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.

(17) R. R. Read and D. B. Mullin, *J. Amer. Chem. Soc.*, **50**, 1763 (1928).

(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).

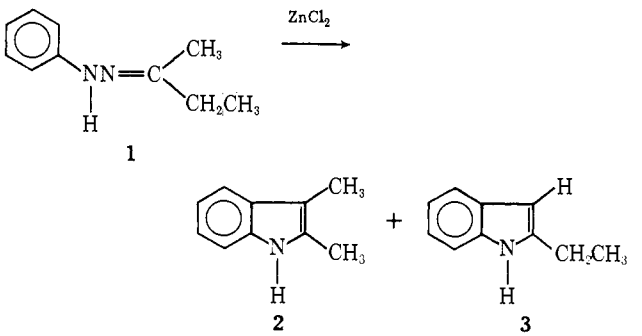
A General Method for the Synthesis of Indoles[1]

Paul G. Gassman,* T. J. van Bergen,[2] David P. Gilbert, and Berkeley W. Cue, Jr.

Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. *Received January 14, 1974*

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

(1) For preliminary reports of this investigation, see P. G. Gassman and T. J. van Bergen, *J. Amer. Chem. Soc.*, **95**, 590, 591 (1973); P. G. Gassman, D. P. Gilbert, and T. J. van Bergen, *J. Chem. Soc., Chem. Commun.*, 201 (1974).

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

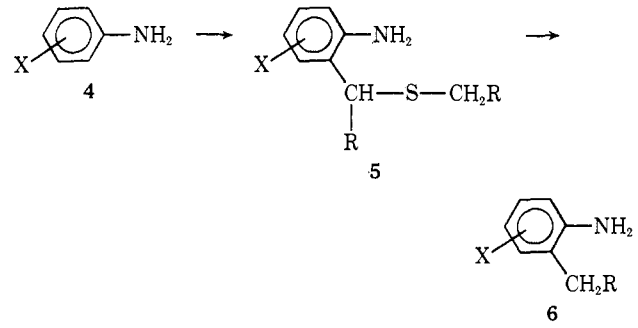
(3) E. Fischer and F. Jourdan, *Chem. Ber.*, **16**, 2241 (1883); E. Fischer and O. Hess, *ibid.*, 17, 559 (1884); E. Fischer, *Justus Liebigs Ann. Chem.*, **236**, 126 (1886).

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

(5) For detailed discussions of the presently known methods of indole synthesis, see R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N. Y., 1970, and R. K. Brown in "Indoles," Part I, W. J. Houlihan, Ed., Wiley-Interscience, New York, N. Y., 1972.

(6) F. R. Japp and F. Klingemann, *Chem. Ber.*, **20**, 2942, 3284, 3398 (1887). For a review, see R. R. Phillips, *Org. React.*, **10**, 143 (1959).

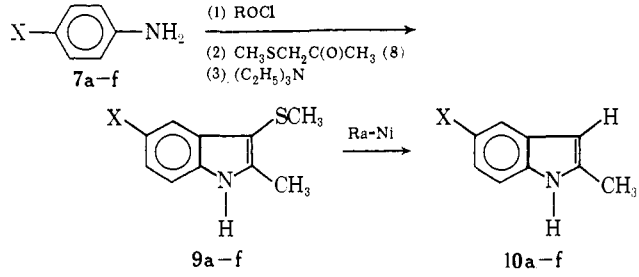
amines.[7] In a relatively straightforward manner, anilines of the general formula **4** could be transformed into **5**, which on desulfurization provided ready access to **6**. The ease with which this overall ortho alkyla-



tion was accomplished suggested to us that the main principle of the reaction mechanism could be utilized with a broad spectrum of aromatic amines and sulfides to provide new synthetic routes to several classes of compounds. This paper deals with the specific use of anilines and β-carbonyl sulfides in our general reaction scheme.

Synthesis

In the prototype of our indole synthesis, aniline was reacted sequentially with *tert*-butyl hypochlorite, methylthio-2-propanone (**8**),[8] and triethylamine to give **9** (X = H) in 69% yield. Raney-nickel desulfurization of **9** then provided 2-methylindole (**10**, X = H) in 79%



yield. The synthetic procedure used with aniline was applicable to substituted anilines bearing a wide variety of substituents.

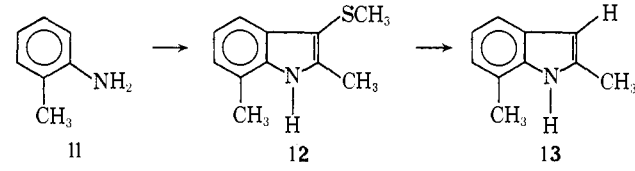
In a general procedure, 1 equiv of a suitable halogenating agent[9] was added to a vigorously stirred solution[10] of 1 equiv of an aniline, of general formula **7**, at −65°,[11] and the reaction was stirred for 5–10 min after the addition was completed. An equivalent of methylthio-2-propanone was added at −65°[11] and the reaction mixture was stirred for an additional hour. An equivalent of base (triethylamine worked quite well) was added at −65°,[11] the cooling bath was removed, and the reaction mixture was stirred and allowed to warm to room temperature. The indole derivatives, **9a–f**, were then isolated by standard techniques. As shown in Table I, the yields of substituted indoles, obtained through the use of this general procedure, were quite good. Reductive desulfurization of **9a–e** with W-2 Raney nickel in ethanol gave **10a–e** in yields which exceeded 70%.

Table I. Yields of 2-Methylindoles Obtained from Methylthio-2-propanone and Substituted Anilines

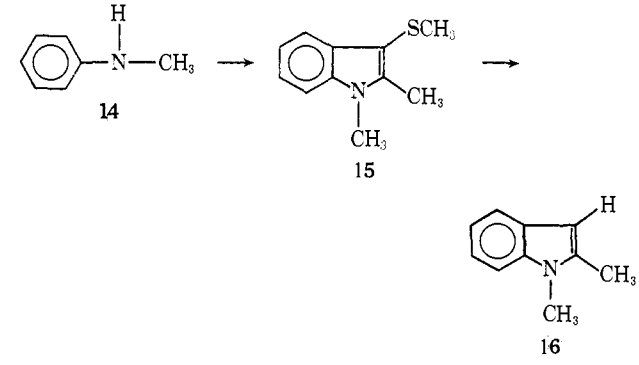
Aniline	X	2-Methyl-3-methylthioindole	% yield	2-Methylindole	% yield
7a	$OC(O)CH_3$	**9a**	68	**10a**	72
7b	CH_3	**9b**	60	**10b**	80
7c	H	**9c**	69	**10c**	79
7d	Cl	**9d**	72	**10d**	74
7e	$CO_2C_2H_5$	**9e**	58	**10e**	83
7f	NO_2	**9f**	30	**10f**	*a*

[a] 2-Methyl-5-nitroindole (**10f**) could not be obtained by Raney-nickel reduction in ethanol due to the susceptibility of the nitro group to reduction under these conditions.

The process was quite general in that it was not limited to para-substituted anilines, primary anilines, or methylthio-2-propanone. Utilizing the conditions described above *o*-toluidine (**11**) was converted into **12** (72% yield), and then **12** was reduced to **13** (73% yield).



Thus, 2,7-disubstituted indoles can be readily prepared from ortho-substituted anilines. Our procedure can also be used to prepare 1-substituted indoles. Under our general conditions *N*-methylaniline (**14**) gave **15** (54% based on unrecovered **14**), which on Raney-nickel reduction gave the 1,2-disubstituted indole **16** (76% yield)



With ortho- and para-substituted anilines the substituents can only reside on the resulting indole at the 7 and 5 positions, respectively. Meta-substituted anilines present a more complicated situation in that the final product can have the substituent at either the 4 position or the 6 position of the indole nucleus. The problem is illustrated by the use of *m*-toluidine (**17**) which gave a 58% yield of a 2:3 mixture of 2,4-dimethyl-3-methylthioindole (**18a**) and 2,6-dimethyl-3-methylthioindole (**18b**).[12] Raney-nickel desulfurization of the mixture of

(7) 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); **96**, 5487 (1974).

(8) C. K. Bradsher, F. C. Brown, and R. J. Grantham, *J. Amer. Chem. Soc.*, **76**, 114 (1954).

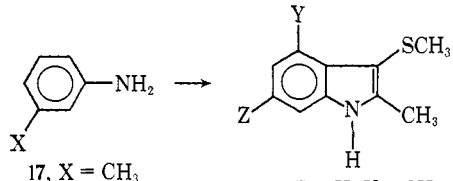
(9) Any active chlorine source can be used in this procedure when appropriate experimental modifications are made. In practice, we found that of the various hypohalites, which can be used, *tert*-butyl hypochlorite was most convenient on a laboratory scale.

(10) The reaction sequence does not appear to be very solvent dependent. Of the various solvents used, we have found methylene chloride to be most convenient.

(11) This reaction can be run over a wide range of temperatures. In general, yields tended to maximize at *ca.* −65°. The extent of the temperature range is a function of the substituents on the aniline.

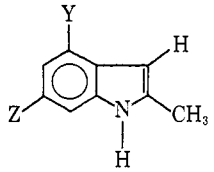
(12) These isomers could not be separated preparatively in our laboratory. The structures were assigned on the basis of spectral evidence. The isomer ratios were assigned on the basis of spectroscopic data.

18 gave 62% of a 1:2 mixture of 2,4-dimethylindole (**19a**) and 2,6-dimethylindole (**19b**).[12] In contrast to the mixture obtained from *m*-toluidine was the result obtained with *m*-nitroaniline (**20**). Utilizing our general procedure, **20** gave an 82% yield of 2-methyl-3-methylthio-4-nitroindole (**21**). None of the 6-nitro



17, X = CH_3
20, X = NO_2

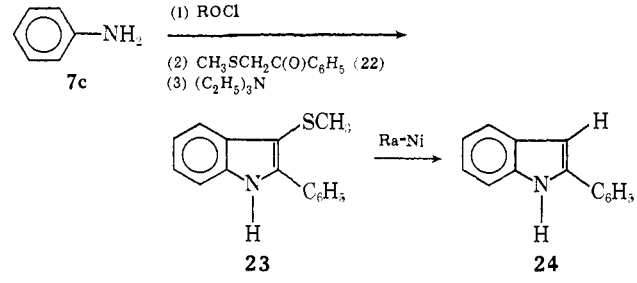
18a, Z = H; Y = CH_3
b, Z = CH_3; Y = H
21, Z = H; Y = NO_2



19a, Z = H; Y = CH_3
b, Z = CH_3; Y = H

isomer was detected; if any were present, the amount would have had to have been relatively small. The interesting feature of the nitro case was the specificity with which substitution occurred at the position ortho to the nitro group. The predominance of the 6-methyl derivative from *m*-toluidine indicates that the position of attack and the degree of specificity in the aromatic substitution step are probably a function of the electron-withdrawing or electron-donating nature of the substituent group.

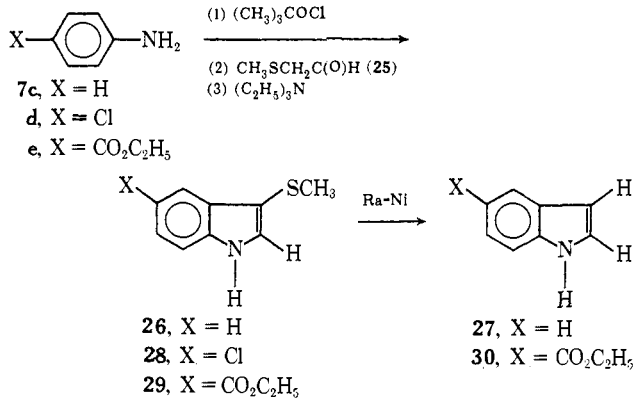
In principle, a wide variety of substituents should be able to be placed at the 2 position of the indole nucleus by varying the nature of the keto sulfide used in the reaction. When methyl phenacyl sulfide (**22**)[13] was used with aniline (**7c**), we obtained an 81% yield of **23**. Raney-nickel reduction of **23** gave **24** in 74% yield.



7c
(1) ROCl
(2) $CH_3SCH_2C(O)C_6H_5$ (**22**)
(3) $(C_2H_5)_3N$
Ra-Ni
23
24

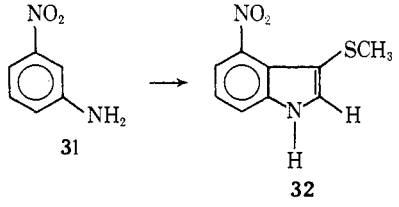
The success observed in the use of β-keto sulfides in the synthesis of 2-substituted indoles prompted us to explore the possibility of using methylthioacetaldehyde as the sulfide in our reaction. This should lead to the production of indoles unsubstituted in the 2 position.

When aniline (**7c**) was treated with 1 equiv of *tert*-butyl hypochlorite in methylene chloride solution at −65°, followed by addition of methylthioacetaldehyde[14] (**25**) at −65° and subsequent treatment with triethylamine, we obtained **26** in 30% yield. Raney-nickel desulfurization of **26** at room temperature gave an 82% yield of indole (**27**). Similar treatment of *p*-chloroaniline (**7d**) gave **28** in 35% yield (50% yield based on unrecovered starting material). With benzocaine (**7e**), we obtained **29** (37%), which on Raney-nickel desulfurization gave a 73% yield of **30**. The



7c, X = H
d, X = Cl
e, X = $CO_2C_2H_5$
(1) $(CH_3)_3COCl$
(2) $CH_3SCH_2C(O)H$ (**25**)
(3) $(C_2H_5)_3N$
Ra-Ni
26, X = H
28, X = Cl
29, X = $CO_2C_2H_5$
27, X = H
30, X = $CO_2C_2H_5$

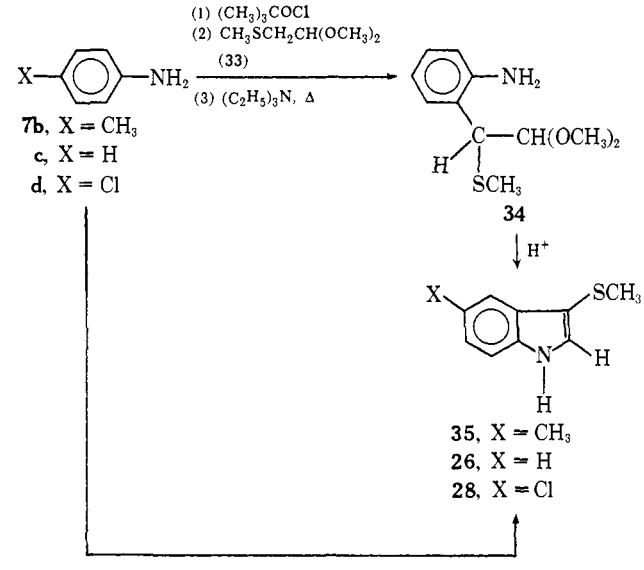
reaction also worked with meta-substituted anilines such as *m*-nitroaniline (**31**), which gave 38% of **32** under



31
32

the conditions described above. Again, only the 4-nitroindole derivative could be isolated from the reaction mixture.

The relatively lower yields obtained when the sulfide was methylthioacetaldehyde (**25**) were of major concern to us. From mechanistic considerations (*vide post*), we felt that the use of **33**,[14] the dimethyl ketal of **25**, might provide some advantage over the use of **25**. When **7c** was treated with *tert*-butyl hypochlorite under the standard conditions, followed by the addition of 1 equiv of **33** and subsequent addition of triethylamine,



7b, X = CH_3
c, X = H
d, X = Cl
(1) $(CH_3)_3COCl$
(2) $CH_3SCH_2CH(OCH_3)_2$
(**33**)
(3) $(C_2H_5)_3N$, Δ
34
H^+
35, X = CH_3
26, X = H
28, X = Cl

we were able to isolate **34** in 57% yield. The structure of **34** was established on the basis of elemental analysis,

(13) V. Prelog, V. Hahn, H. Brauchli, and H. C. Beyerman, *Helv. Chim. Acta*, 27, 1209 (1944).

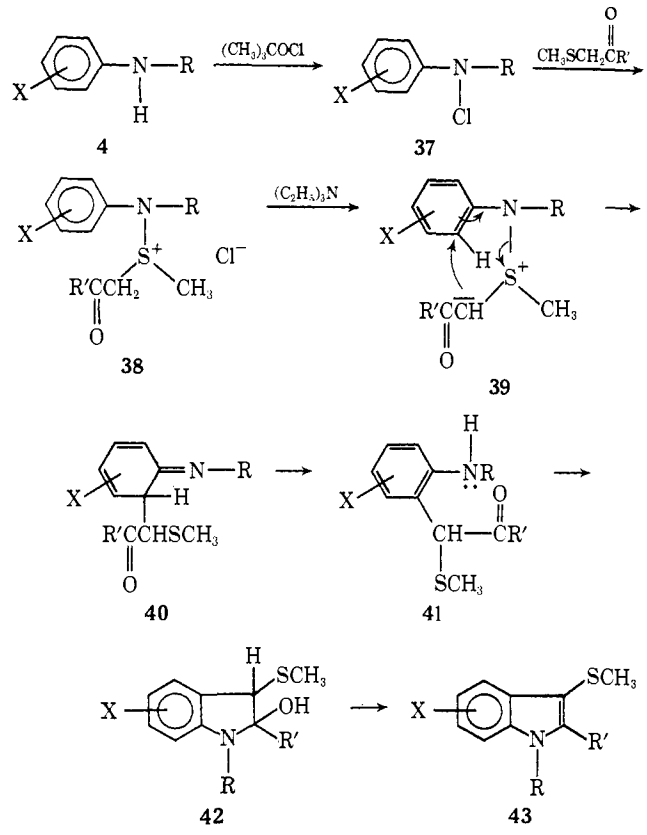
(14) For the preparation of **25** and **33**, see E. H. Wick, T. Yamanishi, H. C. Wertheimer, Y. E. Hoff, B. E. Proctor, and S. A. Goldblith, *J. Agr. Food Chem.*, **9**, 289 (1961). A slight modification of the literature procedure allowed us to improve the yield of **25** from the 21% reported to 65% (see Experimental Section).

ir spectroscopy, and its nmr spectrum, which showed peaks at τ (CCl_4) 2.82–3.67 (4 H, aromatic protons), 5.39 (1 H, d, J = 7 Hz), 6.02 (1 H, d, J = 7 Hz), 6.17 (2 H, broad s, NH_2), 6.65 and 6.88 (3 H, s, diastereomeric OCH_3), and 8.22 (3 H, s, SCH_3). Treatment of an ethereal solution of **34** with a 0.5 *N* aqueous solution of hydrochloric acid gave a 97% yield of **26** for an overall yield of 55% of **26** from **7c**. If, instead of isolating **34**, the crude reaction mixture was treated with acid, we obtained an overall yield of 45% of **26**. The use of *p*-toluidine (**7b**) with **33** gave 5-methyl-3-methylthioindole (**35**) in 39% yield. Raney-nickel desulfurization of **35** gave an 82% yield of 5-methylindole (**36**). When the reaction was run with *p*-chloroaniline (**7d**), the corresponding indole, **28**, was formed in 23% yield.

Mechanistic Discussion

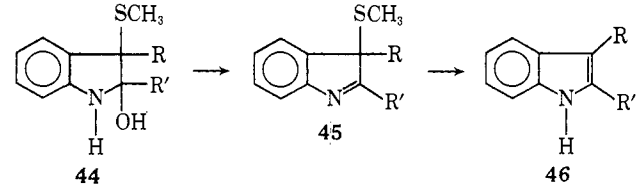
The general mechanism for the formation of indoles from anilines is depicted below. As we have previously shown,[15,16] anilines (**4**) react readily with *tert*-butyl hypochlorite, or with a variety of other hypohalites, to produce *N*-chloroanilines (**37**). These *N*-chloroanilines react readily with sulfides to yield azasulfonium salts (**38**).[17] The azasulfonium salts have fairly acidic hydrogens on the carbons adjacent to the sulfur due to the inductive effect of the positive sulfur. Thus, triethylamine is a strong enough base to abstract a proton from the activated adjacent methylenes.[18] Since the one methylene is also activated by the carbonyl function, it is more acidic and gives up a proton to yield the ylide **39**. Intramolecular attack of the nucleophilic end of the ylide in a Sommelet–Hauser type[16,17,19,20] rearrangement then produces **40**. Proton transfer and rearomatization leads to **41**. In the case where the ketal, **33**, was used instead of a ketone or an aldehyde, the intermediate at this stage was the isolable ketal as illustrated by the characterization of **34**. Intramolecular addition of the free amine to the carbonyl function would be expected to yield the α-amino alcohol **42** after proton transfer. Dehydration would then give the observed polysubstituted indole **43**. The ability to run this series of seven steps in a single reaction vessel in good to excellent overall yields illustrates the efficiency with which each of the individual steps must be occurring.

The very nature of the process described above precludes the preparation of 3-substituted indoles, since the final step involves reductive removal of the methylthio group from the 3 position. However, this problem



can be circumvented either *via* the synthesis of 3-substituted indoles by reduction of the appropriate 3-substituted oxindoles, as described in the following paper,[21] or through a major modification of our general indole synthesis, which involves the use of the α-substituted β-carbonyl sulfides.

In our indole synthesis described above, the formation of **43** was a key step. There was no obvious method for the conversion of **43** into a 3-alkyl- or 3-aryl-substituted indole derivative. Thus, if a route was to be developed for the use of our general concept of indole synthesis in the preparation of 3-substituted indoles, the intermediacy of **43** had to be circumvented. In our general synthetic scheme, the precursor of **43** was **42**, which was dehydrated under the reaction conditions. Since an alternate direction for dehydration of **42** was available (to give an indolenine), it occurred to us that the use of α-alkyl or α-aryl-β-keto sulfides should lead to the intermediate **44**, which might be expected to dehydrate to give **45**. If **45** could be reductively desulfurized, the desired 2,3-disubstituted indoles, **46**, should result.



Treatment of aniline (**7c**) with 1 equiv of *tert*-butyl hypochlorite at −70° gave a mono-*N*-chloroaniline, which was not isolated. Addition of 1 equiv of a sulfide of the general formula **47** led to the formation of an azasulfonium salt. When this azasulfonium salt

(15) P. G. Gassman, G. A. Campbell, and R. C. Frederick, *J. Amer. Chem. Soc.*, **94**, 3884 (1972); P. G. Gassman and G. A. Campbell, *ibid.*, **94**, 3891 (1972); see also P. Haberfield and D. Paul, *ibid.*, **87**, 5502 (1965).

(16) P. G. Gassman and G. Gruetzmacher, *J. Amer. Chem. Soc.*, **95**, 588 (1973).

(17) P. G. Gassman, G. Gruetzmacher, and R. H. Smith, *Tetrahedron Lett.*, 497 (1972); see also R. Appel and W. Büchner, *Chem. Ber.*, **95**, 849, 855 (1962).

(18) When R was hydrogen, the possibility existed that the proton might be removed from nitrogen to give a sulfilimine. If a sulfilimine was formed, it must have been equilibrated with **39** by the triethylamine.

(19) 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).

(20) M. G. Burdon and J. G. Moffatt, *J. Amer. Chem. Soc.*, **88**, 5855 (1966); **89**, 4725 (1967); P. Claus, *Monatsh. Chem.*, **102**, 913 (1971); P. Claus, N. Vavra, and P. Schilling, *ibid.*, **102**, 1072 (1971); P. Claus and W. Vycudilik, *ibid.*, **101**, 396, 405 (1970); P. Claus and W. Vycudilik, *Tetrahedron Lett.*, 3607 (1968); U. Lerch and J. G. Moffatt, *J. Org. Chem.*, **36**, 3861 (1971).

(21) P. G. Gassman and T. J. van Bergen, *J. Amer. Chem. Soc.*, **96**, 5508 (1974).

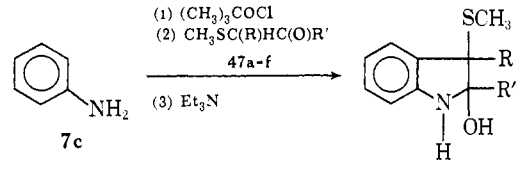
Table II. Yields of 2,3-Disubstituted Indoles Based on Starting Aniline (7c)

Sulfide	Indole	R	R′	Yield, %	Mp or bp, deg (mm)	Lit mp or bp, deg (mm)	Ref
47a	**46a**	CH_3	CH_3	85	104–106	107	*a*
47b	**46b**	CH_3	C_2H_5	60	64–66	65–66	*a*
47c	**46c**	C_2H_5	CH_3	81	107 (0.27)	156 (12)	*a*
47d	**46d**	C_2H_5	C_6H_5	41	74–75	65	*b*
47e	**46e**	CH_3	C_6H_5	69	91–93	91–93	*a*
47f	**46f**	C_6H_5	CH_3	34	58–60	60–60.5	*c*

[a] A. H. Jackson and P. Smith, *Tetrahedron*, **24**, 2227 (1968). [b] J. Fitzpatrick and R. Hiser, *J. Org. Chem.*, **22**, 1703 (1957); A. Korczynski, W. Brydowna, and L. Kierzek, *Gazz. Chim. Ital.*, **56**, 911 (1926). [c] J. Bruce and F. Sutcliffe, *J. Chem. Soc., London*, 4789 (1957).

was treated with 1 equiv of triethylamine, conversion into the indolenine **45** occurred, presumably *via* the initial conversion of the azasulfonium salt into an ylide, followed by Sommelet–Hauser type rearrangement and intramolecular condensation to produce **44**, which on dehydration should yield **45**. Due to their relatively unstable nature, the crude indolenines, **45**, were characterized by ir and nmr spectroscopy (see Experimental Section) and used without further purification.

Whether the indolenines, **45**, could be readily converted to the 2,3-disubstituted indoles, **46**, remained the major question to be answered. Surprisingly, a variety of reducing agents could be used to accomplish the conversion of **45** into **46**. These included W-2 Raney nickel, lithium aluminum hydride, and sodium boro-



hydride. Table II lists the yields of indoles obtained on reduction of the corresponding indolenines with lithium aluminum hydride. Although numerous intermediates are involved in the overall conversion of aniline (**7c**) into **46**, the yields varied from good to excellent. In addition, most of the sulfides were readily available[22] and the laboratory procedure was relatively simple, since it involved the isolation (but not purification) of only one intermediate (**45**).[23] It is worthwhile to indicate one of the many advantages of our synthesis over the Fischer indole synthesis[3,4] at this point. As can be seen from a comparison of the yields of **46b** and **46c**, the substituents can be put on in a very specific manner with virtually no isomer problems, such as would occur if attempts to prepare **46c** were to be made by the Fischer method.

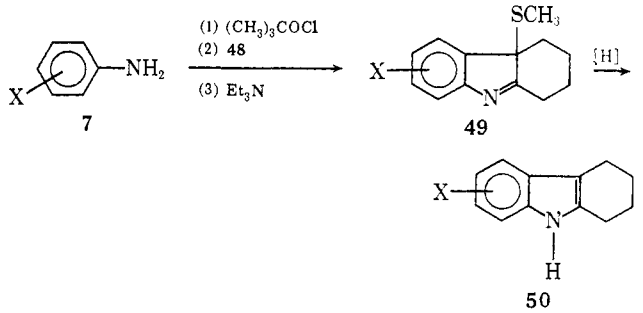
This new modification of our indole synthesis, as described above, offers particular advantage for the synthesis of indoles, which are ring fused to other systems at the 2,3 positions. In principle, the R and R′ of **47** could be joined as part of a cyclic structure. Thus, the use of the known[24] 2-methylthiocyclohexanone (**48**) as the sulfide in our process provides a simple route to tetrahydrocarbazoles. As shown below, sequential treatment of appropriately substituted anilines, **7**, with (a) *tert*-butyl hypohalite, (b) 2-methylthiocyclohexanone, and (c) triethylamine gave the corresponding tetrahydrocarbazolenines, **49**.[25] Table III lists the

Table III. Yields of Tetrahydrocarbazolenines (**49**) Obtained from Appropriately Substituted Anilines and 2-Methylthiocyclohexanone

Starting aniline	X	Tetrahydrocarbazolenine	% yield
7b	*p*-CH_3	**49b**	32[a]
7c	H	**49c**	58
7d	*p*-Cl	**49d**	29[a]
7e	*p*-$CO_2C_2H_5$	**49e**	70[a]
7g	*m*-OCH_3	**49g**	73
7h	*o*-CH_3	**49h**	67
7i	*o*-Cl	**49i**	46

[a] The yields of **49b**, **49d**, and **49e** were based on *unrecovered* starting materials. In these cases, the per cent conversions were 57, 65, and 50, respectively.

yields of tetrahydrocarbazolenines obtained. Desulfurization of **49** gave the tetrahydrocarbazole **50**.



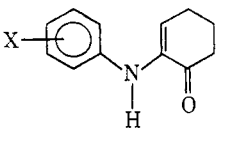
These reductive desulfurizations could be accomplished with a variety of reagents. As shown in Table IV, the

(22) Most of the sulfides used in this study have been reported previously in the literature: (a) **47a**, F. Asinger, M. Thiel, and I. Kalzendorf, *Justus Liebigs Ann. Chem.*, **610**, 25 (1957); (b) **47b**, F. Asinger, M. Thiel, and E. Pallas, *ibid.*, **602**, 37 (1957); (c) **47c**, previously unreported, for details of the synthesis of **10c** see the Experimental Section; (d) **47d**, F. Asinger, W. Schafer, and H. Triem, *Monatsh. Chem.*, **97**, 1510 (1966); (e) **47e**, F. Bohlmann and G. Haffer, *Chem. Ber.*, **102**, 4017 (1969); (f) **47f**, M. Thiel, F. Asinger, and M. Fedtke, *Justus Liebigs Ann. Chem.*, **615**, 77 (1958).

(23) The other intermediates were transitory and were not isolated or characterized as part of this investigation. The overall conversion of **7c** into **45** in a one-pot reaction involved only the sequential addition of (1) the hypohalite, (2) the sulfide, and (3) triethylamine.

(24) H. Britzinger and M. Langbeck, *Chem. Ber.*, **86**, 557 (1953).

(25) In the reactions of **7h**, **7c**, and **7d**, we obtained **51h**, **51c**, and **51d** as side products in 15, 23, and 25% yields, respectively. The mechanistic path to **51** probably involves a Stevens rearrangement of the ylide



51

intermediate followed by elimination of methyl mercaptan. For a previous report of **51c**, see V. N. Kovaleva, N. P. Emel'yanov, and N. S. Koslov, *Dokl. Akad. Nauk, Beloruss. SSR*, 617 (1971); *Chem. Abstr.*, **75**, 118009m (1971).

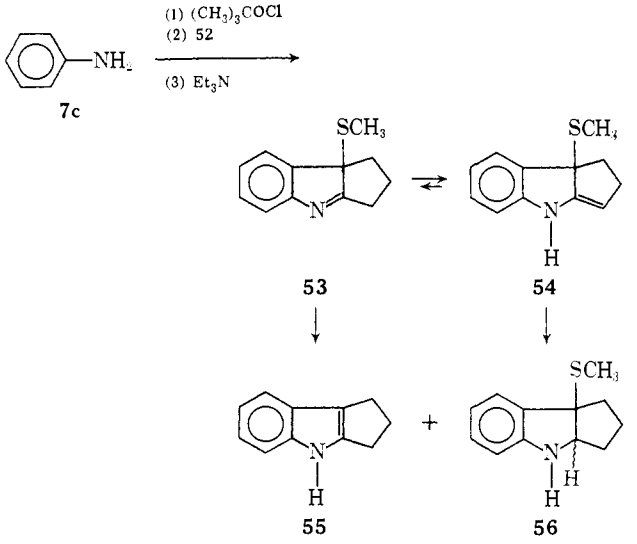
Table IV. Reduction of Tetrahydrocarbazolenines to Tetrahydrocarbazoles

Tetrahydrocarbazolenine	Method of reduction	Tetrahydrocarbazole	% yield	Overall yield from 7
49b	$LiAlH_4$, ether, 0°	**50b** (6-CH_3)	*a*	26[b]
49c	W-2 Raney nickel, 25°	**50c** (H)	83	48
	$LiAlH_4$, ether, 0°	**50c** (H)	80	46
	$NaBH_4$, 2-propanol, reflux	**50c** (H)	64	37
49c	$LiAlH_4$, ether, 0°	**50c** (H)	*a*	48
49d	$LiAlH_4$, ether, 0°	**50d** (6-Cl)	*a*	29[b]
49e	$NaBH_4$, ethanol, 25°	**50e** (6-$CO_2C_2H_5$)	33	23[b]
	$NaBH_4$, 2-propanol, reflux	**50j** [6-$CO_2CH(CH_3)_2$]	72	50[b]
49g	W-2 Raney nickel, 25°	**50g** (7-OCH_3)	76	55
49h	$LiAlH_4$, ether, 0°	**50h** (8-CH_3)	71	48
	$LiAlH_4$, ether, 0°	**50h** (8-CH_3)	*a*	38
49i	W-2 Raney nickel, 25°	**50i** (8-Cl)	40	18

[a] In these reactions, the reduction was carried out on the crude reaction product obtained from **7**. Only the final reduction product was isolated and purified. [b] Overall yields based on starting material consumed.

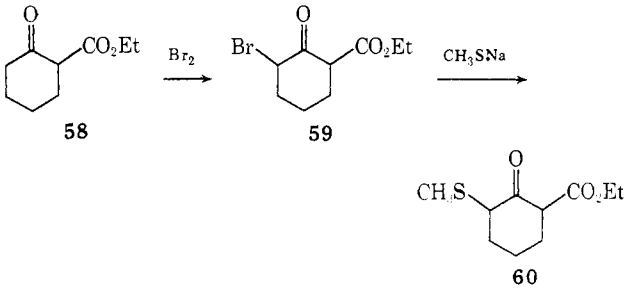
reduction of **49c** with W-2 Raney-nickel in ethanol, lithium aluminum hydride in ether, and sodium borohydride in 2-propanol gave **50c** in yields of 83, 80, and 64%, respectively. One of the more interesting reductions was that of **49e**. With sodium borohydride in ethanol at 25° a rather poor yield (33%) of **50e** was obtained. However, when the reduction was run with sodium borohydride in refluxing 2-propanol, the yield in the reduction increased to 72%, but the reduction was accompanied by transesterification of the carboethoxyl moiety.

The use of 2-thiomethoxycyclopentanone (**52**)[26] in our process gave **53** which was in equilibrium with the enamine **54** (predominant isomer). This mixture of isomers, which was obtained in 62% yield, gave *ca.* 10% of **55** and 43% of **56** on reduction with sodium borohydride in 2-propanol at 90°. It would appear that **55** resulted from the reduction of **53**, while **56** was

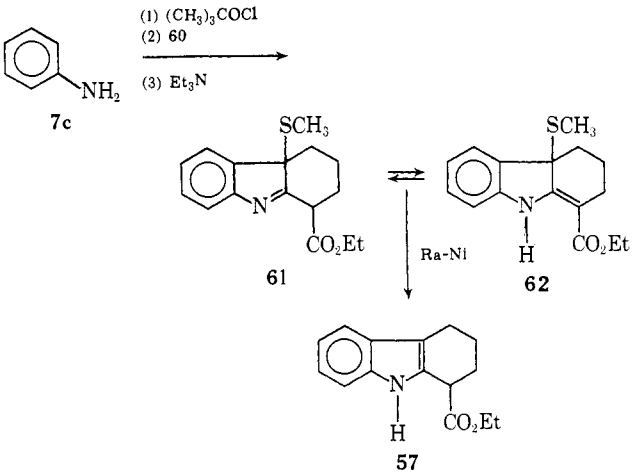


derived from **54**. Raney-nickel reduction of the crude mixture of **53** and **54** gave 38% of **55** based on starting aniline (**7c**).

Lastly, to illustrate the rather extensive versatility of our modified indole synthesis, we have prepared 1-carboethoxytetrahydrocarbazole (**57**). The sulfide required for this preparation was synthesized in two steps from 2-carboethoxycyclohexanone (**58**). Bromination of **58** according to the literature procedure[27] gave the thermodynamically more stable bromide **59** in 96% yield. Treatment of **59** with sodium thiomethoxide in ethanol gave a 53% yield of the known[28] ethyl 6-methylthiocyclohexanone-2-carboxylate (**60**). When aniline



(**7c**) was treated sequentially with (a) *tert*-butyl hypochlorite, (b) **60**, and (c) triethylamine, we obtained **61**, which was shown to be in equilibrium with the enamine **62**. Raney-nickel reduction of this equilibrium mixture gave **57** in 70% yield based on starting aniline (**7c**). This material was identical in all respects with that previously described.[29]



(26) W. E. Truce and R. Knospe, *J. Amer. Chem. Soc.*, 77, 5063 (1955).

(27) J. C. Sheehan and C. Mumaw, *J. Amer. Chem. Soc.*, 72, 2127 (1950).

(28) H. Bohme, K. Kreitz, and E. Nurnberg, *Arch. Pharm.*, **292**, 456 (1959).

(29) M. Julia and J. Lenzi, *Bull. Soc. Chim. Fr.*, 2262 (1962).

The transformations described above illustrate the versatility of this new modification of our indole synthesis. The ease with which α-thiomethoxy derivatives of cyclic ketones have been used in this reaction indicates that the overall process should find numerous applications in the synthesis of polycyclic indole derivatives related to the more complex indole alkaloids.

Advantages and Scope of the General Indole Synthesis

An indication of the scope of the synthesis of indoles by our method can be obtained with reference to the mechanistic scheme presented above. For the substituent on the aromatic ring, X was varied in electronic character from methyl to nitro. Anilines where R has been either hydrogen or methyl have been used successfully. In relation to the sulfide, the indole synthesis has been shown to work well when R′ was hydrogen, methyl, and phenyl. In principle, X, R, and R′ should be able to vary greatly. We anticipate that numerous additional permutations of substituent combinations will work in our procedure to permit the synthesis of desirable polysubstituted indoles.

When compared with the Fischer indole synthesis, our method offers several advantages. First, the starting materials for our process are, in general, readily available and inexpensive. For substitution in the 4, 5, 6, or 7 positions of the indole nucleus, the Fischer method requires the appropriately substituted phenylhydrazines which are often not readily available. For the synthesis of 1-substituted indoles, the Fischer synthesis requires the availability of the appropriate 1,1-disubstituted hydrazine. These are often difficult to prepare. Our method requires the appropriate N-substituted aniline. Many such secondary anilines are commercially available. The β-carbonyl sulfides used in our process are readily obtained either from commercial sources or from the reaction of methyl mercaptide with the appropriate α-halo ketone or α-halo aldehyde.

The very mild conditions under which our reaction proceeds offer yet another advantage. All of the steps can be run below 0°. No acid or strong base need be involved. Hence, our method is applicable to the preparation of indole derivatives with functionality which would be sensitive to elevated temperatures, acids, or strong bases.

Additionally, our process offers certain advantages over the Fischer indole synthesis in terms of specificity. Unless a symmetrical ketone is used in the Fischer method a mixture of indoles can result. As a consequence of the mechanism of formation of the nitrogen-containing ring in our synthesis, this problem is avoided. Finally, the yields obtained in our synthesis of the indole nucleus appear to be superior or comparable to the average yields obtained by the Fischer method.

Limitations

The indole synthesis, as described above, has one serious limitation. Attempts to use anilines of the general type **4**, where X was a cation stabilizing group, such as an *o*-methoxyl or *p*-methoxyl moiety failed to give the desired product. As we have previously demonstrated,[15] *N*-chloroanisidines are extremely unstable, even at temperatures as low as −78°. Thus, our procedure cannot be used to prepare certain indoles such as 5-methoxyindole and 7-methoxyindole, which are of importance in natural product chemistry.[30]

Experimental Section[31]

Methylthio-2-propanone (8). The preparation of **8** was accomplished according to the procedure of Bradsher and coworkers.[8]

Methylthioacetaldehyde Dimethyl Acetal (33). The preparation of **33** was accomplished according to the literature procedure.[14]

Methylthioacetaldehyde (25). In a modification of the literature method,[14] a solution of 13 g (0.095 mol) of **33** in 40 ml of 1% aqueous hydrochloric acid was refluxed for 30 min. After cooling to room temperature, the solution was neutralized with saturated sodium bicarbonate solution and extracted with methylene chloride. The organic layer gave, after drying over anhydrous magnesium sulfate, filtration, and evaporation, a residue that yielded on distillation 5.49 g (0.051 mol, 65%) of **25**: bp 129–134°, n^{25}D 1.4810 (lit.[14] bp 35° (10 mm), n^{25}D 1.4780).

General Procedure for the Synthesis of Indoles from Anilines and β-Carbonyl Sulfides. Method A. 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 *tert*-butyl hypochlorite in 20 ml of the same solvent. After 5–10 min, 0.044 mol of the sulfide dissolved in 20 ml of methylene chloride was added causing an exotherm, and stirring at −65° was continued for 1 hr. Usually the intermediate azasulfonium salt had precipitated at this stage. 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, dried, filtrated, and evaporated. The residue was then purified by column chromatography over silica gel using methylene chloride or a methylene chloride–chloroform mixture as the eluent. Recrystallization then gave the pure indole.

General Procedure for the Synthesis of Indoles from Anilines and Methylthioacetaldehyde Dimethyl Acetal (33). Method B. Method A (*vide supra*) was used with the modification that the β-carbonyl sulfide used was replaced by methylthioacetaldehyde dimethyl acetal (**33**). After the aqueous work-up, the oily residue consisted mainly of the unrearranged sulfilimine as shown by thin layer chromatography. To effect the rearrangement, the residue was refluxed in 150 ml of carbon tetrachloride containing 5 ml of triethylamine overnight or until the rearrangement was complete. The solvent was removed and the residue redissolved in 150 ml of ether. Cyclization of the acetal to the indole ring system was effected by stirring this solution for 3 hr with 50 ml of 2 *N* hydrochloric acid. After separation, the ethereal layer was treated with saturated sodium bicarbonate solution, dried, filtered, and evaporated. The residue contained the indole as the sole product. This was purified by column chromatography on silica gel using methylene chloride as the eluent. Recrystallization then provided the pure indole.

2-Methyl-3-methylthioindole (9c). The preparation of **9c** was accomplished from **7c** and **8** following method A, carried out on a 0.022-mol scale, which gave 2.68 g (0.015 mol, 69%) of **9c**, mp 58–59° (recrystallization from cyclohexane), bp 140–142° (0.85 mm); ir 3400 cm^{-1} (NH); pmr (CCl_4) τ 2.25–3.20 (5 H, m, N–H and aromatic H), 7.76 and 7.83 (s, 3 H, CH_3 and SCH_3).

Anal. Calcd for $C_{10}H_{11}NS$: C, 67.75; H, 6.26; N, 7.90. Found: C, 67.61; H, 6.19; N, 7.87.

2-Methylindole (10c). A solution of 3.86 g (0.022 mol) of **9c** in absolute ethanol was stirred with an excess of W-2 Raney nickel for 30 min. The indole-containing solution was decanted from the catalyst, the catalyst was washed thoroughly with ethanol, and the solvent was evaporated. The residue was dissolved in methylene chloride and dried over anhydrous sodium sulfate. The drying agent was removed by filtration and the filtrate was evaporated to give a 79% yield of 2-methylindole (**10c**), mp 55.0–56.5° (lit.[32] mp 60°). This material was identical with an authentic sample purchased from the Aldrich Chemical Co.

(30) Recently, we have developed a method for the synthesis of 5-methoxyindole derivatives, which involves the reaction of chlorosulfonium chlorides with anilines: P. G. Gassman, G. Gruetzmacher, and T. J. van Bergen, *J. Amer. Chem. Soc.*, **96**, 5512 (1974).

(31) Boiling points and melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 137 infracord. Nmr spectra were recorded on a Varian Associates A-60, A-60A, or HA-100 nuclear magnetic resonance spectrometer.

(32) E. Fischer, *Justus Liebigs Ann. Chem.*, **236**, 127 (1886).

5-Acetoxy-2-methyl-3-methylthioindole (9a). The preparation of **9a** from **7a** and **8** involved method A, carried out on a 0.022-mol scale, which gave 3.55 g (0.015 mol, 68%) of **9a**, mp 129–129.5° (recrystallization from methanol); ir (KBr) 3340 (NH) and 1710 cm^{-1} (C=O); pmr (CCl_4) τ 1.90 (1 H, s, NH), 2.92 and 3.48 (1 H and 2 H, respectively, s, aromatic H), 7.73, 7.78, and 7.94 (3 H each, s, 3 CH_3).

Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.75; N, 5.95; S, 13.63. Found: C, 60.91; H, 5.61; N, 5.90; S, 13.57.

5-Acetoxy-2-methylindole (10a). Under the conditions described above for the desulfurization of **9c**, 0.50 g (2.13 mmol) of **9a** was reduced to give 72% of 5-acetoxy-2-methylindole, mp 129–132° (lit.[33] mp 128–130°).

2,5-Dimethyl-3-methylthioindole (9b). The synthesis of **9b** from **7b** and **8** utilized method A, which gave 5.05 g (0.0265 mol, 60%) of **9b**, mp 110–111° (recrystallization from cyclohexane); ir (KBr) 3350 cm^{-1} (NH); pmr (CCl_4) τ 2.78 (1 H, s, NH), 2.65 and 3.20 (1 H and 2 H, respectively, s, aromatic H), 7.58, 7.79, and 7.86 (3 H each, s, 3 CH_3).

Anal. Calcd for $C_{11}H_{13}NS$: C, 69.09; H, 6.85; N, 7.33; S, 16.73. Found: C, 69.10; H, 6.86; N, 7.25; S, 16.73.

2,5-Dimethylindole (10b). The reductive desulfurization of **9b** was carried out using W-2 Raney nickel, as described above for **9c**, on 0.50 g (2.62 mmol) of **9b**. Work-up gave an 80% yield of 2,5-dimethylindole, mp 108–110° (lit.[34] mp 114–115°). The structure of **10b** was identified by comparison with an authentic sample.[35]

5-Chloro-2-methyl-3-methylthioindole (9d). The synthesis of **9d** from **7d** and **8** was achieved following method A, which gave 6.68 g (0.032 mol, 72%) of **9d**, mp 64.0–65.5° (recrystallization from cyclohexane): ir (KBr) 3350 cm^{-1} (NH); pmr (CCl_4) τ 2.42 (1 H, s, NH), 2.52 and 3.15 (1 H and 2 H, respectively, m, aromatic H), 7.72 and 7.90 (3 H each, s, CH_3 and SCH_3).

Anal. Calcd for $C_{10}H_{10}ClNS$: C, 56.73; H, 4.76; N, 6.62; S, 15.14. Found: C, 56.73; H, 4.72; N, 6.56; S, 15.25.

5-Chloro-2-methylindole (10d). Desulfurization of **9d** with W-2 Raney nickel was carried out, as described above for **9c**, on 1.0 g (4.73 mmol) to give a 74% yield of **10d**, mp 99.0–100.5° (lit.[36] 117–119°).[37] The structure was confirmed through comparison of the ir and nmr spectrum of **10d** with that of an authentic sample.[38]

5-Carboethoxy-2-methyl-3-methylthioindole (9e). Benzocaine (**7e**) and methylthio-2-propanone (**8**) were reacted according to method A with the modification that the suspension of **7e** in 150 ml of methylene chloride was stirred for 30 min at −65° with the hypochlorite solution before addition of the sulfide. After addition of the sulfide, 100 ml of methylene chloride was added to promote stirring. This was continued for 6 hr prior to addition of the base. The oily residue, obtained after work-up, was triturated by stirring with 50 ml of ether, giving on filtration 6.37 g (0.026 mol, 58%) of **9e**, mp 126–127° (recrystallization from absolute ethanol): ir (KBr) 3250 (NH) and 1650 cm^{-1} (C=O); pmr ($CDCl_3$) τ 0.84 (1 H, s, NH), 1.35 (1 H, d, J = 1.5 Hz, 4-aryl H), 2.16 (1 H, dd, J = 8.0 and 1.5 Hz, 6-aryl H), 2.89 (1 H, d, J = 8.0 Hz, 7-aryl H), 5.61 (2 H, q, J = 7.0 Hz, OCH_2), 7.52 and 7.80 (3 H each, s, CH_3 and SCH_3), and 8.59 (3 H, t, J = 7.0 Hz, OCH_2CH_3).

Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 62.63; H, 6.06; N, 5.62; S, 12.86. Found: C, 62.54; H, 6.19; N, 5.63; S, 12.79.

5-Carboethoxy-2-methylindole (10e). Desulfurization of 5-carboethoxy-2-methyl-3-methylthioindole (**9e**) (1.0 g, 4.02 mmol) in the usual manner (see previous examples) gave 0.68 g (3.35 mmol, 83%) of **10e**, mp 140–141° (recrystallization from benzene): ir (KBr) 3250 (NH) and 1650 cm^{-1} (C=O); pmr ($CDCl_3$) τ 1.66 (2 H, br s, NH and 4-aryl H), 2.13 (1 H, dd, J = 8.0 and 1.5 Hz, 6-aryl H), 2.83 (1 H, d, J = 8.0 Hz, 7-aryl H), 3.68 (1 H, s, 3-aryl H), 5.60 (2 H, q, J = 7.0 Hz, OCH_2), 7.56 (3 H, s, CH_3), and 8.58 (3 H, t, J = 7.0 Hz, OCH_2CH_3).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.07; H, 6.43; N, 6.87.

2-Methyl-3-methylthio-5-nitroindole (9f). *p*-Nitroaniline (**7f**) (6.07 g, 0.044 mol) was dissolved in 300 ml of methylene chloride, and the solution was cooled with vigorous stirring to −65°, giving a suspension of the nitro compound. A solution of 5.75 g (0.055 mol) of *tert*-butyl hypochlorite in 10 ml of methylene chloride was added and subsequently, after 3 hr, 7.4 g (0.071 mol) of methylthio-2-propanone (**8**) in 10 ml of methylene chloride was added, while stirring was continued for 10 hr. Triethylamine (4.4 g, 0.044 mol) was dissolved in 10 ml of methylene chloride and the solution was warmed to room temperature. A 50-ml portion of water was added and after separation the organic layer was extracted thoroughly with 2 *N* aqueous hydrochloric acid. Drying over anhydrous magnesium sulfate and filtration of the organic solution was followed by evaporation, leaving a solid residue that was stirred for several hours with 30 ml of benzene. The remaining precipitate was collected by filtration, giving 2.92 g (0.013 mol, 30%) of **9f**, mp 197.5–198.5° (recrystallization from 95% ethanol): ir (KBr) 3250 cm^{-1} (NH); pmr (acetone-d_6) τ −1.40 (1 H, br s, NH), 1.02 (1 H, d, J = 2.0 Hz, 4-aryl H), 2.02 (1 H, dd, J = 8.0 and 2.0 Hz, 6-aryl H), 2.57 (1 H, d, J = 8.0 Hz, 7-aryl H), and 7.42 and 7.73 (3 H each, s, SCH_3 and CH_3).

Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 53.84; H, 4.58; N, 12.55; S, 14.48. Found: C, 54.04; H, 4.54; N, 12.60; S, 14.42.

2,7-Dimethyl-3-methylthioindole (12). The preparation of **12** from **11** and **8** following method A gave 6.04 g (0.0316 mol, 72%) of product, mp 59.5–60.5° (recrystallization from cyclohexane): ir (KBr) 3360 cm^{-1} (NH); pmr (CCl_4) τ 2.30–3.60 (4 H, m, N–H and aromatic H), 7.65, 7.74, and 7.85 (3 H each, s, CH_3, CH_3, and SCH_3).

Anal. Calcd for $C_{11}H_{13}NS$: C, 69.06; H, 6.85; N, 7.32. Found: C, 69.05; H, 6.85; N, 7.24.

2,7-Dimethylindole (13). Reductive desulfurization of **12** (1.0 g, 5.23 mmol), according to the procedure described above for **9c**, gave 2,7-dimethylindole (73%), mp 32–33° (lit.[39] 33–35°).

1,2-Dimethyl-3-methylthioindole (15). The synthesis of **15** from **14** and **8** followed method A. In this case, the organic layer was extracted twice with 2 *N* aqueous hydrochloric acid, after it had been hydrolyzed with 50 ml of water. From the acid extracts 1.53 g (32.5%) of *N*-methylaniline could be recovered. The organic layer gave, in the usual work-up procedure, 3.02 g [0.016 mol, 36% (54% based on unrecovered starting aniline)] of **15**, mp 59.5–60° (recrystallization from *n*-hexane): pmr (CCl_4) τ 2.45 and 2.96 (1 and 3 H, respectively, m, aromatic H), 6.62 (3 H, s, NCH_3), 7.65 and 7.87 (3 H each, s, CH_3 and SCH_3).

Anal. Calcd for $C_{11}H_{13}NS$: C, 69.06; H, 6.85; N, 7.32. Found: C, 68.77; H, 6.79; N, 7.26.

1,2-Dimethylindole (16). The conversion of **15** (1.0 g, 5.23 mmol) into **16** was accomplished in 76% yield according to the procedure described above for **9c**. The 1,2-dimethylindole had mp 50–52° (lit.[40] mp 56°).

2,4-Dimethylindole and 2,6-Dimethylindole (19a and 19b). 2,4-Dimethyl-3-methylthioindole and 2,6-dimethyl-3-methylthioindole (**18a** and **18b**) were obtained as a mixture from the reaction of *m*-toluidine (**17**) and methylthio-2-propanone (**8**) following method A (see general procedure). After column chromatography (silica gel–methylene chloride) there was isolated 4.87 g (0.026 mol, 58%) of **18a** and **18b** (respective ratio 41:59) as an oily mixture: ir 3400 cm^{-1} (NH); pmr (CCl_4) τ 2.50–3.60 (4 H, m, N–H and aryl H), 7.20 (s, 4-CH_3), 7.65 (s, 6-CH_3), 7.08, 7.93, and 7.96 (s, SCH_3 and 2-CH_3) (all of these singlets together account for an integration of 9 H).

Desulfurization of this mixture (2.52 g, 13.2 mmol) was accomplished in the usual manner giving 1.19 g (8.25 mmol, 62.5%) of 2,4-dimethylindole (**19a**) and 2,6-dimethylindole (**19b**) as a solid mixture in a respective ratio of 34:66: pmr (CCl_4) τ 2.60–4.20 (5 H, m, N–H and aryl H), 7.17, 7.62, 7.94, and 8.00 (s, CH_3 and aryl-CH_3, total integration for 6 H).

2-Methyl-3-methylthio-4-nitroindole (21). The synthesis of **21** from **20** and **8** was accomplished following method A with the modifications that (a) tetrahydrofuran (THF) was used as the solvent in view of the solubility and (b) the mixture was stirred for 1 hr after addition of the hypochlorite and 2 hr after addition of the sulfide. In this way 8.07 g (0.036 mol, 82%) of **21** was isolated, mp 148–150° (recrystallization from a $CCl_4/CHCl_3$ mixture): ir (KBr) 3300 cm^{-1} (NH); pmr ($CDCl_3$) τ 1.10 (1 H, s, NH), 1.75–

(33) R. J. S. Beer, K. Clarke, H. G. Khoraner, and A. Robertson, *J. Chem. Soc., London*, 1605 (1948).

(34) J. Raschen, *Justus Liebigs Ann. Chem.*, **239**, 226 (1887).

(35) A commercial sample, purchased from Aldrich Chemical Co., melted at 112–113°.

(36) N. B. Chapman, K. Clarke, and H. Hughes, *J. Chem. Soc., London*, 1424 (1965).

(37) Since our material was adjudged to be pure on the basis of spectral evidence, the rather large difference in our melting point and the literature value would appear to indicate the existence of a crystalline modification.

(38) "The Sadtler Standard Spectra," No. 24382; "Varian NMR Spectra Catalog," No. 228, 1963.

(39) A. R. Bader, R. J. Bridgewater, and P. R. Freeman, *J. Amer. Chem. Soc.*, **83**, 3319 (1961).

(40) J. Degen, *Justus Liebigs Ann. Chem.*, **236**, 153 (1886).

3.00 (3 H, m, aromatic H), 7.40 and 7.75 (3 H each, s, CH_3 and SCH_3).[41]

Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.54; N, 12.60; S, 14.42. Found: C, 54.09; H, 4.58; N, 12.62; S, 14.49.

Methyl Phenacyl Sulfide (22). The synthesis of **22** was accomplished according to the literature procedure.[13]

3-Methylthio-2-phenylindole (23). The preparation of **23** from **7c** and **22** following method A gave 8.57 g (0.036 mol, 81%) of **23**, mp 106–107° (recrystallization from 95% ethanol): ir (KBr) 3300 cm^{-1} (NH); pmr (CCl_4) τ 2.00–3.00 (10 H, m, aromatic H) and 7.84 (3 H, s, SCH_3).

Anal. Calcd for $C_{15}H_{13}NS$: C, 75.28; H, 5.48; N, 5.85. Found: C, 75.16; H, 5.48; N, 5.85.

2-Phenylindole (24). Reduction desulfurization of 1.55 g (6.50 mmol) of **23**, according to the general procedure used for **9c**, gave 74% of **24**, mp 186.5–187.5° (lit.[42] mp 186°). The infrared spectrum of **24** was identical with that of an authentic sample.[43]

3-Methylthioindole (26). The synthesis of **26** from **7c** and **25** followed method A, which gave 1.06 g (6.5 mmol, 30%) of **26**, bp 112.5–113.0° (0.15 mm): $n^{25}D$ = 1.6488; ir 3340 cm^{-1} (NH); pmr (CCl_4) τ 2.40 and 3.05 (2 H and 4 H, respectively, m, aromatic H) and 7.82 (3 H, s, SCH_3).

Anal. Calcd for C_9H_9NS: C, 66.22; H, 5.56; N, 8.58. Found: C, 66.11; H, 5.57; N, 8.52.

Indole (27). Reductive desulfurization of **26** (1.7 g, 0.01 mol) with W-2 Raney nickel, according to the procedure described for **9c**, gave an 82% yield of **27**, mp 49.5–50.5° (lit.[44] 52.5°). The structure of **27** was established through spectral comparison with an authentic sample.[45]

5-Chloro-3-methylthioindole (28). The synthesis of **28** from **7d** and **25** followed method A but used THF as the solvent. On column chromatography, 1.72 g of the starting aniline could be recovered and 3.00 g (0.0152 mol, 35%, 50% calculated on the basis of unrecovered aniline) of **28** was isolated, bp 134.5–135.5° (0.20 mm): ir 3370 cm^{-1} (NH); pmr (CCl_4) τ 1.90 (1 H, s, NH), 2.37 (1 H, s, aromatic H), 2.92 (3 H, m, aromatic H), and 7.72 (3 H, s, SCH_3).

Anal. Calcd for C_9H_8ClNS: C, 54.68; H, 4.08; N, 7.09; S, 16.22. Found: C, 54.44; H, 4.13; N, 7.13; S, 16.02.

5-Carboethoxy-3-methylthioindole (29). The synthesis of **29** was accomplished from benzocaine (**7e**) and methylthioacetaldehyde (**25**) in the same way as described above for **9e**. In the work-up, 50 ml of water was added after warming to room temperature; the layers were separated and the organic solution was concentrated. The residue was redissolved in 100 ml of ether, extracted with 2 *N* aqueous hydrochloric acid to remove **7e**, treated with sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered, and evaporated, leaving a residue which was subjected to column chromatography (silica gel). There was obtained 3.87 g (0.016 mol, 37%) of **29**, mp 89.0–90.5° (recrystallization from CCl_4): ir (KBr) 3220 (NH) and 1650 cm^{-1} (C=O); pmr (CCl_4) τ 0.69 (1 H, s, NH), 1.52 (1 H, d, J = 1.5 Hz, 4-aryl H), 2.10 (1 H, dd, J = 8.0 and 1.5 Hz, 6-aryl H), 2.70 (2 H, m, 2- and 7-aryl H), 5.56 (2 H, q, J = 7.0 Hz, OCH_2), 7.67 (3 H, s, SCH_3), 8.54 (3 H, t, J = 7.0 Hz, OCH_2CH_3). Additional recrystallization gave an analytical sample, mp 96–97°.

Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95; S, 13.63. Found: C, 60.90; H, 5.37; N, 5.74; S, 13.32.

5-Carboethoxyindole (30). Desulfurization of 5-carboethoxy-3-methylthioindole (**29**) (0.53 g, 2.25 mmol) in the usual manner (see previous examples) gave 0.31 g (1.64 mmol, 73%) of **30**, mp 94–95° (recrystallization from cyclohexane): ir (KBr) 3220 (NH) and 1660 cm^{-1} (C=O); pmr (CCl_4) τ 0.68 (1 H, s, NH), 1.60 (1 H, br s, 4-aryl H), 2.14 (1 H, dd, J = 8.0 and 1.5 Hz, 6-aryl H), 2.70 (2 H, m, aryl H), 3.48 (1 H, m, aryl H), 5.62 (2 H, q, J = 7.0 Hz, OCH_2), and 8.61 (3 H, t, J = 7.0 Hz, OCH_2CH_3).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.68; H, 5.81; N, 7.34.

3-Methylthio-4-nitroindole (32). The preparation of **32** was accomplished by the reaction of *m*-nitroaniline (**31**) with **25** following method A, with the modification that tetrahydrofuran was used as the solvent. In addition, the mixture was stirred for 1 hr after addition of the hypochlorite. After hydrolyses with water, the reaction mixture was extracted with 1 *N* aqueous hydrochloric acid to remove any remaining nitroaniline. In this way 3.50 g (0.017 mol, 38%) of **32** was obtained as a black[46] crystalline material, mp 123–124° (recrystallization from ethanol): ir (KBr) 3310 cm^{-1} (NH); pmr ($CDCl_3$) τ 1.03 (1 H, s, NH), 2.20–3.00 (4 H, m, aromatic H),[34] and 7.63 (3 H, s, SCH_3).

Anal. Calcd for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.45; S, 15.37. Found: C, 51.79; H, 3.86; N, 13.37; S, 15.41.

α-Methylthio-α(2-aminophenyl)acetaldehyde Dimethyl Acetal (34). The acetal, **34**, could be obtained from **7c** and methylthioacetaldehyde dimethyl acetal (**33**) by following procedure B as far as the rearrangement. Removal of the solvent gave an oily residue that was separated by column chromatography (silica gel–methylene chloride/ether, 2:1) giving 5.70 g (0.025 mol, 57%) of **34**. An analytical sample was obtained by distillation, bp 125–128° (0.15 mm): $n^{25}D$ 1.5678; pmr (CCl_4) τ 2.82–3.67 (4 H, aromatic protons), 5.39 (1 H, d, J = 7 Hz), 6.02 (1 H, d, J = 7 Hz), 6.17 (2 H, broad s, NH_2), 6.65 and 6.88 (3 H, s, diastereomeric OCH_3), and 8.22 (3 H, s, SCH_3).

Anal. Calcd for $C_{11}H_{17}NO_2S$: C, 58.12; H, 7.54; N, 6.16; S, 14.11. Found: C, 58.01; H, 7.42; N, 6.15; S, 13.66.

Conversion of the Acetal 34 into 3-Methylthioindole (26). A solution of 0.50 g (2.20 mmol) of **34** in 25 ml of ether was stirred for 2 hr with 10 ml of 0.5 *N* aqueous hydrogen chloride. The ethereal layer was separated, treated with a saturated sodium bicarbonate solution, dried, filtered, and evaporated to yield 0.35 g (2.14 mmol, 97%) of the oily **26**, which was identical with the sample of **26** prepared as described above.

3-Methylthioindole (26). The preparation of **26** in a direct process from **7c** and **33** by method B gave 3.32 g (0.0198 mol, 45%) of a product identical with the above described **26**.

5-Chloro-3-methylthioindole (28). The synthesis of **28** from **7d** and **33** by method B gave 2.00 g (0.0102 mol, 23%) of a product identified as **28** by comparison with a previously prepared sample.

5-Methyl-3-methylthioindole (35). The synthesis of **35** from **7b** and **33** by method B gave 2.75 g (0.017 mol, 39%) of the indole (**35**), bp 125–126° (0.20 mm): $n^{25}D$ 1.6332; ir 3340 cm^{-1} (NH); pmr (CCl_4) τ 2.45 (1 H, s, NH), 2.55 (1 H, s, aromatic H), 3.06 (3 H, m, aromatic H), 7.57 and 7.75 (3 H each, s, CH_3 and SCH_3).

Anal. Calcd $C_{10}H_{11}NS$: C, 67.75; H, 6.26; N, 7.90. Found: C, 67.52; H, 6.26; N, 7.90.

5-Methylindole (36). Raney-nickel desulfurization of **35** (1 g, 5.65 mmol), according to the procedure described for **9c**, gave an 82% yield of **36**, mp 55.0–56.5° (lit. 58.5°).

General Procedure for the Preparation of 2,3-Disubstituted Indoles. To a vigorously stirred solution of 4.09 g (0.044 mol) of aniline (**7c**) in 200 ml of dichloromethane at −70° was added dropwise a solution of 4.8 g (0.044 mol) of *tert*-butyl hypochlorite in 20 ml of the same solvent. After 5 min, 0.044 mol of the sulfide (**47a–f**) in 30 ml of dichloromethane was added dropwise. The stirring was continued at −70° for 6–48 hr at which time 4.4 g (0.044 mol) of triethylamine in 20 ml of the same solvent was added and the mixture was permitted to warm to room temperature over a 4–12-hr period. A 75-ml portion of water was added and the reaction mixture was stirred for 15 min at which time the organic layer was separated and washed three additional times with water and twice with a saturated sodium chloride solution. The solution was then dried over anhydrous magnesium sulfate and filtered, and the solution was evaporated to give the oily, crude indolenine, **45a–f**. The dichloromethane was very difficult to remove completely from the indolenine. The indolenine was checked by tlc, ir, and nmr before reduction with 3.34 g (0.088 mol) of lithium aluminum hydride in ether. The reaction mixture was hydrolyzed by the addition of 0.5 *N* aqueous sulfuric acid and removal of the organic layer. The aqueous layer was then extracted three additional times with 100-ml portions of ether. The ether extracts were com-

(41) The assignment of the nitro group to the 4 position of the indole nucleus was based on careful examination of the nmr spectrum of **21** in acetone-d_6, which caused some separation of the aromatic region. The spectrum showed a triplet at τ 2.92 (1 H, J = 8 Hz) and two overlapping doublet of doublets at τ 2.44 and 2.57 (1 H each, J = 8 and 1.5 Hz). In CD_3CN these doublet of doublets can be even more extensively resolved. This was only consistent with the three aromatic hydrogens being on adjacent carbons. A similar study of **32** in acetone-d_6 showed the 2 proton as a singlet at τ 2.26, with a triplet at τ 2.68 (1 H, J = 8 Hz) and two overlapping doublet of doublets at τ 2.12 and 2.37 (1 H each, J = 8 and 1.5 Hz).

(42) E. Fischer and T. Schmitt, *Chem. Ber.*, 21, 1072 (1888).

(43) "The Sadtler Standard Spectra," No. 8638.

(44) G. Ciamician and C. Zatti, *Chem. Ber.*, 22, 1976 (1889).

(45) Purchased from Columbia Organic Chemicals, mp 51.5–52.5°.

(46) The color of **32** was somewhat curious. The black solid gave concentrated solutions which were deep red and dilute solutions which appeared yellow. Neither repeated recrystallizations nor sublimation changed these optical properties.

bined and washed twice with 0.5 *N* aqueous hydrochloric acid, once with a 100-ml portion of water, with saturated sodium bicarbonate until neutral, and twice with saturated sodium chloride. The solution was dried over anhydrous magnesium sulfate and filtered, and the solution was evaporated to yield the indole, **46a–f**. The crude indoles were purified by distillation, recrystallization, or column chromatography over silica gel with either dichloromethane or benzene as the eluent.

3-Bromo-2-butanone (63). Compound **63** was prepared by the procedure of Faworsky and Issatschenko.[47]

3-Methylthio-2-butanone (47a). To a stirred solution of 14.1 g (0.255 mol) of sodium methoxide at 0° in 500 ml of methanol was added 30 ml (0.57 mol) of methanethiol. The reaction mixture was stirred for 15 min. A 38.5-g (0.255 mol) portion of 3-bromo-2-butanone (**63**) was added slowly while keeping the temperature below 5°. The reaction mixture was then stirred for 24 hr before being poured into 300 ml of water and extracted three times with 100-ml portions of ether. The combined ether extracts were washed with water until neutral and once with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and evaporated, and the residue was distilled to give 12.7 g (0.0107 mol, 42%) of **47a**, bp 59° (19 mm) [lit.[22a] bp 45–47° (15 mm)].

2,3-Dimethylindole (46a). Indole **46a** was prepared according to the general procedure from 5.20 g (0.044 mol) of 3-methylthio-2-butanone (**47a**) and 4.09 g (0.044 mol) of **7c**. The reaction mixture was stirred at −70° for 7 hr before the addition of 4.4 g (0.044 mol) of triethylamine which was followed by warming to room temperature over a 4-hr period. Reduction of the crude indolenine yielded, after sublimation and recrystallization (pet. ether), 5.42 g (0.0374 mol, 85%) of **46a**, mp 104–106° (lit.[48] mp 107°).

Interruption of the procedure at an earlier stage gave 8.9 g of the crude intermediate 2,3-dimethyl-3-methylthioindolenine (**45a**): ir 1712 (w), 1610 (w), and 1587 (s) cm^{-1};[49] pmr ($CDCl_3$) τ 2.36–3.45 (4 H, m, aromatic H), 7.66 (3 H, s, 2-CH_3), 8.49 (3 H, s, 3-CH_3), and 8.71 (3 H, s, SCH_3).[50]

2-Penten-3-ol Acetate (64). Compound **64** was prepared by the procedures of House and Kramer.[51]

2-Bromo-3-pentanone (65). An 18.7-g (0.117 mol) portion of bromine in 80 ml of carbon tetrachloride was added over a period of 1 hr to a stirred solution of 14.3 g (0.112 mol) of **64** and 21 g of anhydrous sodium carbonate in 100 ml of carbon tetrachloride at 5–10°.[52] To speed the addition of bromine, the reaction mixture was cooled in a bath at −40° and the rate of addition of bromine was increased. After the addition was complete, the mixture was warmed to room temperature and let stand for 30 min. The carbon tetrachloride was decanted, the sodium carbonate was dissolved in water, and this solution was extracted three times with 50-ml portions of carbon tetrachloride. The organic layers were combined and washed subsequently with 5% sodium bisulfite solution, with water, twice with saturated sodium bicarbonate, and again with water. It was dried over anhydrous magnesium sulfate, filtered, and evaporated, and the residue was distilled to give 11.9 g (0.072 mol, 65%) of **65**, bp 68–78° (40 mm) [lit.[53] bp 48° (12 mm)].

2-Methylthio-3-pentanone (47b). To a stirred solution of 3.9 g (0.072 mol) of sodium methoxide in 150 ml of methanol was added 10 ml (0.19 mol) of methanethiol at 0° and the reaction mixture was stirred for 15 min. A 16.5-g (0.072 mol) portion of 2-bromo-3-pentanone (**65**) was added slowly while keeping the temperature below 5°. The reaction mixture was stirred for 12 hr at room temperature before being poured into 300 ml of water and extracted three times with 50-ml portions of ether. The combined ether extracts were washed with water until neutral, once with saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered, evaporated, and the residue was distilled to give 8.18 g (0.062 mol, 86%) of **47b**, bp 87° (42 mm) [lit.[22b] bp 66° (17 mm)].

2-Ethyl-3-methylindole (46b). Indole **46b** was prepared according to the general procedure on a 0.0159-mol scale with 2.1 g (0.0159 mol) of **47b** and 1.48 g (0.0159 mol) of **7c**. All of the amounts of the reagents and solvents were reduced to keep the concentrations the same as in the preparation of **46a**. The reaction was stirred for 8 hr at −70° before the addition of 1.59 g (0.0159 mol) of triethylamine. The reaction mixture was permitted to warm to room temperature over a 4-hr period. After reduction, work up, and recrystallization from an ether–hexane mixture, 1.52 g (0.096 mol, 60%) of **46b**, mp 64–66° (lit.[48] mp 65–66°), was isolated.

Isolation prior to reduction gave 9.0 g of the crude intermediate 2-ethyl-3-methyl-3-methylthioindolenine (**45b**); ir 1704 (w), 1610 (w), and 1572 (s) cm^{-1}; pmr ($CDCl_3$) τ 2.35–3.50 (4 H, m, aromatic H), 7.38 (2 H, m, CH_2CH_3), 8.52 (3 H, s, 3-CH_3), 8.63 (3 H, t, J = 7 Hz, CH_2CH_3), and 8.73 (3 H, s, SCH_3).

3-Bromo-2-pentanone (66). Compound **66** was prepared by slowly adding 31.96 g (0.2 mol) of bromine in 50 ml of acetic acid to a stirred solution of 17.23 g (0.2 mol) of 2-pentanone in 100 ml of acetic acid. After addition was complete, the mixture was heated to 80° and gaseous hydrogen bromide was bubbled in for 2 hr. After cooling to room temperature the mixture was poured into 200 ml of water and extracted four times with 50-ml portions of ether. The ether extracts were combined and washed sequentially with water, saturated sodium bicarbonate solution until neutral, and saturated sodium chloride solution. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and evaporated, and the resulting residue was distilled to give 21.2 g (0.129 mol, 64.5%) of **66**, bp 75–76° (47 mm) [lit.[54] bp 77–78° (44 mm)].

3-Methylthio-2-pentanone (47c). To a stirred solution of 6.96 g (0.129 mol) of sodium methoxide in 100 ml of methanol was added at 0° 12 ml (0.23 mol) of methanethiol, and the reaction mixture was stirred for 15 min. A 21.2-g (0.129 mol) portion of **66** was added slowly while keeping the temperature below 5°. The reaction mixture was stirred for 24 hr at room temperature before being poured into 300 ml of water and extracted three times with 75-ml portions of ether. The ethereal extracts were combined and washed with water until neutral and once with saturated sodium chloride. Then the ethereal solution was dried over anhydrous magnesium sulfate, filtered, and evaporated, and the residue was distilled to give 15.4 g (0.117 mol, 91%) of **47c**, bp 87° (36 mm): $n^{24.4}$D 1.4648; ir 1705 cm^{-1} (C=O); pmr ($CDCl_3$) τ 6.90 (1 H, t, J = 7 Hz, −C*H*CH_2–), 7.74 (3 H, s, SCH_3), 8.00–8.60 (2 H, m, $CHCH_2CH_3$), 8.09 (3 H, s, CH_3), and 9.03 (3 H, t, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_6H_{12}OS$: C, 54.50; H, 9.19; S, 24.25. Found: C, 54.47; H, 9.01; S, 24.24.

3-Ethyl-2-methylindole (46c). Indole **46c** was prepared according to the general procedure using 5.81 g (0.044 mol) of **47c** and 4.09 g (0.044 mol) of **7c**. The mixture was stirred at −70° for 6 hr before the addition of 4.4 g (0.044 mol) of triethylamine. The reaction mixture was then allowed to warm to room temperature over an 8-hr period. After lithium aluminum hydride reduction, work up, and distillation, there was obtained 5.7 g (0.036 mol, 81%) of **46c**, bp 107° (0.27 mm) [lit.[48] bp 156° (12 mm)].

Isolation of the intermediate prior to reduction gave 8.7 g of the crude 3-ethyl-2-methyl-3-methylthioindolenine (**45c**): ir 1709 (w), 1605 (w), 1579 (s) cm^{-1}; pmr ($CDCl_3$) τ 2.40–3.50 (4 H, m, aromatic H), 7.81 (3 H, s, 2-CH_3), 8.02 (2 H, m, CH_2CH_3), 8.73 (3 H, s, SCH_3), and 9.48 (3 H, t, J = 7 Hz, CH_2CH_3).

2-Methylthiobutyrophenone (47d). A 54.5-g (0.340 mol) portion of bromine was slowly added to a stirred solution of 50.0 g (0.337 mol) of butyrophenone in 500 ml of carbon tetrachloride at 0°. After warming to room temperature the solution was washed sequentially with water, with saturated sodium bicarbonate until neutral, and with saturated sodium chloride. The solution was dried over anhydrous magnesium sulfate and filtered, and the solution was evaporated to give 76.6 g (0.337 mol, 100%) of crude α-bromobutyrophenone, which was used directly in the preparation of **47d**. To a stirred solution of 18.2 g (0.337 mol) of sodium methoxide in 450 ml of methanol was added, at 0°, 33 ml (0.63 mol) of methanethiol and the reaction mixture was stirred for 15 min. A 76.6-g (0.337 mol) portion of crude α-bromobutyrophenone was added slowly while keeping the temperature below 5°. The reaction mixture was stirred at room temperature for 24 hr before

(47) A. Faworsky and B. Issatschenko, *J. Prakt. Chem.*, [2], **88**, 657 (1913).

(48) A. H. Jackson and P. Smith, *Tetrahedron*, 24, 2227 (1968).

(49) Infrared data are relatively scarce for indolenines. The most characteristic absorption appears to be the $\nu_{C=N}$ at 1550–1625 cm^{-1}; see J. B. Patrick and B. Witkop, *J. Amer. Chem. Soc.*, 72, 634 (1950); B. Witkop and J. B. Patrick, *ibid.*, **73**, 1558 (1951); B. Witkop and J. B. Patrick, *ibid.*, **73**, 2188 (1951); and M. Nakazaki and M. Maeda, *Bull. Chem. Soc. Jap.*, **35**, 1380 (1962).

(50) Assignment of the chemical shifts was made by reference to known alkyl indolenines; see A. H. Jackson and P. Smith, *J. Chem. Soc. C*, 1667 (1968).

(51) H. O. House and U. Kramer, *J. Org. Chem.*, **28**, 3367 (1963).

(52) A similar procedure has been used to prepare 2α-bromo-10β-pinan-3-one: M. P. Hartshorn and A. F. A. Wallis, *Tetrahedron*, 21, 273 (1965).

(53) C. Rappe and R. Kumar, *Ark. Kemi*, **23**, 475 (1965).

(54) M. D. Mehta, D. Miller, and D. J. D. Tidy, *J. Chem. Soc., London*, 4614 (1963).

being poured into 500 ml of water and then extracted three times with 100-ml portions of ether. The ether extracts were combined, washed with water until neutral and once with saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was distilled to yield 54.1 g (0.28 mol, 83%) of **47d**, bp 90–91° (0.11 mm) [lit.[22d] bp 110° (0.4 mm)].

3-Ethyl-2-phenylindole (46d). Indole **46d** was prepared according to the general procedure from 8.56 g (0.044 mol) of α-methylthiobutyrophenone (**47d**) and 4.09 g (0.044 mol) of **7c**. The reaction mixture was stirred at −70° for 24 hr before 4.4 g (0.044 mol) of triethylamine was added. The reaction mixture was warmed to room temperature over a 5-hr period. After reduction, work-up, column chromatography on silica gel with benzene, and recrystallization from an ether–hexane mixture, 4.0 g (0.018 mol, 41%) of **46d**, mp 74–75° (lit.[55] mp 65°), was obtained.

Isolation prior to reduction gave 10.5 g of the impure intermediate 3-ethyl-3-methylthio-2-phenylindolenine (**45d**). The nmr ($CDCl_3$) showed τ 2.3–3.5 (9 H, m, aromatic H) and 9.6 (3 H, t, J = 7 Hz, CH_2CH_3) among other absorbances.

α-Methylthiopropiophenone (47e). Compound **47e** was prepared by the procedure of Bohlmann and Haffer.[22e]

3-Methyl-2-phenylindole (46e). Indole **46e** was prepared following the general procedure from 7.91 g (0.044 mol) of **47e** and 4.09 g (0.044 mol) of **7c**. The reaction mixture was stirred for 27 hr at −70° before addition of 4.4 g (0.044 mol) of triethylamine. The reaction mixture was then allowed to warm to room temperature over a 12-hr period. After reduction, work up, and recrystallization from an ether–pentane mixture, 6.3 g (0.03 mol, 69%) of **46e**, mp 91–93° (lit.[48] mp 91–93°), was obtained.

Work-up prior to reduction gave 9.2 g of 3-methyl-3-methylthio-2-phenylindolenine (**45e**): ir 1610 (s) cm^{-1}; pmr ($CDCl_3$) τ 2.20–3.70 (9 H, m, aromatic H), 8.38 (3 H, s, 3-CH_3), and 8.75 (3 H, s, SCH_3).

1-Chloro-1-phenyl-2-propanone (67). Compound **67** was prepared according to the procedure of Bordwell and Scamehorn.[56]

1-Methylthio-1-phenyl-2-propanone (47f). Compound **47f** was prepared by the addition of 20 ml (0.39 mol) of methanethiol to a stirred suspension of 60 g of potassium carbonate in 200 ml of ether at 0°, which was stirred for 15 min before 41.2 g (0.244 mol) of 1-chloro-1-phenyl-2-propanone (**67**) was added dropwise. The reaction mixture was stirred at 0° for 24 hr, at which time the reaction mixture was poured into 300 ml of water and extracted three times with 100-ml portions of ether. The ether extracts were combined and washed sequentially with dilute hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride solution. The organic solution was dried over anhydrous magnesium sulfate, filtered, and evaporated, and the residue was distilled to give 18.8 g (0.104 mol, 43%) of **47f**, bp 76° (0.25 mm), $n^{26}D$ 1.5339 [lit.[22f] bp 140–141° (11 mm), $n^{20}D$ 1.5572], that solidified in the refrigerator.

2-Methyl-3-phenylindole (46f). Indole **46f** was prepared according to the general procedure from 7.91 g (0.044 mol) of **47f** and 4.09 g (0.044 mol) of **7c**. The reaction mixture was stirred for 48 hr at −70° before the addition of 4.4 g (0.044 mol) of triethylamine, which was followed by warming to room temperature over a 7-hr period. After reduction, workup, chromatography on silica gel with dichloromethane and recrystallization from hexane, 3.1 g (0.015 mol, 34%) of **46f**, mp 58–60° (lit.[57] mp 60.0–60.5°) was obtained.

Work-up prior to reduction gave 3.9 g of the crude 2-methyl-3-methylthio-3-phenylindolenine (**45f**) by chromatography on silica gel with dichloromethane:[58] ir 1585 (s) cm^{-1}; pmr ($CDCl_3$) τ 2.35–3.1 (9 H, m, aryl H), 7.76 (3 H, s, 3-CH_3), and 8.57 (3 H, s, SCH_3).

2-Methylthiocyclohexanone (48). To a stirred solution of 17.4 g (0.322 mol) of sodium methanolate in 250 ml of absolute methanol at −40° was added *ca.* 30 ml of methanethiol. After about 15 min, 42.5 g (0.322 mol) of 2-chlorocyclohexanone[59] dissolved in 75 ml of absolute methanol was added dropwise over a 1-hr period. The mixture was stirred overnight while allowing it to warm to room temperature. The precipitated salt was removed by filtration and the solvent was evaporated. The residue was redissolved in 100 ml of ether and then extracted twice with 50-ml portions of water. The ethereal solution was dried over anhydrous magnesium sulfate and filtered, and the solvent was removed on a rotary evaporator. On distillation of the residue, 36.5 g (0.255 mol, 79%) of **48** was obtained, bp 45.5–48.0° (0.20 mm), $n^{24}D$ 1.5088 [lit.[24] bp 109–112° (14 mm)].

2-Methylthiocyclopentanone (52). The preparation of **52** was carried out with some modification of the literature[26] procedure. To a stirred solution of 16.5 g (0.305 mol) of sodium methoxide in 250 ml of absolute methanol, that was cooled to −40°, was added 30 ml (0.50 mol) of methanethiol. After a 15-min period, a solution of 36 g (0.305 mol) of 2-chlorocyclopentanone[60] in 60 ml of absolute methanol was added dropwise while the temperature was maintained below −35°. The addition was completed after 2 hr. The cooling bath was removed to allow warming to room temperature and stirring was continued overnight. Subsequently, 200 ml of a saturated aqueous sodium chloride solution was added, followed by extraction with three 100-ml portions of ether. The organic solutions were dried over anhydrous magnesium sulfate, filtered, and evaporated. The residual liquid gave, on distillation, 23.9 g (0.18 mol, 60%) of **52**, bp 90–100° (20 mm), $n^{24}D$ 1.5013 [lit.[26] bp 71–72° (6 mm), $n^{25}D$ 1.5018–1.5054, 45% yield].

General Procedure for the Synthesis of 11-Methylthio-1,2,3,4-tetrahydrocarbazolenines from Anilines and 2-Methylthiocyclohexanone. To a vigorously stirred solution of 0.044 mol of an aniline in 150 ml of methylene chloride at −65° was added dropwise a solution of 0.044 mol of *tert*-butyl hypochlorite in 20 ml of the same solvent. After a 5-min period, 0.044 mol of 2-methylthiocyclohexanone in 20 ml of methylene chloride was added causing a slight exotherm and stirring was continued for 1 hr. The intermediate azasulfonium salt did not precipitate. Subsequently, 0.044 mol of triethylamine in 20 ml of methylene chloride was added, and after addition was completed the cooling bath was removed to allow the solution to warm to room temperature. A 50-ml portion 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 to give the pure 11-methylthio-1,2,3,4-tetrahydrocarbazolenine as a viscous oil that had to be stored in the cold. On standing, the 11-methylthio-1,2,3,4-tetrahydrocarbazolenines are equilibrated with their enamine forms.

7-Methoxy-11-methylthio-1,2,3,4-tetrahydrocarbazolenine (49g). The preparation of **49g** was accomplished from **7g** and **48** following the general procedure. The reaction mixture was stirred for 5 hr at −65° following the addition of **14** and overnight at −65° following the addition of triethylamine. The reaction was worked up in the described manner and the residue was chromatographed on silica gel (elution with methylene chloride) to give 8.09 g (73%) of **49g** as a light yellow oil; ir 3400 (enamine NH), 1680, 1620 (C=N), and 730 cm^{-1}; pmr (CCl_4) τ 2.70–3.70 (3 H, m, aromatic protons), 6.30 and 6.35 (3 H, 2 s, OCH_3 and OCH_3 of enamine form), 7.70 and 8.75 (3 H, 2 s, SCH_3 of enamine and imine, respectively), 7.00–8.00 (4 H, m, C-1 and C-4 protons), and 8.00–9.00 (4 H, m, C-2 and C-3 protons).

8-Methyl-11-methylthio-1,2,3,4-tetrahydrocarbazolenine (49h). Compound **49h** was prepared from **7h** and **48** following the general procedure. Purification of the reaction mixture by column chromatography using silica gel and a 1:4 carbon tetrachloride–methylene chloride mixture gave 6.80 g (0.029 mol, 67%) of **49h** as a viscous oil: ir 1680 cm^{-1} (N=C); pmr (CCl_4) τ 2.70–3.65 (3 H, m, aryl H), 7.48 (3 H, s, CH_3), 8.78 (3 H, s, SCH_3), and 7.00–9.00 (8 H, m, aliphatic H); exact m/e 231.1084 (calcd for $C_{14}H_{17}NS$ m/e 231.1081).

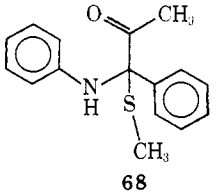
The first fraction eluted, 1.35 g (0.007 mol, 15%), was 2-(2-methylanilino)2-cyclohexen-1-one (**51h**), bp 120–124° (0.08 mm):

(55) J. Fitzpatrick and R. Hiser, *J. Org. Chem.*, 22, 1703 (1957); A. Korczynski, W. Brydowna, and L. Kierzck, *Gazz. Chim. Ital.*, **56**, 911 (1926).

(56) F. G. Bordwell and R. G. Scamehorn, *J. Amer. Chem. Soc.*, **90**, 6751 (1968).

(57) J. Bruce and F. Sutcliffe, *J. Chem. Soc., London*, 4789 (1957).

(58) A second product corresponding to a Stevens rearrangement product was tentatively identified as 1-*N*-anilino-1-methylthio-1-phenyl-2-propanone (**68**) by ir, pmr, and mass spectral analysis.



68

(59) 2-Chlorocyclohexanone was purchased from Aldrich Chemical Co.

(60) 2-Chlorocyclopentanone was purchased from the Aldrich Chemical Co.

n^{24}D 1.5880; ir 3440 (NH) and 1680 cm^{-1} (C=O); pmr (CCl_4) τ 2.70–3.40 (4 H, m, aryl H), 3.90 (1 H, br s, NH), 4.04 (1 H, t, vinyl H), 7.25–8.30 (6 H, m, aliphatic H), and 7.83 (3 H, s, CH_3); exact *m/e* 201.1156 (calcd for $C_{13}H_{15}NO$: *m/e* 201.1153).

Anal. Calcd for $C_{13}H_{14}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 76.92; H, 7.57; N, 6.87.

6-Methyl-11-methylthio-1,2,3,4-tetrahydrocarbazolenine (49b). Compound **49b** was prepared from **7b** and **48** on a 0.022-mol scale according to the general procedure but using dry tetrahydrofuran as the solvent. Separation of the residue by careful column chromatography using silica gel and successively methylene chloride and a 3:1 methylene chloride–ether mixture afforded 0.39 g (1.85 mmol, 8%) of 4,4′-dimethylazobenzene, characterized spectroscopically by comparison with an authentic sample, 1.37 g (43%) of **48**, and 0.95 g (4.12 mmol, 18%, 32% based on unrecovered **48**) of **49b** as a viscous oil. The spectral characteristics of the latter showed it to exist to the extent of *ca.* 50% in the corresponding enamine form: ir 3400 (NH) and 1700 cm^{-1} (C=N); pmr (CCl_4) τ 2.60–3.70 (m, aryl and vinyl H), 6.40 (br s, NH), 6.70–8.70 (m, aliphatic H), 7.62, 7.82, 8.03, and 8.76 (s for CH_3 and SCH_3 of the two forms).

11-Methylthio-1,2,3,4-tetrahydrocarbazolenine (49c). The preparation of **49c** was accomplished from **7c** and **48** following the general procedure. Column chromatography using silica gel and methylene chloride gave 5.58 g (0.0257 mol, 58%) of **49c** as an oil that solidified on standing in the refrigerator, mp 48–50° (recrystallization from *n*-hexane): ir 1690 cm^{-1} (N=C); pmr (CCl_4), τ 2.50–3.20 (4 H, m, aryl H), 7.00–8.95 (8 H, m, aliphatic H), 8.84 (3 H, s, SCH_3); exact *m/e* 217.0928 (calcd for $C_{13}H_{15}NS$: *m/e* 217.0925).

Anal. Calcd for $C_{13}H_{15}NS$: N, 6.45. Found: N, 6.40.

Before the elution of the carbazolenine a fraction containing 1.87 g (0.010 mol, 23%) of **51c** was eluted from the column: mp 54.0–55.5° (recrystallization from *n*-hexane) (lit.[25] mp 50.5–51.5°); bp 112–114° (0.10 mm); ir (KBr) 3420 (NH), 1670 cm^{-1} (C=O) (identical with the reported[25] ir spectrum); uv, $\lambda_{max}^{CH_3OH}$ 263 (ϵ 7400), 308 (3400), and 332 nm (2900, sh); pmr (CCl_4) τ 2.60–3.35 (4 H, m, aryl H), 3.62 (1 H, br s, NH), 3.70 (1 H, t, J = 5 Hz, vinyl H), and 7.30–8.25 (6 H, m, aliphatic H); *m/e* 187.

8-Chloro-11-methylthio-1,2,3,4-tetrahydrocarbazolenine (49i). The preparation of **49i** was accomplished from **7i** and **48** following the general procedure. After the triethylamine had been added, stirring at −70° was continued for another 2 hr before the cooling bath was removed. Work-up in the above described manner and column chromatography of the residue using silica gel and methylene chloride gave as the only isolable material, 5.12 g (0.020 mol, 46%) of **49i** as a viscous oil: ir 1680 cm^{-1} (C=N); pmr (CCl_4) τ 2.66–7.25 (3 H, m, aryl H), 7.00–8.74 (8 H, m, aliphatic H), and 8.74 (3 H, SCH_3); exact *m/e* 251.0538 (calcd for $C_{13}H_{14}ClNS$: *m/e* 251.0535).

6-Chloro-11-methylthio-1,2,3,4-tetrahydrocarbazolenine (49d). Compound **49d** was prepared from **7d** and **48** on a 0.022-mol scale according to the general procedure replacing methylene chloride as solvent by dry tetrahydrofuran. Purification of the residue by careful column chromatography over silica gel with methylene chloride gave as the first fraction eluted 1.23 g (5.5 mmol, 25%) of **18d**, mp 73.0–74.5° (recrystallization from *n*-hexane): ir (KBr) 3350 (N–H) and 1670 cm^{-1} (C=O); pmr (CCl_4) τ 2.80–2.30 (4 H, m, aryl H), 3.70 (1 H, br s, NH), 3.85 (1 H, t, J = 4.5 Hz, vinyl H), 7.35–7.80 (4 H, m, aliphatic H), and 7.80–8.25 (2 H, m, aliphatic H).

Anal. Calcd for $C_{12}H_{12}ClNO$: C, 65.02; H, 5.46; N, 6.32; Cl, 15.99. Found: C, 65.07; H, 5.58; N, 6.32; Cl, 15.87.

The second fraction eluted gave 0.99 g (7.8 mmol, 35%) of **7d**, and the third fraction contained 1.07 g (4.3 mmol, 19%, 29% based on unrecovered **7d**) of the viscous **49d** that existed mainly in the imine form: ir 3400 (weak NH) and 1680 cm^{-1} (C=N); pmr (CCl_4) τ 8.32 (m, aryl H), 6.80–8.60 (m, aliphatic H), and 8.67 (s, SCH_3); exact *m/e* 251.0538 (calcd for $C_{13}H_{14}ClNS$: *m/e* 251.0535).

6-Carboethoxy-11-methylthio-1,2,3,4-tetrahydrocarbazolenine (49e). Compound **49e** was prepared from **7e** and **48** on a 0.022-mol scale according to the general procedure with the modification that after addition of the *tert*-butyl hypochlorite solution stirring was continued for 30 min before **48** was added. Separation of the residual mixture was accomplished by careful column chromatography using silica gel and methylene chloride. The first fraction eluted contained 1.85 g (50%) of **7e**. Subsequently, 2.23 g (7.70 mmol, 35%, 70% based on unrecovered **7e**) of **49e** was isolated as a viscous oil: ir 1720 cm^{-1} (C=O); pmr (CCl_4) τ 1.80–2.05 (2 H, m, aryl H), 2.42 (1 H, d, J = 8.0 Hz, 8-aryl H), 5.59 (2 H, q, OCH_2), 6.95–8.70 (8 H, m, aliphatic H), 8.58 (3 H, t, CH_3), and 8.72 (3 H, s, SCH_3); exact *m/e* 289.1141 (calcd for $C_{15}H_{19}NO_2S$: *m/e* 289.1136).

General Procedure for the Synthesis of 1,2,3,4-Tetrahydrocarbazoles from Anilines. The above described general procedure for the preparation of 11-methylthio-1,2,3,4-tetrahydrocarbazolenines (**49**) was followed, but instead of purifying the residue by column chromatography it was redissolved in 50 ml of anhydrous ether. Sometimes this solution had to be filtered to remove traces of triethylamine hydrochloride before further use. The clear solution was added dropwise to a stirred, ice-cooled suspension of 2.5 g (0.066 mol) of lithium aluminum hydride in 50 ml of anhydrous ether. After 1 hr the mixture was hydrolyzed through cautious addition of 100 ml of 0.5 *N* aqueous sulfuric acid, while cooled in ice. The organic layer was separated and extracted twice with 0.5 *N* aqueous hydrochloric acid to remove all basic contaminants and then was treated with saturated sodium bicarbonate solution. After drying over anhydrous magnesium sulfate and filtration, the ethereal solution was evaporated to dryness to give a residue that was purified by column chromatography to give the appropriate 1,2,3,4-tetrahydrocarbazole.

8-Methyl-1,2,3,4-tetrahydrocarbazole (50h). Compound **50h** was prepared from **7h** and **48** without the isolation of the intermediary **49h** according to the hydride reduction procedure described above. Column chromatography of the residue over silica gel with methylene chloride afforded 3.92 g (0.017 mol, 38%) of **50h**, mp 92.0–94.5° (lit.[61] mp 97–98°).

6-Methyl-1,2,3,4-tetrahydrocarbazole (50b). Compound **50b** was prepared from **7b** and **48** without the purification of the intermediary **49b**, following the above described hydride reduction process. Column chromatography of the residue with silica gel and methylene chloride gave 1.22 g (6.6 mmol, 15%) of **50b**, mp 143–145°, after recrystallization from *n*-hexane (lit.[61] 141–142°).

1,2,3,4-Tetrahydrocarbazole (50c). Compound **50c** was derived from **7c** and **48** without purification of the intermediate compound **49c** according to the hydride reduction procedure described above. Column chromatography of the residue with methylene chloride and silica gel afforded 3.65 g (0.012 mol, 48%) of **50c**, mp 118–119.5° (lit.[62] mp 116°).

6-Chloro-1,2,3,4-tetrahydrocarbazole (50d). Compound **50d** was prepared from **7d** and **48** without purification of the intermediate **49d** according to the hydride reduction procedure described above. Column chromatography of the residue using silica gel and a 4:1 methylene chloride–carbon tetrachloride mixture gave 1.75 g (8.5 mmol, 19%) of **50d**, mp 146.5–148° (lit.[63] mp 146–147°).

7-Methoxy-1,2,3,4-tetrahydrocarbazole (50g) from Raney-Nickel Reduction of 49g. A solution of 2.40 g (0.01 mol) of **49g** in 100 ml of absolute ethanol was stirred with 10.0 g of W-2 Raney nickel at 25° for 18 hr. The solution was filtered and the filtrate was evaporated *in vacuo* to give a solid residue, which on recrystallization from aqueous ethanol gave 1.52 g (76% yield) of **50g**, mp 141–143° (lit.[64] mp 143–144°): ir (KBr) 3400 (indole NH) cm^{-1}; pmr (CCl_4) τ 2.92 (1 H, d, J_{5-6} = 9 Hz, H-5), 3.52 (1 H, d of d, J_{5-6} = 9 Hz, J_{6-8} = 3 Hz, H-6), 3.65 (1 H, d, J_{8-6} = 3 Hz, H-8), 7.30 (3 H, s, OCH_3), 7.40 (4 H, m, C-1 and C-4 protons), and 8.20 (4 H, m, C-2 and C-3 protons).

8-Methyl-1,2,3,4-tetrahydrocarbazole (50h) by Lithium Aluminum Hydride Reduction of 49h. A solution of 596 mg (2.58 mmol) of **49h** in 20 ml of anhydrous ether was treated with 163 mg (4.30 mmol) of lithium aluminum hydride at ice-bath temperature. The mixture was stirred for 40 min at room temperature and hydrolyzed carefully with 30 ml of 0.5 *N* aqueous sulfuric acid. The layers were separated and the aqueous phase was extracted twice with 30-ml portions of ether. The combined organic solutions were treated with saturated sodium carbonate solution, dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness, leaving 450 mg of crude **50h**. This was purified by column chromatography over silica gel with methylene chloride, resulting in 328 mg (1.77 mmol, 71%) of pure **50h**, mp 93–95° (lit.[61] mp 97–98°).

1,2,3,4-Tetrahydrocarbazole (50c) by Lithium Aluminum Hydride Reduction of 49c. This conversion was achieved by reacting 634 mg (2.92 mmol) of **49c** with 159 mg (4.18 mmol) of lithium aluminum hydride as described above for **49h**. The work-up procedure gave 520 mg of crude **50c**, mp 110–116.5°, that was purified by

(61) B. M. Barclay and N. Campbell, *J. Chem. Soc., London*, 530 (1945).
(62) W. Borsche, *Justus Liebigs Ann. Chem.*, **359**, 60 (1908).
(63) E. E. Campaigne and R. D. Lake, *J. Org. Chem.*, 24, 478 (1959).
(64) J. R. Chalmers, H. T. Openshaw, and G. F. Smith, *J. Chem. Soc., London*, 1115 (1957).

column chromatography using silica gel and methylene chloride. In this way 400 mg (2.34 mmol, 80%) of **50c**, mp 114.5–117.0° (lit.[65] mp 116°), was obtained.

1,2,3,4-Tetrahydrocarbazole (50c) by W-2 Raney-Nickel Reduction of 49c. This conversion was achieved by stirring 798 mg (3.67 mmol) of **49c** in 30 ml of absolute ethanol for 30 min with two teaspoonsful[66] of W-2 Ra Ni. Stirring was stopped and the supernatant liquid was decanted. The remaining residue was washed three times with 20-ml portions of absolute ethanol and the combined alcoholic solutions were evaporated to dryness. The residue was redissolved in 40 ml of methylene chloride, dried over anhydrous magnesium sulfate, filtered, and evaporated. There was obtained 521 mg (3.05 mmol, 83%) of **50c**, mp 115.0–117.5°.

8-Chloro-1,2,3,4-tetrahydrocarbazole (50i) by W-2 Raney-Nickel Reduction of 49i. This conversion was achieved with 705 mg (2.80 mmol) of **49i** in 10 ml of absolute ethanol with 1 teaspoonful of W-2 Ra Ni as described above for **50c**. On work-up, 416 mg of viscous **50i** was obtained. This was purified by column chromatography over silica gel with a 3:1 cyclohexane–methylene chloride mixture. There was obtained 233 mg (1.14 mmol, 40%) of pure **50i**, mp 57.5–59.5° (lit.[67] mp 55–56°).

1,2,3,4-Tetrahydrocarbazole (50c) by Sodium Borohydride Reduction of 49c. A mixture of 687 mg (3.17 mmol) of **49c** and 363 mg (9.81 mmol) of sodium borohydride in 20 ml of 2-propanol was refluxed for 16 hr. A 20-ml portion of water was added, and the mixture was extracted twice with 30-ml portions of methylene chloride. The extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated, leaving 500 mg of a residue, mp 105–111°. Purification by column chromatography over silica gel with methylene chloride gave 438 mg (2.02 mmol, 64%) of **50c**, mp 111–114°.

6-Carboisopropoxy-1,2,3,4-tetrahydrocarbazole (50j) by Sodium Borohydride Reduction of 49e. A solution of 380 mg (1.31 mmol) of **49e** and 183 mg (5.08 mmol) of sodium borohydride in 10 ml of isopropyl alcohol was refluxed for 4 hr. The mixture was cooled to room temperature, and a 20-ml portion of water was added, followed by extraction with three 15-ml portions of methylene chloride. The extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated. A solid residue, mp 113–117°, was obtained. This was purified by recrystallization from a *n*-hexane cyclohexane mixture, giving 243 mg (0.94 mmol, 72%) of **50j**, mp 125–126° (repeated recrystallization from cyclohexane): ir (KBr) 3370 (NH), and 1690 cm^{-1} (C=O); pmr (CCl_4) τ 1.58 (1 H, br s, NH), 1.98 (1 H, s, 5-aryl H), 2.33 (1 H, d, J = 8.0 Hz, 7-aryl H), 2.99 (1 H, d, J = 8.0 Hz, 8-aryl H), 4.80 (1 H, h, J = 6.0 Hz, 2-propyl H), 7.15–7.63 and 7.90–8.40 (4 H, m, aliphatic H), and 8.63 (6 H, d, J = 6.0 Hz, isopropyl CH_3).

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.51; H, 7.46; N, 5.27.

6-Carboethoxy-1,2,3,4-tetrahydrocarbazole (50e) by Sodium Borohydride Reduction of 49e. A solution of 256 mg (0.88 mmol) of **49e** and 115 mg (3.02 mmol) of sodium borohydride in 10 ml of absolute ethanol was stirred at ambient temperature for 9 hr. A 20-ml portion of water was added and the mixture was extracted three times with 15-ml portions of methylene chloride. After drying of the extracts over anhydrous magnesium sulfate, filtration, and evaporation, a residue was obtained, which was purified by column chromatography over silica gel with methylene chloride. This gave 71 mg (0.29 mmol, 33%) of **50e**,[68] mp 119–120.5° (recrystallization from cyclohexane): ir (KBr) 3350 (N–H), and 1690 cm^{-1} (C=O); pmr (CCl_4) τ 1.60 (1 H, br s, NH), 1.84 (1 H, s, 5-aryl H), 2.16 (1 H, d, J = 8.0 Hz, 7-aryl H), 2.82 (1 H, d, J = 8.0 Hz, 8-aryl H), 5.58 (2 H, q, J = 7.0 Hz, OCH_2), 7.10–7.60 and 7.90–8.25 (4 H, m, aliphatic H), and 8.56 (3 H, t, J = 7.0 Hz, CH_3); exact m/e 243.1261 (calcd for $C_{15}H_{17}NO_2$: m/e 243.1259).

3-Methylthio-2,3-trimethylene-3*H*-indole (53). Compound **53** was prepared from **7c** and **52** as described above for **49c**. Column chromatography of the residue using silica gel and methylene chloride followed by ether as eluents gave as the only isolable product 5.55 g (0.027 mol, 62%) of a viscous oil, which existed to the extent of *ca.* 65% in the enamine form **54**: ir 3360 (NH) and 1700 cm^{-1} (C=N); pmr (CCl_4) τ 2.40–3.70 (m, aryl H), 5.93 (br, s, NH), 6.80–8.60 (m, aliphatic H), and 8.23 and 8.63 (s, SCH_3 of the two isomeric forms); exact m/e 203.0770 (calcd for $C_{12}H_{13}NS$: m/e 203.0768).

2,3-Trimethyleneindole (55). Indole **55** was obtained from **7c** and **52** when the crude 3*H*-indole **53** was redissolved in 150 ml of absolute ethanol and stirred for 1 hr with an excess of W-2 Raney nickel. Stirring was stopped and the supernatant liquid was decanted. The remaining Raney nickel was washed twice with 100-ml portions of absolute ethanol, and the ethanolic solutions were evaporated to dryness. The residue was redissolved in 100 ml of ether and then extracted three times with 30-ml portions of 2 *N* aqueous hydrochloric acid, followed by treatment with saturated sodium bicarbonate solution. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to give a solid, which on recrystallization from *n*-hexane gave 2.65 g (0.017 mol, 38%) of pure **55**, mp 103–106° (lit.[69] mp 108°).

2,3-Trimethyleneindole (55). Compound **55** was prepared from **7c** and **52** by subjecting the crude 3*H*-indole **53** to lithium aluminum hydride reduction as described above in the general procedure for the synthesis of tetrahydrocarbazoles from anilines. Final purification of the mixture by column chromatography over silica gel with a 5:3 cyclohexane/methylene chloride mixture gave 2.0 g (0.013 mol, 29%) of **55**, mp 103–105°.

3-Methylthio-2,3-trimethyleneindoline (56). Compound **56** was formed when 593 mg (2.92 mmol) of **53** was refluxed for 7 hr with 186 mg (5.0 mmol) of sodium borohydride in 10 ml of isopropyl alcohol. After cooling to room temperature a 10-ml portion of water was added and the mixture was extracted three times with 15-ml portions of methylene chloride. The extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was subjected to column chromatography over silica gel with a *n*-hexane/methylene chloride mixture allowing the isolation of a trace amount (*ca.* 10%) of **55** and 259 mg (1.26 mmol, 43%) of **56** as a colorless oil: ir 3410 cm^{-1} (N–H); pmr (CCl_4) τ 2.70–3.62 (4 H, m, aryl H), 5.74 (1 H, d, J = 5.5 Hz, NCH), 6.38 (1 H, br s, NH), 7.70–8.60 (6 H, m, aliphatic H), and 8.22 (3 H, s, SCH_3). An analytically pure sample was obtained by means of a molecular distillation [bath temperature 100° (0.04 mm)].

Anal. Calcd for $C_{12}H_{15}NS$: C, 70.20; H, 7.36; N, 6.82. Found: C, 70.28; H, 7.52; N, 6.81.

Ethyl 6-Bromocyclohexanone-2-carboxylate (59). Ethyl 6-bromocyclohexanone-2-carboxylate was prepared according to the procedure of Sheehan and Mumaw[27] in 96% yield and was used in the next step without further purification.

Ethyl 6-Methylthiocyclohexanone-2-carboxylate (60). To a solution of sodium ethoxide prepared from 2.3 g of sodium and 100 ml of ethanol was added slowly at 5°, 10 ml of methanethiol. The reaction mixture was stirred for 15 min and then a solution of 23.5 g (0.044 mol) of **59** in 100 ml of absolute ethanol was added dropwise over a 1-hr period. The reaction mixture was stirred for 20 hr and filtered and 20 ml of water was added. The solution was concentrated *in vacuo* and the residue was extracted twice with 100-ml portions of methylene chloride. The methylene chloride extracts were combined, dried over anhydrous magnesium sulfate, and filtered, and the solvent was evaporated. The residue was fractionally distilled to give 11.5 g (53% yield) of **60** as a colorless liquid, bp 109–111° (0.6 mm) [lit.[28] bp 86–88° (0.01 mm)]; ir (neat) 1750 (ester C=O), 1700 (C=O) cm^{-1}; pmr (CCl_4) τ 5.86 (2 H, q of d, $CO_2CH_2CH_3$), 6.79 (1 H, m, $CHCO_2R$), 7.60–8.50 (7 H, broad m, cyclohexyl protons), 7.99 (3 H, s, SCH_3), and 8.76 (3 H, t of d, $CO_2CH_2CH_3$).

1-Carboethoxy-11-methylthio-1,2,3,4-tetrahydrocarbazolenine (61). A solution of 4.09 g (0.044 mol) of aniline in 100 ml of methylene chloride was cooled to −70° and a solution of 4.78 g (0.044 mol) of *tert*-butyl hypochlorite in 20 ml of methylene chloride was added dropwise with vigorous stirring. When the addition was complete, the reaction mixture was stirred for 5 min, followed by the dropwise addition of 9.95 g (0.044 mol) of **60** in 25 ml of methylene chloride. After stirring the reaction mixture for 2 hr at −70°, a solution of 4.40 g (0.044 mol) of triethylamine in 20 ml of methylene chloride was added dropwise and stirring was continued at −70° for 1 hr. The reaction mixture was allowed to warm to 25°, water was added, and the organic phase was separated

(65) W. Borsche, *Justus Liebigs Ann. Chem.*, **359**, 60 (1908); the reported melting points for **17d** vary between 114 and 120°.

(66) A teaspoonful is *ca.* 3 g of W-2 Raney nickel: R. Mozingo, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 181.

(67) F. P. Robinson and R. K. Brown, *Can. J. Chem.*, 42, 1940 (1964). These authors report that **50i** is a rather unstable compound failing to give a satisfactory elemental analysis. This may explain the considerable loss of material on chromatography.

(68) Formerly described by L. A. Aksanova and I. N. Pidevich, *Khim.-Farm. Zh*, 2(7), 3 (1968); *cf. Chem. Abstr.*, **70**, 68209a (1969). The available source (C.A.) did not report physical data.

(69) W. H. Perkin and S. G. P. Plant, *J. Chem. Soc., London*, **123**, 3244 (1923).

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, $CO_2CH_2CH_3$).

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

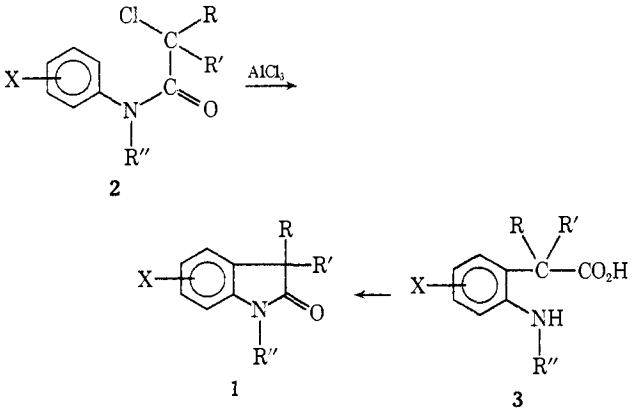
Oxindoles. A New, General Method of Synthesis[1]

Paul G. Gassman* and T. J. van Bergen[2]

Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. *Received January 14, 1974*

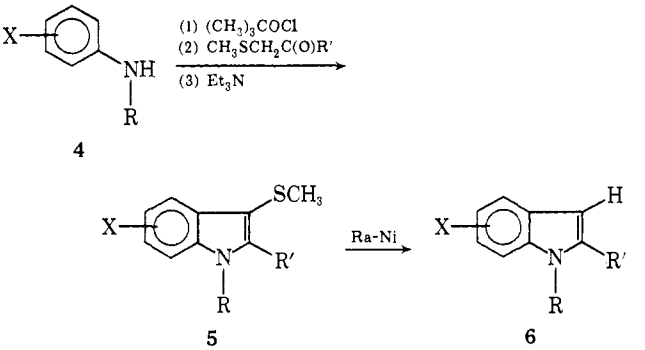
Abstract: A new general method has been developed for the synthesis of oxindoles. The procedure involves sequential treatment of an aniline derivative with (a) *tert*-butyl hypochlorite, (b) an α-carboalkoxy sulfide, (c) triethylamine, and (d) acid to produce a 3-methylthiooxindole derivative. Reductive 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).