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Methylsulfenylation of 1-substituted pyrroles and indoles was observed using 1-(methylthio)morpholine and an acid catalyst or with methylsulfenyl chloride and excess pyridine. 1-Substituents which are activating or weakly deactivating towards electrophilic substitution such as alkyl, 2-cyanoethyl, dimethylamino, trialkylsilyl, 2-chloroethyl and 2-phenylsulfonylethyl were used. The 2-chloroethyl and 2-phenylsulfonylethyl groups which can be removed with a strong base can be used to obtain 1*H*-methylthiopyrroles and indoles. 1-Phenylsulfonyl and 1-acetyl substituents are too strongly deactivating for these sulfenylations to be successful. Mono and disubstituted pyrroles and monosubstituted indoles can be isolated from these reactions, however, because the methylthio group is activating towards electrophilic substitution the main advantage of these reactions is the synthesis of tri and tetrasubstituted pyrroles and disubstituted indoles. 1-Methyl-2,3,4,5-tetramethylthiopyrrole and 1-methyl-2,3-dimethylthioindole are oxidized to the corresponding 3,4-disulfoxide and 3-sulfoxide and with excess oxidizing agent to the tetrasulfone and disulfone, respectively.

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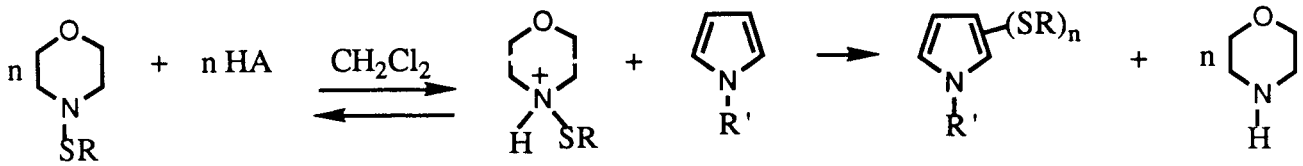
Alkyl thioethers of pyrroles and indoles, which are very reactive towards electrophilic substitution, are usually synthesized by indirect methods [1]. For example, base catalyzed decomposition of thiocyanopyrroles [2], or *S*-pyrrolylisothiouronium salts [3] in the presence of alkylating agents yield alkylthiopyrroles and alkylthioindoles. 2-Pyrrolyl sulfides can be prepared from sulfenylation of 1-phenylsulfonyl-2-lithiopyrrole [2c] and 2,5-pyrrolyl sulfides from the sulfenylation of 1-BOC-2,5-dilithiopyrrole [4]. Recently, the anions of pyrrole and indole were observed to form 1-alkylthioazines with *N*-alkylthioimides [5].

Aromatic substitution with sulfenyl chlorides is a useful technique [6]. However, the sulfenyl chlorides usually have electron withdrawing groups such as 2,4-dinitrophenyl [7], polyhaloalkyl [8], or phenyl [9] preventing polysubstitution. Aryl sulfenyl iodides, formed *in situ* from thiophenols and iodine-potassium iodide in aqueous ethanol, in the presence of pyrroles and indole form pyrrolyl and indolyl aryl sulfides [10]. Methanesulfenyl chloride with aluminum chloride has been used to sulfenylate benzene [11], phenols [12], and anisole [13]. Pyrrole and methanesulfenyl chloride in the presence of potassium bicarbonate give low yields of 2-methylthiopyrrole and 2,5-dimethylthiopyrrole [14]. Aromatic amines [15] and phenols can also be sulfenylated with dimethyl disulfide in the presence of an acid catalyst [13] or aluminum phenoxide [16].

The addition of trifluoroacetic acid to a mixture of 1-methylthiopyrrole and 1-methylpyrrole results in the transfer of the methylthio group to 1-methylpyrrole [5]. Because sulfenamides, of the type R_2NSR', are known to coordinate with electrophiles at nitrogen [17,18] it was thought that under acidic conditions sulfenamides might facilitate electrophilic aromatic substitution of reactive aromatics. We report the sulfenylation of some 1-substituted pyrroles and indoles with sulfenamides and an acid catalyst or with sulfenyl chlorides in the presence of pyridine. We also

Scheme 1



1 R = CH_3
2 R = CH_2CH_3
3 R = $CH(CH_3)_2$

4

5 R' = CH_3
6 R' = $CH_2CH_2CH_2CH_3$
7 R' = $C(CH_3)_3$
8 R' = CH_2CH_2CN
9 R' = CH_2CH_2Cl
10 R' = $N(CH_3)_2$
11 R' = $Si(CH_3)_2C(CH_3)_3$

report the oxidation of tetraalkylthiopyrroles and dialkylthioindoles to the corresponding unique sulfoxides and sulfones not available by other synthetic procedures.

Sulfenylation of Some Pyrroles with Sulfenamides.

Acid catalyzed methylsulfenylation of pyrrole with 1-(methylthio)morpholine (**1**) results in considerable decomposition and small amounts of 1-, 2-, 3-methylthiopyrrole and polysubstituted products. It is not a useful preparative procedure. Attempted methylsulfenylation of 1-methylthiopyrrole gave similar results. However, methylsulfenylation of 2,5-dimethylpyrrole with an equal molar amount of **1** forms primarily the 3-methylthio derivative and some of the 3,4-dimethylthio derivative which can be readily separated and isolated on a preparative gc. Treatment of 2,5-dimethylpyrrole with an excess of **1** forms the 3,4-dimethylthio derivative. Less than 1% 1-substitution was observed.

1-Substituted pyrroles can be methylthiolated with **1** in the presence of an acid catalyst as shown in Scheme 1.

Addition of an acid such as trifluoroacetic, chloroacetic, or some acid of similar acidity forms the electrophile **4** [19] and substitution of the pyrrole is usually complete in a few minutes at room temperature. 1-(Ethylthio)morpholine (**2**) or 1-(isopropylthio)morpholine (**3**) may be used rather than **1**, however, 1-(*tert*-butylthio)morphiline, 1-(benzylthio)-morphiline, or 1-(phenylthio)morphiline were not successful. The rate of sulfenylation was sensitive to the 1-substituents on pyrrole. Relative rates of sulfenylation of some typical pyrroles are given in Table I. 1-Acetylpyrrole and 1-phenylsulfonylpyrrole are too unreactive because, presumably, the sulfenamides decompose before substitution occurs. Sulfenylation will tolerate weakly electron withdrawing substituents in the 1-position such as CH_2CH_2CN, CH_2CH_2Cl, and $N(CH_3)_2$. 1-Phenylpyrrole (**12**) undergoes sulfenylation slowly and only forms small amounts of methylthio-1-phenylpyrroles.

Table I

Relative Rates of Sulfenylation of Some 1-Substituted Pyrroles With 1-(Methylthio)-morpholine and Trifluoroacetic Acid

	No.	Rel. Rate
R = H	12	1.0[a]
R = CH_3	5	3.3
R = $CH_2CH_2CH_2CH_3$	6	3.8
R = $C(CH_3)_3$	7	3.5
R = CH_2CH_2CN	8	0.094
R = $N(CH_3)_2$	10	0.42
R = $Si(CH_3)_2C(CH_3)_3$	11	0.69[b]

[a] Some decomposition of pyrrole occurred during the reaction. Some 1-substitution.

[b] Some decomposition of the pyrrole occurred during the reaction.

A typical sulfenylation is the methylsulfenylation of **5** with **1** and trifluoroacetic acid at room temperature in methylene chloride. Using chloroacetic acid as a catalyst rather than trifluoroacetic acid gives similar results except that the solution remains almost colorless, suggesting less decomposition, and the reaction is somewhat slower. In either case there is little or no rearrangement under the conditions of the reaction. A mixture of products is observed but overall yields are good as shown in Table II.

The major monosubstituted product is the 2-substituted product (only small amounts of 3-substitution) suggesting that the sulfenylating agent acts as a soft electrophile. The methylthio group is an activating group towards electrophilic substitution and hence polysubstitution occurs even with limited amounts of sulfenylating agent. Theoretically, the 2-methylthio group of pyrrole should activate the 3- and the 5-positions. Appreciable amounts of 2,5- and 2,3-dimethylthio-1-methylpyrrole are observed. The major product of the reaction with excess sulfenylating agent is the trisubstituted product, 2,3,5-trimethylthio-1-methylpyrrole. Only small amounts of the tetrasubstituted product formed, even with a large excess of **1** and acid catalyst. Pure 2-, 2,5-, 2,3-, and the 2,3,5-methylthio-1-methylpyrroles can be readily isolated using preparative gas chromatographic techniques. 2-Methylthio-1-methylpyrrole and 2,3,5-trimethylthio-1-methylpyrrole can also be isolated by fractional distillation.

Other 1-substituted pyrroles such as 1-butyl, 1-*tert*-butyl, 1-(2-cyanoethyl), and 1-(2-chloroethyl)pyrrole have

Table II

Methylsulfenylation of 1-Methylpyrrole with 1-(Methylthio)morpholine and Trifluoroacetic Acid

	Methylthio-1-methylpyrrole,%[a]						
Mole Ratio[b]	2-	3-	2,5-	2,3-	2,3,5-	2,3,4,5-	Overall Yield,%
0.5	33	1	27	8	5	-	74
1.0	21	1	31	9	8	-	70
2.0	10	-	31	13	22	1	77
3.0	5	-	25	15	31	1	77
4.0	1	-	6	15	58	3	83
5.0	-	-	-	9	75	5	89
5.0[c]	-	-	-	10	78	9	97

[a] The percentages give the ratio of the products.

[b] The mole ratio of 1-(methylthio)morpholine to 1-methylpyrrole. An equal molar amount of 1-(methylthio)morpholine and trifluoroacetic acid was used.

[c] Two additional moles of trifluoroacetic acid was added.

similar substitution patterns as does **5** except for 1-*tert*-butylpyrrole which shows some steric effects to substitution in the 2- and 5-positions. In contrast to this the 1-dimethylamino group has a different substitution pattern as shown in Table III.

Table III

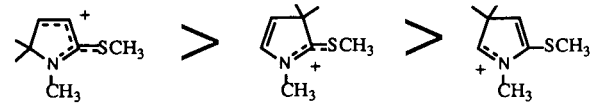
Methylsulfenylation of 1-Dimethylaminopyrrole with 1-(Methylthio)morpholine and Trifluoroacetic Acid

	Methylthio-1-dimethylaminopyrrole,%[a]					
Mole Ratio[b]	2-	3-	2,5-	2,3-	2,3,5- and 2,3,4-	2,3,4,5-
1.0	1	4	1	55	26	15
2.0	-	2	-	50	25	22
3.0	-	-	-	44	22	34
4.0	-	-	-	38	22	40
6.0	-	-	-	8	18	74
8.0	-	-	-	-	10	90

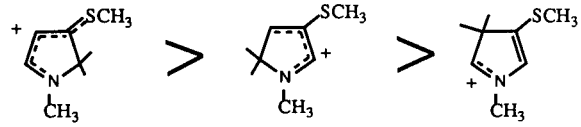
[a] The percentages give the ratio of products.
[b] The mole ratio of 1-(methylthio)morpholine to 1-dimethylaminopyrrole. Two moles of trifluoroacetic acid catalyst were added for every mole of 1-(methylthio)morpholine.

The 1-dimethylamino group is somewhat deactivating towards sulfenylation (see Table I) and therefore some of the sulfenylating agent decomposes during the reaction. Even with limited amounts of sulfenylating agent polysubstitution predominates and only minor amounts of monosubstitution are observed. Of the monosubstitution observed 3-substitution is the major product. Disubstitution occurs predominately in the 2,3-positions with only one percent or less 2,5-disubstitution. To our knowledge this is the only case of electrophilic substitution of a 1-substituted pyrrole taking place essentially only in the 2,3-positions. Unfortunately the 1-dimethylamino group cannot be readily removed or this would be a method to synthesize 2,3-disubstituted pyrroles. Smaller amounts of trisubstitution are observed because with an excess of sulfenylating agent the 2,3,4,5-tetrasubstituted pyrrole predominates in contrast to other 1-substituted pyrroles where trisubstitution is the major product and only a small amount of tetrasubstitution is observed even with a large excess of the sulfenylating agent **1**. Both possible trisubstituted products are observed in a 5:1 ratio. From the mass spectrum it appears as if the major product is the 2,3,5-trisubstituted pyrrole but the structures of the trisubstituted pyrroles have not been determined conclusively.

The methylthio group, which is inductively weakly electron withdrawing and a relatively strong resonance stabilizing group [20], in the 2-position of 1-methylpyrrole enhances the reactivity of the 5-position and to a smaller degree the 3-position. The same group in the 3-position enhances the reactivity of the 2-position. Molecular orbital calculations confirm the relative stabilities of the intermediates resulting from electrophilic attack of 1-methyl-2-methylthiopyrrole and 1-methyl-3-methylthiopyrrole as shown below. The ratio of disubstituted products reported in Table II are consistent with this.

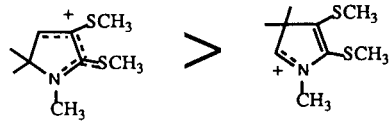


Relative order of stability for intermediates resulting from electrophilic attack of 1-methyl-2-methylthiopyrrole.



Relative order of stability for intermediates resulting from electrophilic attack of 1-methyl-3-methylthiopyrrole

The only trisubstituted product observed is 2,3,5-trimethylthio-1-methylpyrrole which is consistent with the relative stabilities of the intermediates resulting from electrophilic attack of 2,3-dimethylthio-1-methylpyrrole as shown below. This is the only possible trisubstituted product resulting from methylsulfenylation of 2,5-dimethylthio-1-methylpyrrole.



Relative order of stability for intermediates resulting from electrophilic attack of 2,3-dimethylthio-1-methylpyrrole.

Although acid catalyzed isomerization was not observed during thiolation of 1-substituted pyrroles some methylthiopyrroles can be isomerized with excess trifluoroacetic acid. For example, when 2-methylthio-1-methylpyrrole is treated with a two molar excess of trifluoroacetic acid an equilibrium mixture of 67% 2-methylthio-1-methylpyrrole and 33% 3-methylthio-1-methylpyrrole formed after one hour at room temperature. Similarly, 2,5-dimethylthio-1-methylpyrrole was converted to 2,4-dimethylthio-1-methylpyrrole with only 3% of the 2,5-isomer remaining. In all cases no other substituted products were observed. 2,3-Dimethylthio-1-methylpyrrole was not isomerized under these conditions.

Sulfenylation of 1-Substituted Pyrroles with Sulfenyl Chlorides.

Methylsulfenylation of **5** with methylsulfenylchloride in the presence of an excess of pyridine forms a mixture of

methylthiopyrroles shown in Table IV. No significant amount of 3-substitution is observed and considerably less 2,3-disubstitution than in the acid catalyzed methylsulfenylation with **1**. With an excess of sulfenylating agent 2,3,4,5-tetrasubstitution occurs. The 2,3,4,5-tetramethylthio derivative of 1-methyl, 1-(2-chloroethyl), 1-dimethylamino, and 1-phenylpyrrole and the 2,3,4,5-tetraphenylthio derivatives of 1-methyl and 1-phenylpyrrole have been synthesized using this method.

Table IV

Methylsulfenylation of 1-Methylpyrrole with Methylsulfenylchloride

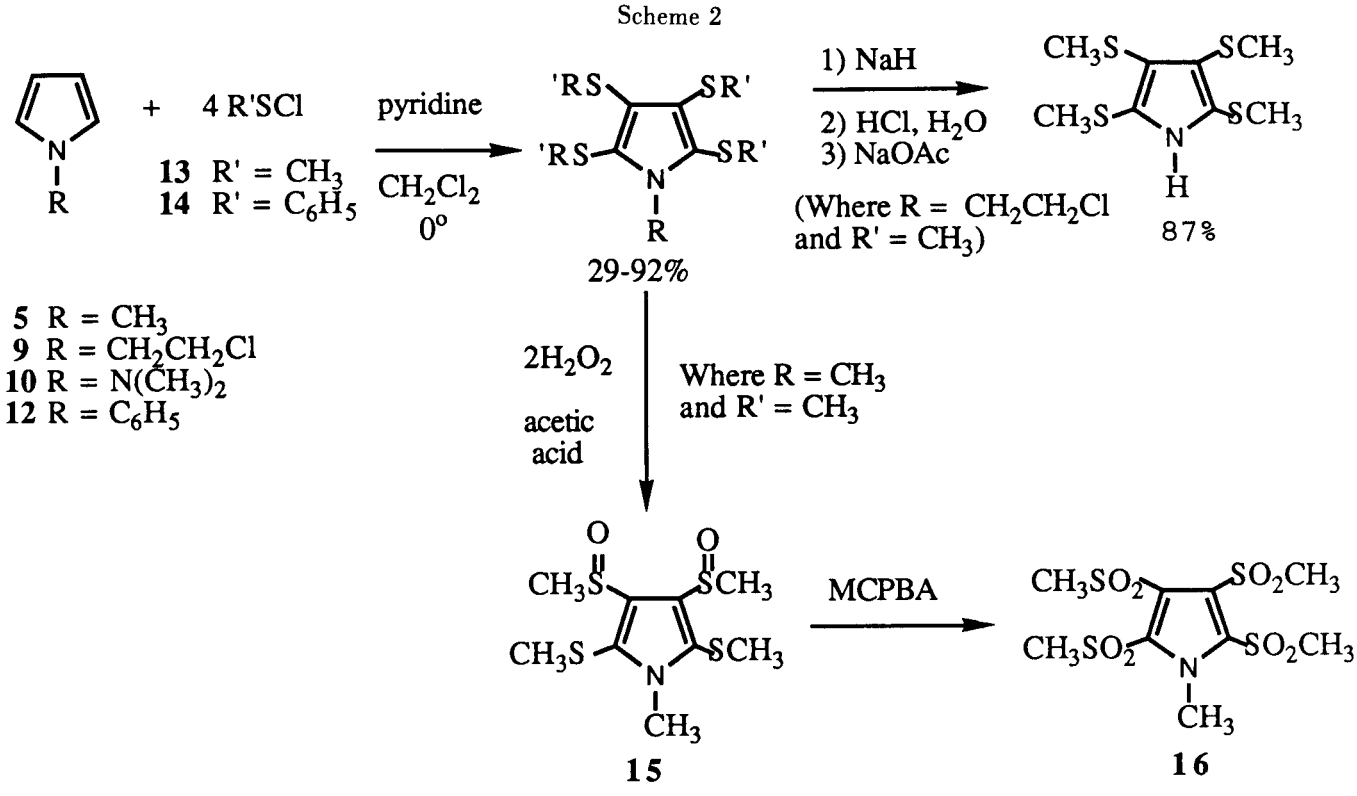
	Methylthio-1-methylpyrrole,%					
Mole Ratio[a]	2-	2,5-	2,3-	2,3,5-	2,3,4,5-	overall yield,%
0.5	16	15	3	3	-	37
1.0	14	20	3	3	-	40
2.0	9	50	5	12	1	77
3.0	1	38	8	40	10	97
4.0	-	2	3	25	66	96
5.0	-	-	-	-	98	

[a] The mole ratio of methylsulfenylchloride to 1-methylpyrrole. An excess of pyridine was present.

Methylsulfenylation of pyrrole forms low yields of 1-, 2-, and 3-monosubstituted products and a mixture of polysubstituted products with significant decomposition. The major product observed is 2,5-dimethylthiopyrrole. A suitable blocking group for pyrrole (Stable to acid, electron donating or very weakly electron withdrawing, and readily removed) was found to be the 1-(2-chloroethyl) group. Methylsulfenylation of 1-(2-chloro-ethyl)pyrrole with methylsulfenyl chloride in the presence of excess pyridine formed 1-(2-chloroethyl)-2,3,4,5-tetramethylthiopyrrole in a 71% yield. Removal of the blocking group according to the procedure of Gonzales *et al.* formed an 87% yield of 2,3,4,5-tetramethylthiopyrrole. Methylsulfenylation of 2,5-dimethylpyrrole with an excess of methylsulfenyl chloride in the presence of pyridine forms a mixture of mono, di and trisubstituted products with considerable decomposition. Therefore, just as in the case of pyrrole, when the ring nitrogen is unprotected sulfenylation is not a suitable synthetic procedure.

1-Methyl-2,3,4,5-tetramethylthiopyrrole can be oxidized to the disulfoxide **15** with a limited amount of hydrogen peroxide in acetic acid at room temperature. A mixture of the racemic and meso forms are detected on gc analysis. Oxidation of the tetramethylthio derivative in acetic acid with an excess of hydrogen peroxide results in the formation of a granular white precipitate which has a C, H, N analysis consistent with the trisulfone monosulfoxide but in fact appears to be a mixture. Complete oxidation to the tetrasulfone **16** could only be accomplished with an excess of *m*-chloroperoxybenzoic acid.

Scheme 2



Methylsulfenylation of Indoles with 1-(Methylthio)morpholine.

Methylsulfenylation of indole (**17**) with **1** forms a mixture of products with some decomposition. From the mixture of products observed (See Table V) the most reactive position of indole, towards electrophilic substitution, is the 3-position as expected. The next most reactive positions appear to be the 1-position because a small amount of 1-methylthioindole was observed. However, none of the 2-methylthioindole was observed. The 1-position of 3-methylthioindole is somewhat more reactive than the 2-position of 3-methylthioindole as seen from the ratio of disubstituted products. No 3,3-disubstitution was observed. Monomethylsulfenylation of **17** with **1** can be accomplished in good yield (84%) with only small amounts of disubstitution if chloroacetic acid is used as an acid catalyst rather than trifluoroacetic acid.

Table V

Methylsulfenylation of Indole with 1-(Methylthio)morpholine and Trifluoroacetic Acid

	Methylthioindole, %					
Mole Ratio[a]	indole	1-	3-	1,3-	2,3-	1,2,3-
1.5	27	1	57	9	7	1
2.5	_	_	11	61	22	6

[a] The mole ratio of 1-(methylthio)morpholine to indole. One mole of trifluoroacetic acid was added for every mole of 1-(methylthio)morpholine.

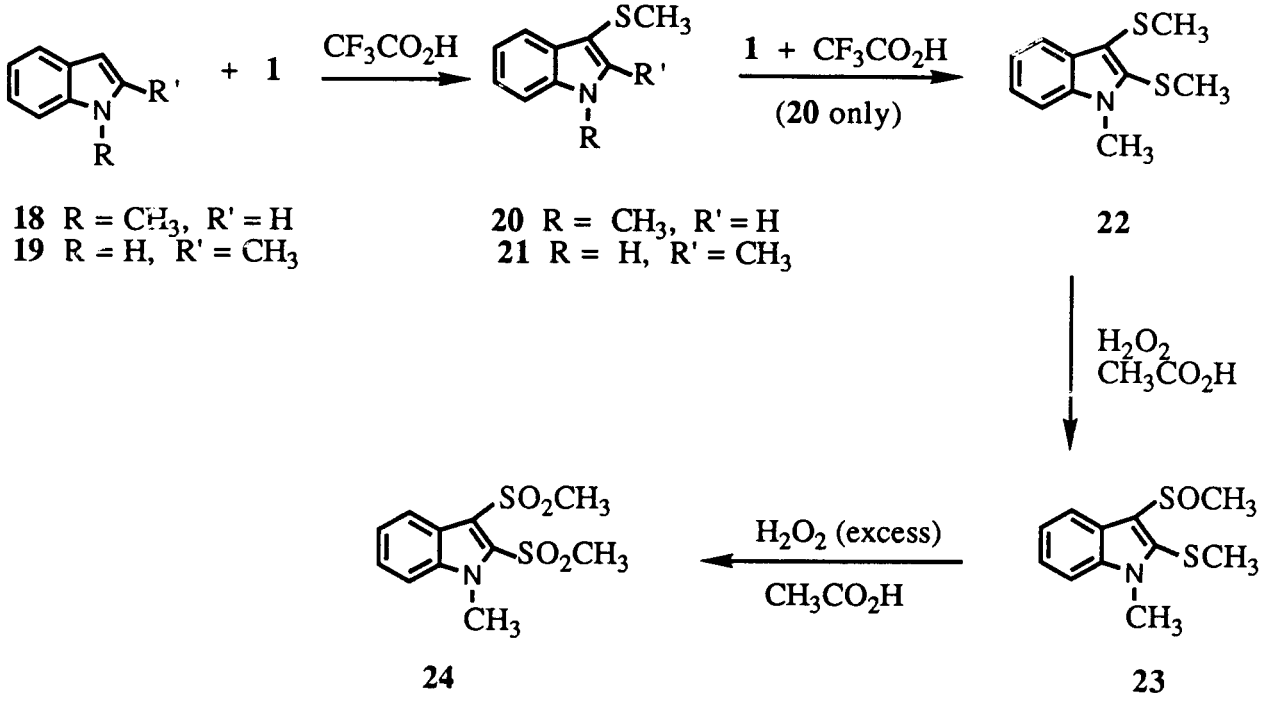
Sulfenylation of 1-methylindole (**18**) and 2-methylindole (**19**) can be methylthiolated in the 3-position in good yield with little contamination by other mono or polysubstitution products (Scheme 3). With an excess of **1** and trifluoroacetic acid **18** forms disulfide **22** which can be oxidized to sulfoxide **23** and disulfone **24** with excess hydrogen peroxide. Treatment of **19** with an excess of **1** gives similar amounts of 3,3- and 1,3-dimethylthio-2-methylindole.

Sulfenylation of Indoles with Sulfenyl Chlorides.

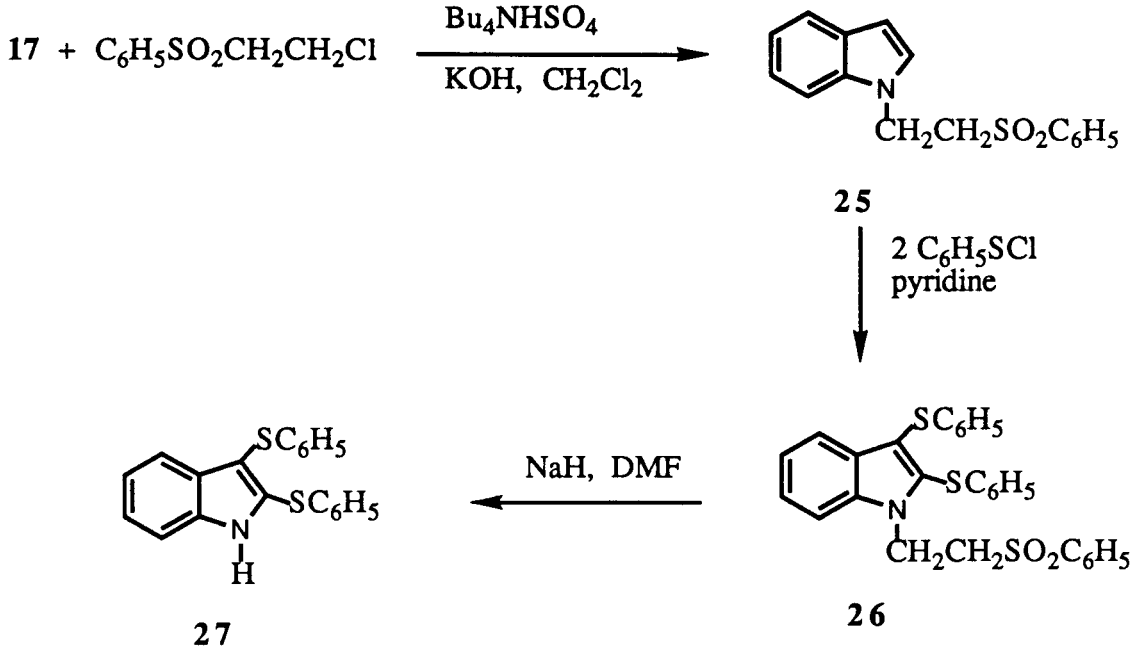
Sulfenylation of indole (**17**) with methylsulfenyl chloride in the presence of excess pyridine is more selective than is sulfenylation with **1**. For example, **17** and an equal molar amount of methylsulfenyl chloride forms primarily 3-methylthioindole. With 2 moles of methylsulfenyl chloride **17** forms 78% 2,3-dimethylthioindole with the remainder of the mixture consisting of 3-, 1,3-, and 1,2,3-methylthioindoles. A pure sample of 2,3-dimethylthioindole can be obtained by column chromatography.

Pure samples of 2,3-disubstituted indoles can also be obtained by blocking the 1-position of indole with the 2-phenylsulfonylethyl group. This group deactivates the ring towards sulfenylation only slightly and can be readily removed under basic conditions. For example, 1-(2-phenylsulfonylethyl)indole (**25**) (synthesized by a phase transfer process with 2-chloro-1-phenylsulfonylethane and indole) forms the 2,3-disubstituted product **26** in 78% yield with two moles of phenylsulfenyl chloride. Treatment of **26** with sodium hydride in DMF forms the pure 1*H*-indole **27** (Scheme 4).

Scheme 3



Scheme 4



EXPERIMENTAL

Infrared spectra were recorded on a Nicolet 5PC FT-IR spectrometer as neat liquids or as potassium bromide pellets. Proton nmr spectra were run on a Varian EM 360A spectrometer. Chemical shifts are reported in ppm downfield from tetramethylsilane using deuterated chloroform as solvent, and coupling constants are given in Hz. Mass spectra were obtained with a Hewlett Packard 5880A GC and a 5970A mass spectrometer equipped with a 20 m x 0.21 mm (i.d.) methylsilicone column and reported as mass (%). Product ratios were determined on a Hewlett Packard 5890 GC with a 5 m x 0.53 mm (i.d.) methylsilicone column and a flame ionization detector. Preparative gc was carried out on a GOW-MAC 350 Preparative GC equipped with a 6' x 1/4" 20% carbowax 20M column and thermal conductivity detector. Aluminum oxide for column chromatography was neutral Brockman I 150 mesh, (deactivated with 1% water) using a 18" x 1" column. Melting points were determined on a Thomas Hoover Uni-Melt melting point apparatus and are uncorrected. Elemental analyses were determined by Atlantic Microlab Inc., Norcross, GA. All reagents were purchased from Aldrich Chem. Co. The liquid pyrroles were distilled before use and the solids were used with no further purification. Hexane and methylene chloride were stored over calcium chloride and anhydrous tetrahydrofuran was purchased from Aldrich Chem. Co. and used as such.

1-(Alkylthio)morpholine.

A freshly prepared solution of methylsulfenyl chloride in hexane was prepared from dimethyl disulfide (9.40 g, 0.10 mole) and chlorine using the procedure of Behforouz and Kerwood [20] and added dropwise with vigorous stirring to a solution of morpholine (21.8 g, 0.25 mole) in hexane at ice-bath temperature over a period of 20 minutes. The mixture was filtered, the precipitate was washed with hexane, and the solvent was evaporated using a rotary evaporator. Distillation of the residual oil resulted in the isolation of 21 g, 75% yield of **1**, bp 75-77°/25 mm [21]. Using a similar procedure the following sulfenimides were synthesized: 1-methylthiopiperidine, bp 64-67°/25 mm [21]; 1-methylthiopyrrolidine, bp 51-54°/25 mm; 1-(ethylthio)morpholine (**2**), bp 95-97°/25 mm; 1-(isopropylthio)morpholine (**3**), bp 105-108°/25 mm (contaminated with 1-(isopropenylthio)morpholine); 1-(phenylthio)pyrrolidine, bp 95-97°/1 mm; 1-(benzylthio)morpholine, mp 72-74° [21]. 1-(*Tert*-Butylthio)morpholine, bp 90-92°/15 mm, was synthesized from *tert*-butylsulfenyl chloride [22] and morpholine.

General Procedure for Sulfenylation of 1-Methylpyrrole (**5**) with 1-(Methylthio)morpholine (**1**).

To a solution of **1** (1.60 g, 12 mmoles) and **5** (0.81 g, 10 mmoles) in 25 ml of anhydrous methylene chloride was added dropwise with stirring a solution of trifluoroacetic acid (1.40 g, 12 mmoles) in 25 ml of anhydrous methylene chloride over a period of 20 minutes at room temperature. The colored solution was washed twice with 10% sodium carbonate, water, dried over anhydrous sodium sulfate, and the solvent removed on a rotary evaporator. Refer to Table II for isomer ratios and overall yields. The following compounds could be isolated using preparative gc:

1-Methyl-2-Methylthiopyrrole [23].

This compound had ^{1}H nmr: 2.17 (3H, s, SCH_3), 3.62 (3H, s, NCH_3), 6.02 (1H, dd, 4-H, $J_{3,4}$ = 3.56, $J_{4,5}$ = 2.84), 6.25 (1H, dd, 3-H, $J_{3,4}$ = 3.56, $J_{3,5}$ = 1.81), 6.67 (1H, t, 5-H, $J_{3,5}$ = 1.81, $J_{4,5}$ = 2.84); ms: 127 (m^+, 100), 128 (m^{+1}, 8), 129 (m^{+2}, 5), 112 (82), 85 (23), 78 (43), 68 (24), 45 (21).

Anal. Calcd. for C_6H_9NS: C, 56.65; H, 7.13; N, 11.01. Found: C, 56.56; H, 7.14; N, 10.93.

1-Methyl-3-methylthiopyrrole.

This compound was not isolated; ms: 127 (m^+, 100), 128 (m^{+1}, 8), 129 (m^{+2}, 4), 112 (98), 81 (22), 80 (20), 71 (53), 45 (28), 42 (28).

1-Methyl-2,5-dimethylthiopyrrole.

This compound had ^{1}H nmr: 2.38 (6H, s, SCH_3), 3.77 (3H, s, NCH_3), 6.37 (2H, s, 3,4-H); ms: 173 (m^+, 74), 174 (m^{+1}, 8), 175 (m^{+2}, 7), 158 (74), 117 (100), 96 (23), 69 (21), 45 (20).

Anal. Calcd. for $C_7H_{11}NS_2$: C, 48.49; H, 6.40; N, 8.08. Found: C, 48.58; H, 6.40; N, 8.01.

1-Methyl-2,3-dimethylthiopyrrole.

This compound had ^{1}H nmr: 2.17 (3H, s, 3-SCH_3), 2.29 (3H, s, 2-SCH_3), 3.60 (3H, s, NCH_3), 6.11 (1H, d, 4-H, $J_{4,5}$ = 2.92), 6.66 (1H, d, 5-H, $J_{4,5}$ = 2.92); ms: 173 (m^+, 100), 174 (m^{+1}, 10), 175 (m^{+2}, 9), 158 (25), 125 (32), 114 (23), 94 (98), 69 (24).

Anal. Calcd. for $C_7H_{11}NS_2$: C, 48.49; H, 6.40; N, 8.08. Found: C, 48.59; H, 6.50; N, 7.95.

1-Methyl-2,3,5-trimethylthiopyrrole.

This compound had ^{1}H nmr: 2.20 (3H, s, 3-SCH_3), 2.24 (3H, s, 2-SCH_3), 2.32 (3H, s, 5-SCH_3), 3.68 (3H, s, NCH_3), 6.21 (1H, s, 4-H); ms: 219 (m^+, 100), 220 (m^{+1}, 12), 221 (m^{+2}, 15), 204 (81), 171 (27), 157 (23), 156 (27), 140 (42), 101 (38), 69 (35), 45 (21).

Anal. Calcd. for $C_8H_{13}NS_3$: C, 43.80; H, 5.97; N, 6.38. Found: C, 43.87; H, 6.00; N, 6.36.

1-Methyl-2,3,5-trimethylthiopyrrole was also isolated by fractional distillation. The general procedure for sulfenylation was followed starting with 80 mmoles of **1**, 20 mmoles of **5**, and 320 mmoles of chloroacetic acid. Fractional distillation of the crude reaction mixture resulted in the isolation of 2.56 g (11.7 mmoles, 58% yield), bp 127-129°/0.5 mm.

Sulfenylation of 1-Dimethylaminopyrrole (**10**) with 1-(Methylthio)-morpholine (**1**).

Sulfenylation of **10** (1.10 g, 10 mmoles) with **1** (2.94 g, 20 mmoles) in the presence of trifluoroacetic acid (3.57 g, 30 mmoles) following the general procedure for sulfenylation (except that the reaction mixture was allowed to stand 24 hours) resulted in the isolation of 0.95 g of 1-dimethylamino-2,3-dimethylthiopyrrole (4.7 mmoles, 47%) an oil by fractional distillation, bp 130-135°/0.2 mm. The oil crystallized on standing. Crystallization from methanol gave white needles, mp 37-38°; ^{1}H nmr: 2.31 (3H, s, 3-SCH_3), 2.36 (3H, s, 2-SCH_3), 2.87 (6H, s, $N(CH_3)_2$), 6.17 (1H, d, 4-H, J = 3.0), 6.97 (1H, d, 5-H, J = 3.0); ms: 202 (m^+, 78), 203 (m^{+1}, 8), 204 (m^{+2}, 8), 155 (100), 143 (30), 142 (25), 128 (30), 112 (33), 85 (29), 80 (35), 70 (23), 69 (43), 61 (36), 58 (25), 45 (38), 44 (20), 42 (47).

Anal. Calcd. for $C_8H_{14}N_2S_2$: C, 47.49; H, 6.97; N, 13.84. Found: C, 47.57; H, 6.99; N, 13.77.

The general procedure for the sulfenylation of **10** was followed using various ratios of sulfenylating agent and acid catalyst. Results are given in Table III. The following methylthio derivatives of 1-dimethylaminopyrrole were identified only by gc-mass spectral techniques as they are minor components of the reaction mixture:

1-Dimethylamino-2-methylthiopyrrole.

This compound had ms: 156 (m^+, 84), 157 (m^{+1}, 7), 158 (m^{+2}, 4), 109 (100), 98 (50), 82 (35), 70 (20), 68 (49), 45 (32), 44 (26), 42 (52), 39 (32).

1-Dimethylamino-3-methylthiopyrrole.

This compound had ms: 156 (m^+, 100), 157 (m^{+1}, 10), 158 (m^{+2}, 5), 141 (67), 114 (31), 112 (28), 98 (32), 85 (43), 70 (30), 69 (21), 45 (24), 44 (25), 42 (55).

1-Dimethylamino-2,5-dimethylthiopyrrole.

This compound had ms: 202 (m^+, 100), 203 (m^{+1}, 11), 204 (m^{+2}, 11), 157 (27), 155 (68), 144 (35), 114 (47), 112 (22), 96 (68), 69 (26), 45 (37), 42 (41).

1-Dimethylamino-2,3,5-Trimethylthiopyrrole.

This compound had ms: 248 (m^+, 100), 249 (m^{+1}, 14), 250 (m^{+2}, 15), 204 (85), 201 (69), 190 (22), 189 (25), 174 (32), 158 (42), 157 (60), 156 (25), 142 (61), 126 (22), 101 (42), 91 (20), 69 (28), 58 (21), 45 (32), 42 (39).

1-Dimethylamino-2,3,4-trimethylthiopyrrole.

This compound had ms: 248 (m^+, 64), 249 (m^{+1}, 9), 250 (m^{+2}, 10), 201 (100), 190 (29), 174 (25), 156 (20), 115 (43), 69 (29), 61 (28), 45 (20), 42 (30).

The ratio of the 2,3,5- and 2,3,4-trimethylthiopyrroles above is 5 to 1, respectively, as tentatively assigned.

Relative Rates of Sulfenylation of Some 1-Substituted Pyrrole with 1-(Methylthio)morpholine (**1**) and Trifluoroacetic Acid.

Relative rates of 1-substituted pyrroles were determined by making a solution of 5 mmoles each of two different pyrroles and 0.5 mmoles of **1** in 20 ml of methylene chloride. To this solution was added dropwise a solution of 1.5 mmoles of trifluoroacetic acid in 10 ml of methylene chloride. The solutions were analyzed using gc techniques and the components of the reaction mixture were identified from gc-mass spectrometer techniques. The relative rates of the following pairs of pyrroles were determined by averaging three determinations: **5** and **1**, **5** and **6**, **5** and **7**, **5** and **8**, **8** and **10**, and **10** and **11** [24]. See Table I for results.

Acid Catalyzed Rearrangement of Methylthio-1-methylpyrroles.

A mixture of 0.05 mmoles of 1-methyl-2-methylthiopyrrole and 0.01 mmoles of trifluoroacetic acid in 1 ml of methylene chloride at room temperature was monitored gas chromatographically. After fifteen minutes 11% of 1-methyl-3-methylthiopyrrole was observed and 33% after an hour, at which time the system was near equilibrium. The solution becomes dark on standing; however, no disubstitution was observed.

2,5-Dimethylthio-1-methylpyrrole was isomerized in the same manner as above. After one hour 97% of 2,4-dimethylthio-1-methylpyrrole was observed and only 3% of 2,5-dimethylthio-1-methylpyrrole remained. No other methylthiopyrroles were observed. When chloroacetic acid was used instead of trifluoroacetic acid very little isomerization had occurred after one hour at room temperature.

1-Methyl-2,4-dimethylthiopyrrole.

This compound had ^{1}H nmr: 2.17 (3H, s, 4-SCH_3), 2.23 (3H, s, 2-SCH_3), 3.56 (3H, s, NCH_3), 6.28 (1H, d, 3-H, $J_{3,5}$ = 1.9), 6.67 (1H, d, 5-H, $J_{3,5}$ = 1.9); ms: 173 (m^+, 100), 174 (m^{+1}, 11), 175 (m^{+2}, 10), 158 (78), 143 (22), 42 (33).

1-Methyl-2,3-dimethylthiopyrrole was not isomerized under these conditions.

Sulfenylation of 1-Methylpyrrole with Methylsulfenyl Chloride.

Methylsulfenyl chloride (20 mmoles), prepared by passing chlorine into a solution of dimethyl disulfide in anhydrous hexane at 0°, was added dropwise to a rapidly stirred solution of 1-methylpyrrole (20 mmoles), pyridine (40 mmoles), and 25 ml of anhydrous methylene chloride with cooling. After the addition

was complete the solution was washed three times with water, dried over sodium sulfate, and evaporated on a rotary evaporator. The remaining oil was analyzed. Various molar amounts of methylsulfenyl chloride, with twice the molar amount of pyridine, were reacted with 1-methylpyrrole. See results in Table IV. Pyrrole and 2,5-dimethylpyrrole were sulfenylated similarly but in each case gave complex mixtures with considerable decomposition.

2,3,4,5-Tetramethylthiopyrroles.

Methylsulfenyl chloride, prepared by passing chlorine into a solution of dimethyl disulfide (4.70 g, 50 mmoles) in 50 ml of anhydrous hexane at 0°, was added dropwise to a rapidly stirred solution of the appropriate pyrrole (20 mmoles) and pyridine (15.8 g, 20 mmoles) in 50 ml of methylene chloride with cooling. After the addition was complete the mixture was filtered. The filtrate was washed three times with water and the organic layer was dried over anhydrous sodium sulfate and the solvent evaporated on a rotovap. The remaining oil partially crystallized on standing. Addition of the appropriate solvent, decolorization with charcoal, and cooling in the freezer overnight resulted in the isolation of the tetramethyl sulfide.

2,3,4,5-Tetramethylthio-1-methylpyrrole.

This compound was crystallized from methanol, 2.8 g (10.4 mmoles, 52% yield), mp 36-37°; ^{1}H nmr: 2.30 (6H, s, 3,4-SCH_3), 2.37 (6H, s, 2,5-SCH_3), 3.83 (3H, s, NCH_3); ms: 265 (m^+, 100), 266 (m^{+1}, 13), 267 (m^{+2}, 18), 250 (46), 220 (25), 202 (27), 115 (43), 100 (29), 91 (35).

Anal. Calcd. for $C_9H_{15}NS_4$: C, 40.72; H, 5.70; N, 5.28. Found: C, 40.63; H, 5.72; N, 5.25.

2,3,4,5-Tetramethylthio-1-dimethylaminopyrrole.

This compound was crystallized from ethanol, 4.37 g (14.8 mmoles, 74% yield), mp 86-87°; ^{1}H nmr: 2.43 (12H, s, 2,3,4,5-SCH_3), 3.18 (6H, s, $N(CH_3)_2$); ms: 294 (m^+, 100), 295 (m^{+1}, 13), 296 (m^{+2}, 18), 250 (80), 247 (72), 235 (25), 220 (25), 220 (71), 217 (39), 204 (34), 203 (24), 202 (54), 199 (29), 188 (46), 156 (24), 126 (23), 115 (66), 102 (30), 100 (38), 94 (34), 91 (42), 88 (23), 58 (39), 45 (30), 44 (23), 43 (26), 42 (53).

Anal. Calcd. for $C_{10}H_{18}N_2S_4$: C, 40.78; H, 6.16; N, 9.51. Found: C, 40.83; H, 6.18; N, 9.43.

2,3,4,5-Tetramethylthio-1-phenylpyrrole.

This compound was crystallized from ethanol, 4.0 g (12.2 mmoles, 61% yield), mp 76-77°; ^{1}H nmr: 2.45 (6H, s, 3,4-SCH_3), 2.83 (6H, s, 2,5-SCH_3), 7.3-7.9 (5H, m, C_6H_5); ms: 327 (m^+, 100), 328 (m^{+1}, 19), 329 (m^{+2}, 20), 312 (37), 219 (23), 115 (67), 100 (33), 91 (63), 77 (46), 51 (29).

Anal. Calcd. for $C_{14}H_{17}NS_4$: C, 51.34; H, 5.23; N, 4.28. Found: C, 51.38; H, 5.23; N, 4.26.

2,3,4,5-Tetramethylthio-1-(2-chloroethyl)pyrrole.

This compound was crystallized from methanol, 4.46 g (14.2 mmoles, 71% yield), mp 56-57°; ^{1}H nmr: 2.40 (12H, s, 2,3,4,5-SCH_3), 3.77 (2H, t, CH_2Cl), 4.64 (2H, t, CH_2N); ms: 313 (m^+, 100), 315 (m^{+2}, 47), 300 (34), 298 (72), 219 (57), 115 (47), 91 (55).

Anal. Calcd. for $C_{10}H_{16}ClNS_4$: C, 38.26; H, 5.14; N, 4.46. Found: C, 38.40; H, 5.20; N, 4.52.

2,3,4,5-Tetraphenylthiopyrroles.

A solution of phenylsulfenyl chloride (1.44 g, 10 mmoles) in 25 ml of methylene chloride was added dropwise to 1-methylpyrrole (0.16 g, 2 mmoles) and pyridine (1.58 g, 20 mmoles) in 25 ml of methylene chloride with stirring and cooling. After addition was complete the solution was stirred an additional 30 minutes. The mixture was filtered, washed with water three times, the organic layer was dried over anhydrous sodium sulfate, and evaporated on a rotary evaporator.

2,3,4,5-Tetraphenylthio-1-methylpyrrole.

This compound was crystallized from ethanol, 0.93 g (1.82 mmoles, 91% yield), mp 147-148°; ^{1}H nmr: 3.66 (3H, s, CH_3), 7.07 (20H, s, C_6H_5).

Anal. Calcd. for $C_{29}H_{23}NS_4$: C, 67.80; H, 4.51; N, 2.73. Found: C, 67.64; H, 4.53; N, 2.81.

2,3,4,5-Tetraphenylthio-1-phenylpyrrole.

1-Phenylpyrrole (0.143 g, 1 mmole), phenylsulfenyl chloride (0.718 g, 5 mmoles), and pyridine (0.948 g, 12 mmoles) were reacted as describe above. The product was crystallized from ethanol, 0.164 g (0.29 mmole, 29%), mp 144-145°.

Anal. Calcd. for $C_{34}H_{25}NS_4$: C, 70.92; H, 4.38; N, 2.43. Found: C, 70.83; H, 4.46; N, 2.42.

Sulfenylation of Indoles with 1-(Methylthio)morpholine (**1**).

Indole (**17**) was sulfenylated using the general procedure for the sulfenylation of **5** with **1**. The ratio of products is given in Table V. The following components were identified from gc-ms data and by comparison with reported compounds.

1-Methylthioindole [5].

This compound had ms: 163 (m^+, 64), 164 (m^{+1}, 8), 165 (m^{+2}, 3), 148 (100), 116 (40), 89 (35), 63 (22).

3-Methylthioindole [25].

This compound had ms: 163 (m^+, 64), 164 (m^{+1}, 8), 165 (m^{+2}, 3), 148 (100).

1,3-Dimethylthioindole.

This compound had ms: 209 (m^+, 62), 210 (m^{+1}, 8), 211 (m^{+2}, 6), 162 (100), 120 (36).

Methylsulfenylation of 1-methylthioindole, synthesized by an independant procedure [5], forms 1,3-dimethylthioindole and 1,2,3-trimethylthioindole but no 2,3-dimethylthioindole.

2,3-Dimethylthioindole [26].

This compound had ^{1}H nmr: 2.32 (3H, s, SCH_3), 2.36 (3H, s, SCH_3), 7.0-8.0 (5H, broad, ArH and NH); ms: 209 (m^+, 100), 210 (m^{+1}, 13), 211 (m^{+2}, 10), 194 (50), 161 (41), 130 (76), 117 (34).

1,2,3-Trimethylthioindole.

This compound had ms: 209 (m^+, 96), 256 (m^{+1}, 16), 257 (m^{+2}, 13), 240 (23), 209 (23), 208 (96), 194 (25), 193 (100), 192 (83), 178 (55), 162 (55), 161 (36), 146 (31), 120 (25), 117 (22), 102 (43), 45 (28).

Indole (**17**) (468 mg, 4.00 mmoles) was sulfenylated with **1** (661 mg, 4.50 mmoles) using the general procedure for sulfenylation except that chloroacetic acid was used as the acid catalyst rather than trifluoroacetic acid. Pure 3-methylthioindole was isolated by passing the crude oil through a neutral amunina column (50% hexane and 50% methylene chloride) (550 mg, 3.37 mmoles, 84% yield).

1-Methyl-3-methylthioindole [22].

1-Methylindole (**18**) (377 mg, 2.88 mmoles) was sulfenylated with **1** (477 mg, 3.24 mmoles) using the general procedure for sulfenylation. 1-Methyl-3-methylthioindole [22] was isolated as a yellow oil which was contaminated with 5% 1-methyl-2,3-dimethylthioindole and 2% of **18**. The sample was purged by passing through a neutral alumina column using hexane as a solvent (387 mg, 2.19 mmoles, 76% yield); ^{1}H nmr: 2.27 (3H, s, SCH_3), 3.70 (3H, s, NCH_3), 7.0-7.2 and 7.5-7.8 (5H, broad, ArH); ms: 177 (m^+, 31), 178 (m^{+1}, 5), 179 (m^{+2}, 2), 162 (100), 120 (25), 118 (23), 77 (33), 45 (22).

1-Methyl-2,3-dimethylthioindole (**22**).

1-Methylindole (**18**) (524 mg, 4.00 mmoles) was sulfenylated with **1** (1470 mg, 10.0 mmoles) using the general procedure for sulfenylation. A crude yellow oil (883 mg) was isolated. The oil was dissolved in isopropyl alcohol and on cooling to 0° overnight 795 mg (3.56 mmoles, 89% yield) of 1-methyl-2,3-dimethylthioindole (**22**), mp 39-40°, was isolated; ^{1}H nmr: 2.30 (3H, s, 3-SCH_3), 2.33 (3H, s, 2-SCH_3), 7.1-7.3 (3H, broad, ArH), 7.69 (1H, d, ArH, J = 7.9); ms: 223 (m^+, 100), 224 (m^{+1}, 14), 225 (m^{+2}, 10), 208 (56), 175 (47), 144 (71), 131 (32).

Anal. Calcd. for $C_{11}H_{13}NS_2$: C, 59.15; H, 5.87; N, 6.32. Found: C, 59.01; H, 5.88; N, 6.24.

2-Methyl-3-methylthioindole (**21**).

2-Methylindole (**19**) (656 mg, 5.00 mmoles) was sulfenylated with **1** (882 mg, 6.00 mmoles) using the general procedure for sulfenylation except that chloroacetic acid was used instead of trifluoroacetic acid. A crude oil was obtained which was purified by passing through a neutral alumina column (hexane). 2-Methyl-3-methylthioindole (**21**) [20] (756 mg, 4.27 mmoles, 85% yield); ^{1}H nmr: 2.24 and 2.34 (6H, S and S, CH_3 and SCH_3), 6.95-7.30 and 7.50-7.85 (5H, broad, ArH and NH).

Oxidation of **22**. 3-Methylsulfinyl-2-methylthio-1-methylindole (**23**).

One g of 30% hydrogen peroxide was slowly added dropwise at room temperature to a solution of **22** (446 mg, 2.0 mmoles) in 5 ml of acetic acid with stirring. After 30 minutes, 5 ml of a 10% solution of sodium dithionate was added. To this mixture was added 50 ml of methylene chloride and extracted with 10% sodium carbonate, water, and the organic layer was dried over anhydrous sodium sulfate and the solvent removed on a rotary evaporator. The crystalline sulfoxide **23** (364 mg, 1.52 mmoles, 76% yield) was decolorized with charcoal and crystallized from acetone to yield needles, mp 131-132.5°; ^{1}H nmr: 2.30 (3H, s, SCH_3), 2.98 (3H, s, $SOCH_3$), 3.77 (3H, s, NCH_3), 7.28 (1H, m, ArH), 8.13 (3H, m, ArH).

Anal. Calcd. for $C_{11}H_{13}NOS_2$: C, 55.20; H, 5.47; N, 5.85. Found: C, 55.27; H, 5.48; N, 5.90.

2,3-Dimethylsulfonyl-1-methylindole (**24**).

The general procedure for sulfenylation was used for the methylsulfenylation of **18** (262 mg, 2.00 mmoles) with **1** (294 mg, 4.50 mmoles) to form **22**. To the crude yellow oil **22** dissolved in 5 ml of acetic acid was added 1.0 g of 30% hydrogen peroxide. After heating for 3 hours at 60° the solution was evaporated on a rotary evaporator at 60°. The residual disulfone **24** was crystallized from 95% alcohol after decolorization with charcoal, 285 mg (0.99 mmoles, 50% yield) of yellow needles, mp 186-187°; ^{1}H nmr: 3.40 (3H, s, 3-SO_2CH_3), 3.50 (3H, s, 2-SO_2CH_3), 4.14 (3H, s, 1-CH_3), 7.50 and 8.49-8.37 (4H, m, ArH).

Anal. Calcd. for $C_{11}H_{13}NS_2O_4$: C, 45.98; H, 4.56; N, 4.87. Found: C, 45.88; H, 4.59; N, 4.84.

1-(2-Phenylsulfonylethyl)indole (**25**).

A mixture of 2-chloro-1-phenylsulfonylethane [27] (2.46 g, 12.0 mmoles), indole (1.17 g, 10.0 mmoles), tetrabutylamminium hydrogen sulfate (0.34 g, 1.0 mmoles), 10 ml of 50% potassium hydroxide, and 50 ml of methylene chloride was vigorously stirred at room temperature for one hour. The methylene chloride layer was separated from the aqueous layer by gravity filtration and evaporated on a rotary evaporator. The brown crystalline residue was flushed through an alumina column with methylene chloride. Evaporation of the methylene chloride left a yellow solid which was crystallized from 95% ethanol (2.14 g, 7.50 mmoles, 75% yield), mp 104-105°; ir: 1142, 1305 cm^{-1}; ^{1}H nmr: 3.50 (2H, t, N-CH_2-), 4.50 (2H, t, S-CH_2-), 6.40 (1H, d, 3-H), 6.90 (1H, d, 2-H), 7.10-8.00 (9H, m, ArH); ms: 285 (m^+, 14), 286 (m^{+1}, 3), 287 (m^{+2}, 1), 143 (100), 130 (22).

Anal. Calcd. for $C_{16}H_{15}NO_2S$: C, 67.38; H, 5.26; N, 4.91. Found: C, 67.32; H, 5.35; N, 4.90.

1-(2-Phenylsulfonylethyl)-2,3-diphenylthioindole (**26**).

To a solution of **25** (699 mg, 2.45 mmoles), pyridine (1.16 g, 14.7 mmoles), and 20 ml of methylene chloride was added dropwise phenylsulfenyl chloride (1.23 g, 8.59 mmoles) dissolved in 10 ml of methylene chloride at ice-bath temperature with vigorous stirring. After one and one-half hours the reaction mixture was washed with water, dried over anhydrous sodium sulfate and evaporated on a rotary evaporator. The crude product was eluted with hexane on a neutral alumina column until all of the diphenyl disulfide was removed and then eluted with methylene chloride until all of the product **26** was removed from the column. Evaporation of the solvent left a crystalline material which was crystallized from 95% alcohol (0.96 g, 1.91 mmoles, 78% yield), mp 128-129°; ir: 1142, 1305 cm^{-1}; ^{1}H nmr: 3.35 (2H, t, NCH_2), 4.85 (2H, t, SCH_2-), 7.1-8.1 (19H, m, ArH).

Anal. Calcd. for $C_{28}H_{23}NO_2S_3$: C, 67.04; H, 4.62; N, 2.79. Found: C, 66.92; H, 4.64; N, 2.74.

2,3-Diphenylthioindole (**27**).

A mixture of **26** (250 mg, 0.499 mmole), 60% sodium hydride (60 mg, 1.50 mmoles) and 7 ml of anhydrous dimethylformamide was stirred at room temperature for two and one-half hours. The mixture was decomposed with excess water, extracted with ether, dried over anhydrous sodium sulfate and evaporated on a rotary evaporator. The crude residue was flushed through an alumina column using methylene chloride as the solvent. Evaporation of the solvent left a solid, **27**, which was crystallized from ethanol (62 mg, 0.185 mmole, 37% yield), mp 98-99°; ir: 3414 cm^{-1}; ms: 333.7 (m^+, 24), 334.7 (m^{+1}, 11), 335.7 (m^{+2}, 2), 332.7 (99), 225 (36), 224 (100), 223 (80), 222 (29), 102 (24), 77 (32), 51 (37).

Anal. Calcd. for $C_{20}H_{15}NS_2$: C, 72.04; H, 4.53; N, 4.20. Found: C, 71.90; H, 4.56; N, 4.11.

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