.4 mol) of aniline in 2 l. of methylene chloride at −70° over *ca.* 45 min 43.2 g (0.4 mol) of *tert*-butyl hypochlorite. The solution was stirred for a 15-min period before dropwise addition, at −70°, of a solution of 53.6 g (0.4 mol) of ethyl methylthioacetate in 130 ml of methylene chloride was started. The addition was completed after *ca.* 1 hr and stirring was continued for a 2-hr period. A solution of 41 g (0.4 mol) of triethylamine in 50 ml of methylene chloride was added over *ca.* 30 min, and the cooling bath was removed after another 15 min at −70° to allow the solution to warm to room temperature. A 300-ml portion of water was added, the mixture was stirred vigorously for 15 min, and the layers were separated. Subsequently, the organic solution was evaporated to dryness; the residual oil was redissolved in 400 ml of ether and stirred overnight with 100 ml of 2 *N* aqueous hydrochloric acid. When stirring was stopped, the mixture was transferred to a beaker, and crystallization of the oxindole was initiated by scratching. The mixture was left overnight in the open beaker to allow partial evaporation of the ether and the next day the oxindole was collected by filtration. The solid was dried in a vacuum oven and then recrystallized from absolute ethanol giving a first fraction of 49.7 g (mp 125.5–127°) and, on concentration of the mother liquor, a second crystalline fraction of 10.3 g (mp 122–125.5°). In this manner the total yield of **8a** was 60.0 g (0.34 mol, 84%).

5-Methyl-3-methylthiooxindole (8b). Oxindole **8b** was obtained from **4b** and ethyl methylthioacetate by the general procedure, which gave on concentration of the ethereal layer 2.88 g (0.015 mol, 34%) of the oxindole (**8b**), mp 136–137° (recrystallization from methanol): ir (KBr) 3350 (NH) and 1680 cm^{-1} (C=O); pmr (acetone-d_6) τ 0.78 (1 H, s, NH), 2.80–3.30 (3 H, m, aromatic H), 5.75 (1 H, s, SCH), 7.72 and 7.94 (3 H each, s, CH_3, and s, SCH_3).

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25; S, 16.59. Found: C, 61.85; H, 5.81; N, 7.14; S, 16.49.

5-Methyloxindole (9b). Compound **9b** was obtained when 1.0 g (5.2 mmol) of **8b** was stirred with 2 tsp of W-2 Raney nickel in 50 ml of absolute ethanol. On work-up as described for **9a**, 5-methyloxindole (**9b**) was obtained in a 55% yield, mp 171.5–174.0° (lit.[15] mp 168°).

7-Methyl-3-methylthiooxindole (8c). Oxindole **8c** was obtained from **4c** and ethyl methylthioacetate following the general procedure, which gave 5.65 g (0.029 mol, 67%) of **8c**, mp 194–195.5° (recrystallization from methanol): ir (KBr) 3350 (NH) and 1680 cm^{-1} (C=O); pmr (DMSO-d_6) τ −0.42 (1 H, s, NH), 2.80–3.30 (3 H, m, aromatic H), 5.58 (1 H, s, SCH), 7.82 and 8.02 (3 H each, s, CH_3, and s, SCH_3).

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25; S, 16.59. Found: C, 61.90; H, 5.79; N, 7.17; S, 16.46.

7-Methyloxindole (9c). The desulfurization of 1.0 g (5.2 mmol) of **8c** was carried out in 100 ml of absolute ethanol as described for **8b**, giving 0.55 g (3.7 mmol, 72%) of **9c**, mp 206–207° (lit.[16] mp 203–204°).

1-Methyl-3-methylthiooxindole (8d). Oxindole **8d** was prepared from **4d** and ethyl methylthioacetate following the general procedure. Before the ring closure to the oxindole ring system was effected, the ethereal solution was extracted three times with 20-ml portions of 2 *N* aqueous hydrochloric acid. From these extracts 2.30 g (49%) of starting **4d** was recovered. The remainder of the ethereal solution was evaporated to dryness, and the residue was refluxed overnight in 100 ml of 95% ethanol with 3 ml of concentrated hydrochloric acid. The solvent was removed on a rotary evaporator, and the residue, redissolved in 100 ml of methylene chloride, was treated with saturated sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The solid residue, 3.92 g [0.0203 mol, 46% (or 90% calculated on unrecovered aniline)], consisted of 1-methyl-3-methylthiooxindole (**8d**), mp 87.5–88.5° (recrystallization from ether): ir (KBr) 1680 cm^{-1} (C=O); pmr (CCl_4) τ 2.60–3.5 (4 H, m, aromatic H), 5.98 (1 H, s, SCH), 6.88 and 7.88 (3 H each, s, NCH_3, and s, SCH_3).

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25; S, 16.59. Found: C, 62.09; H, 5.71; N, 7.43; S, 16.57.

1-Methyloxindole (9d). Compound **9d** was obtained when 0.50 g (2.59 mmol) of **8d** was reacted with W-2 Raney nickel as described for **8b**. Oxindole **9d** was isolated in 77% yield, mp 83.0–84.5° (lit.[17] mp 86–88°).

5-Carboethoxy-7-methyl-3-methylthiooxindole (8e). Oxindole **8e** was obtained from **4e**[18] and ethyl methylthioacetate following the general procedure, which was carried out on a 0.015-mol scale and which gave 2.45 g (0.0099 mol, 66%) of **8e**, mp 195–196° (recrystallization from methanol): ir (KBr) 3350 (NH), 1700 and 1680 cm^{-1} (C=O); pmr ($CDCl_3$) τ 0.12 (1 H, s, NH), 2.08 (2 H, m, aryl H), 5.58 (2 H, q, OCH_2), 5.65 (1 H, s, SCH), 7.62 and 7.90 (3 H each, s, CH_3, and s, SCH_3), 8.59 (3 H, t, CH_3).

Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28; S, 12.08. Found: C, 58.84; H, 5.77; N, 5.17; S, 11.93.

5-Carboethoxy-7-methyloxindole (9e). Oxindole **9e** was obtained by desulfurization of 0.80 g (3.0 mmol) of **8e** in 130 ml of absolute ethanol as described for **8b** giving 0.44 g (2.0 mmol, 67%) of **9e**, mp 238–241°: ir (KBr) 1700 and 1670 cm^{-1} (C=O); pmr (DMSO-d_6) τ −0.50 (1 H, s, NH), 2.54 (2 H, s, aryl H), 5.83 (2 H, q, J = 6.0 Hz, OCH_2), 6.52 (2 H, s, CH_2), 7.80 (3 H, s, CH_3), 8.71 (3 H, t, J = 6.0 Hz, OCH_2CH_3).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.71; H, 5.94; N, 6.43.

3-Methylthio-5-nitrooxindole (8f). Oxindole **8f** was obtained from **4f** and ethyl methylthioacetate by the general procedure with some modifications. The nitroaniline (0.044 mol) was dissolved in 300 ml of dichloromethane. This solution was subsequently cooled under vigorous stirring to −70° resulting in a suspension to which the *tert*-butyl hypochlorite (0.044 mol), dissolved in 10 ml of dichloromethane, was added. After a 3-hr period of stirring, most of the nitroaniline had dissolved and a solution of the ethyl methylthioacetate (0.044 mol) in 10 ml of dichloromethane was added followed by an 8-hr period of stirring at −70°. From here on, the general procedure as described above was followed giving 4.92 g (0.024 mol, 51%) of product, mp 196–197° (recrystallization from methanol): ir (KBr) 3200 (N–H) and 1700 cm^{-1} (C=O); pmr (DMSO-d_6) τ −1.53 (1 H, s, NH), 2.00 and 3.15 (1 H each, dd, J = 8 Hz, aryl H), 2.10 (1 H, broad s, aryl H), 5.44 (1 H, s, SCH), and 8.18 (3 H, s, SCH_3).

Anal. Calcd for $C_9H_8N_2O_5S$: C, 48.21; H, 3.60; N, 12.49; S, 14.30. Found: C, 47.97; H, 3.75; N, 12.51; S, 14.17.

3-Methylthio-4-nitrooxindole (13). Oxindole **13** was obtained from *m*-nitroaniline and ethyl methylthioacetate following the general procedure which gave 5.90 g (0.027 mol, 61%) of **13**, mp 228–230° (recrystallization from methanol): ir (KBr) 3350 (NH) and 1700 cm^{-1} (C=O); pmr (DMSO-d_6) τ −0.70 (1 H, s, NH), 2.37 and 2.90 (1 H each, dd, J = 8.0 and 2.0 Hz, 5- and 7-aryl H), 2.60 (1 H, t, J = 8.0 Hz, 6-aryl H), 5.18 (1 H, s, SCH), 8.08 (3 H, s, SCH_3).

Anal. Calcd for $C_9H_8N_2O_5S$: C, 48.21; H, 3.60; N, 12.49; S, 14.30. Found: C, 48.27; H, 3.65; N, 12.38; S, 14.19.

Methylthioacetamide (15). Sulfide **15** was prepared according to the literature[19] procedure.

Preparation of 16. The sulfonium salt **16** was prepared by adding to a stirred solution of 8.0 g (0.088 mol) of **4a** in 250 ml of tetrahydrofuran (THF) at −70° a solution of 9.2 g (0.088 mol) of *tert*-butyl hypochlorite[20] in 15 ml of THF. After 10 min, a warm solution of 9.3 g (0.088 mol) of **15** in 200 ml of THF was added quickly to prevent crystallization of the amide while maintaining the temperature below −40°. Almost instantaneously a precipitate was formed. Stirring was continued for 2 hr and after warming to room temperature the precipitate was collected by filtration. After drying, we obtained 18.10 g (0.078 mol, 89%) of **16**, 105–106° dec: ir (KBr) 1670 cm^{-1} (C=O); pmr (DMSO-d_6) τ −0.57 (1 H, s, NH), 1.70 and 2.20 (1 H each, s, NH_2), 2.30–3.10 (5 H, m, aryl H), 5.00 and 5.20 (1 H each, d, J = 16 Hz, $^+SCH_2$), and 6.60 (3 H, s, $^+SCH_3$).

An analytical sample was obtained by dissolving 0.5 g of the salt in 3 ml of dimethyl sulfoxide and pouring it into 20 ml of THF. The solid was collected by filtration, washed with THF, and dried to give an analytical sample, 107–108° dec.

Anal. Calcd for $C_9H_{13}ClN_2OS$: C, 46.45; H, 5.63; N, 12.04; S, 13.78; Cl, 15.23. Found: C, 46.15; H, 5.65; N, 11.95; S, 13.86; Cl, 15.44.

α-(2-Aminophenyl)-α-methylthioacetamide (17). Compound **17** was obtained by stirring a suspension of 4.0 g (0.017 mol) of **16** in 100 ml of methylene chloride with 2.3 g (0.021 mol) of triethylamine for 1 hr. To the clear solution, 25 ml of water was added and, after separation, the organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated, leaving 2.83 g (0.014 mol, 84%) of **17** as a solid residue, mp 98.5–99.5° (recrystallization from

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(20) Mixtures of THF and *tert*-butyl hypochlorite are potentially dangerous due to occasional exothermic decomposition and should be handled with care.

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°).

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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

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