Mechanism of the Second Sulfenylation of Indole

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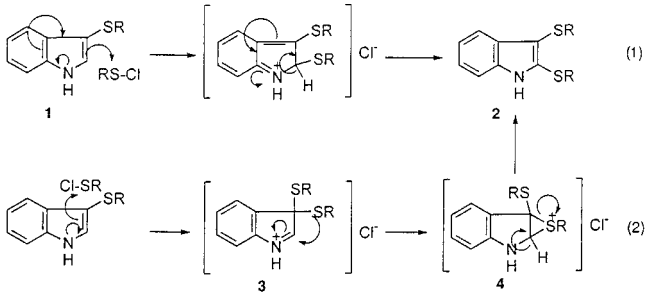
Sulfenylation of indole using a sulfenyl chloride occurs initially at the 3-position of the ring, leading to a 3-indolyl sulfide. When an excess of sulfenyl chloride is used, a second sulfide group is introduced at the 2-position, and an indolyl 2,3-bis-sulfide results. We have demonstrated that this second sulfenylation occurs not by direct introduction of the second sulfide at the 2-position but via initial formation of an indolenium 3,3-bis-sulfide intermediate, followed by migration of one of the sulfide groups to the 2-position. This was achieved by the isolation of two examples of 3*H*-indole 3,3-bis-sulfides and by subsequent demonstration that they rearrange to the indolyl 2,3-bis-sulfides by treatment with sulfenyl halides.

Introduction

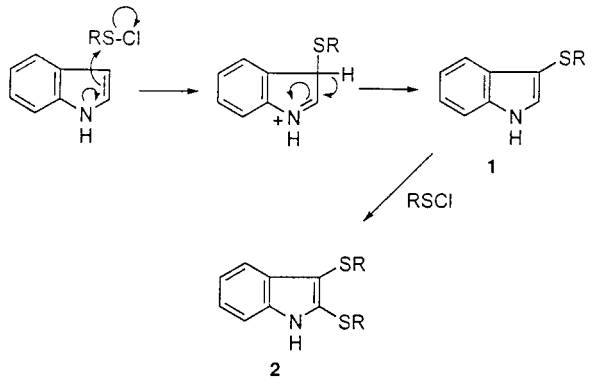
One of the most convenient methods for the preparation of 3-indolyl sulfides **1** is by sulfenylation of indoles using sulfenyl chlorides.[1−5] These are easily generated from alkyl or aryl disulfides and a source of chlorine, ideally sulfuryl chloride, in 1,2-dichloroethane or tetrachloroethane. In most cases, this reaction is practically instantaneous and the sulfenyl chloride is produced nearly quantitatively and used as such in solution, after a few minutes. The sulfenyl chlorides are extremely reactive, and sulfenylation of indole occurs rapidly at room temperature, without the need for the preliminary generation of the anion of indole, leading to good to excellent yields of 3-indolyl sulfides. The mechanism of this sulfenylation is well-known[4] and follows the usual substitution pathway[6] depicted in Scheme 1. One drawback to the use of sulfenyl chlorides for the sulfenylation of indoles derives from their exceptional reactivity, and if the 2-position of the indole is unoccupied, the slightest excess of reagent leads to a second sulfenylation, and a full second equivalent leads to excellent yields of 2,3-indolyl bis-sulfides **2**.[1,3,4,7]

For the past few years we have been attempting to establish the mechanism of this second sulfenylation of indole. The question to be resolved is the following: is the second sulfide group introduced directly at the 2-position of the indole ring (eq 1), or does the reaction proceed via a second sulfenylation at the 3-position, leading to an intermediate 3,3-bis-substituted indolenium intermediate such as **3** (eq 2), with subsequent migration



of one of the sulfide groups to the 2-position, possibly through a transient episulfonium species such as **4**? The latter pathway was suggested several years ago by Ottenheijm et al.[3,4] with no experimental support, and it intuitively appears more plausible than the direct introduction into the 2-position, which would require a temporary disruption of the aromaticity of the ring system. The 3-position is the most nucleophilic site of the indole nucleus, and where steric hindrance is not a factor, the presence of a sulfide group would not be expected to deactivate the 3-position toward further substitution. The data that we present herein serve as strong evidence to demonstrate that indeed the mechanism proceeds via an initial second sulfenylation at the 3-position followed by rearrangement.

Scheme 1



Results and Discussion

In an initial report[8] we presented the results of a study in which we performed a second sulfenylation on a series

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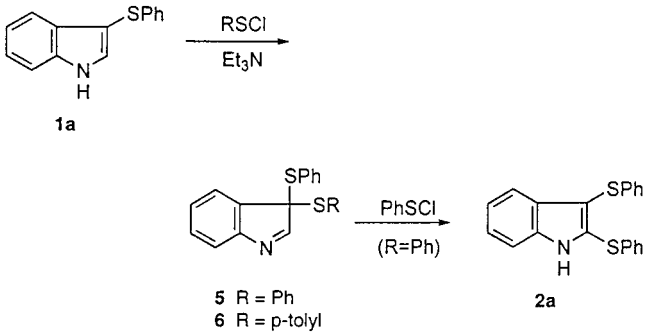
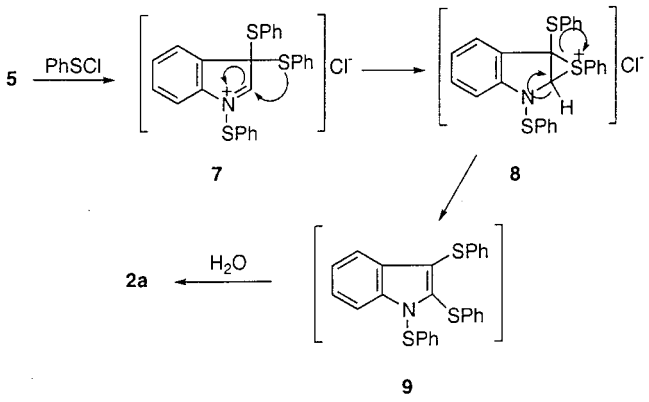
Scheme 2



Scheme 3



of 3-indolyl sulfides using a different sulfenyl chloride from the one used for the first sulfenylation. The fact that in all cases mixtures of two isomeric mixed 2,3-bis-sulfides were obtained instead of a single isomer bearing the second sulfide group in the 2-position lent strong support to the hypothesis of initial second sulfenylation at the 3-position followed by migration of one of the sulfide groups. In addition, the presence of the sulfide bearing the most electron-rich substituent at the 2-position of the ring in the major isomer produced was strongly indicative of a preferential migration induced by the positive charge on the nitrogen atom of the proposed indolenium intermediate **3**.

We then proceeded to examine the possibility of isolating an intermediate of type **3** bearing the two sulfide groups at the 3-position of the ring. Although 3-alkythio-3-alkyl-3*H*-indoles have been reported previously, as intermediates of the Gassman synthesis of indoles and carbazoles[9] and also by sulfenylation of 2,3-dialkylindoles, [10a,b] alkyl substituents were always present at the 2-position. No examples bearing two sulfide groups at the 3-position, with or without a 2-substituent, had been reported. We successfully isolated two examples[11] (**5** and **6**, Scheme 2) of the neutralized form of **3** from the reaction of 3-phenylthioindole **1a** with either benzenesulfenyl chloride or *p*-toluenesulfenyl chloride in the presence of triethylamine. We were convinced that regeneration of the positive charge on the nitrogen atom of the isolated intermediates by protonation would lead to immediate rearrangement. However, the molecules proved to be totally inert to acids and we could not provoke protonation of the ring at room temperature, even in neat trifluoroacetic acid, while heating led to decomposition products. In contrast, when 3,3-bis-phenylthio intermediate **5** is treated with benzenesulfenyl chloride at room temperature, generation of 2,3-bis-phenylthioindole **2a** results. We did not perform a similar experiment on the unsymmetrical 3,3-bis-sulfide **6** to avoid the complications due to the generation of two different mixed 2,3-bis-sulfides.

It is difficult to rationalize the transformation of **5** to **2a** under these conditions other than by proposing that the interaction consists of initial quaternization of **5** by the sulfenyl chloride, leading to a charged *N*-sulfenyl intermediate such as **7** (Scheme 3). In our representation of the subsequent events leading to the rearrangement, the positive charge on the nitrogen of intermediate **7** induces the migration of one of the sulfide groups, possibly via the formation of the episulfonium species **8** with subsequent cleavage of the three-membered ring to yield the *N*-phenylsulfenyl 2,3-bis-sulfide **9**. The labile *N*-sulfenamide is cleaved during the aqueous workup to afford **2a**. The proposal that the *N*-substituent remains throughout the process until workup is supported by the fact that at least a full equivalent of sulfenyl chloride is required for the process to go to completion.

As an extension to the concept of quaternization of the intermediate **5**, we proceeded to experiment with the possibility of provoking the quaternization using alkyl halides. We expected that if quaternization did occur, the rearrangement would proceed to afford *N*-alkylated analogues of **2a**, easily accessible via alkylation for structural confirmation. Treatment of **5** in DMF with an excess of benzyl bromide at room temperature showed no discernible transformation after 2.5 h, and heating at 85 °C led to the formation of unidentified side products without generation of the desired end product. Similar results were obtained with methyl iodide and with the highly reactive methyl trifluoromethanesulfonate. In the light of these results, the rearrangement of **5** in the presence of benzenesulfenyl chloride leads us to assume that the latter is much more reactive than alkyl halides or trifluoromethylsulfonates in leading to the quaternization of **5**. This reactivity of sulfenyl halides is demonstrated by the facile sulfenylations of indole, where no base is required for the reaction to occur, whereas the well-known alkylation of indole[6] requires initial generation of the anion to lead to 1- or 3-alkylated products.

The preceding experiments aimed at the rearrangement of **5** to **2a** confirm that it does occur, providing that a positive charge can be generated on the nitrogen atom to drive the migration. Under the actual conditions of the second sulfenylation, where a 3-indolyl sulfide is reacted with a sulfenyl chloride, our proposal suggests that such a charged species automatically results in situ when the 3,3-disubstituted indolenium intermediate **3** is formed. This species presumably has sufficient longevity to allow the migration of one of the sulfide groups to proceed, initiating the events leading to the final reaction product, the indolyl 2,3-bis-sulfide **2**.

As a further extension to this mechanistic study, we designed an experiment aimed at establishing that the transformation of the indolenium intermediate **3** to the bis-sulfide **2** occurs via an intramolecular migration of one of the sulfide groups, rather than by some more exotic

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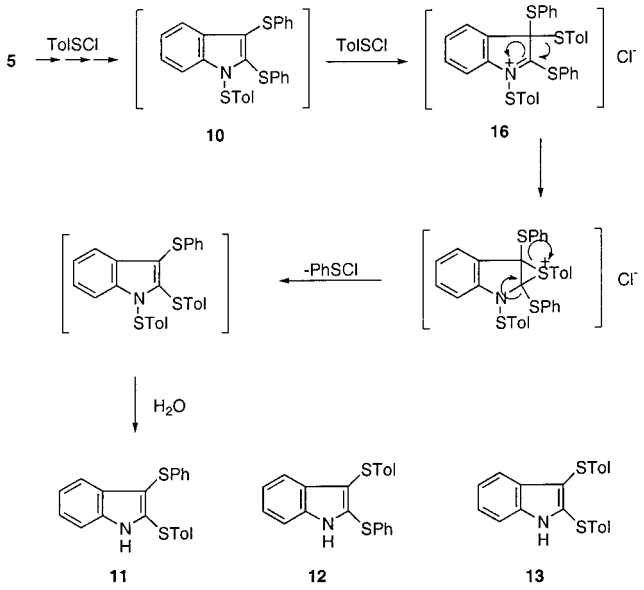
Scheme 4



intermolecular pathway. For this purpose, we reacted the isolated 3,3-bis-sulfide **5** with 1 equiv of *p*-toluenesulfenyl chloride with the expectation that quaternization would occur and that the process would lead, after the migration of one of the phenylthio groups, to intermediate **10** (Scheme 4), similar to **9** but bearing an *N*-*p*-tolylsulfenyl substituent. Upon aqueous workup, the *N*-tolylsulfenyl substituent would be cleaved, leading to the 2,3-bis-phenylthioindole **2a** with no incorporation of a *p*-tolylthio group on the indole nucleus, as might be expected to result if an intermolecular event were proceeding. However, after workup and chromatography, what appeared to be a single spot product on TLC, corresponding to **2a**, was revealed by proton NMR to consist of a mixture of components, and multiple signals corresponding to methyl groups indicated the presence of components bearing *p*-tolylthio groups. The pattern of the protons on the phenyl portion of the indole ring appeared intact, indicating that no substitution had occurred on that portion of the molecule. The obvious conclusion was that one or both of the phenylthio groups had been displaced by a *p*-tolylthio group, leading to compounds such as **11**−**13**. This was confirmed by mass spectral analysis of the compound mixture, where mass units of 347 and 361 were observed, corresponding to compounds **11** and/or **12** and **13**, respectively.

To provide confirmation of these results, authentic samples of these three compounds were prepared for comparison of their NMR data, and their syntheses are reported in Scheme 5. Sulfenylation of 2-phenylthioindole **14**[12,13] with *p*-toluenesulfenyl chloride cleanly affords 2-phenylthio-3-(*p*-tolylthio)indole **12**, whereas 2,3-bis(*p*-tolylthio)indole **13** results from double sulfenylation of indole with the same sulfenyl chloride. Access to the isomeric 3-phenylthio-2-(*p*-tolylthio)indole **11** is achieved via initial regiospecific desulfenylation[7] of **13** in trifluoroacetic acid in the presence of thiosalicylic acid, leading to 2-(*p*-tolylthio)indole **15**, which is sulfenylated with benzenesulfenyl chloride to yield **11.** The ^{1}H NMR spectra of these compounds confirmed that they were indeed all present in the above compound mixture.

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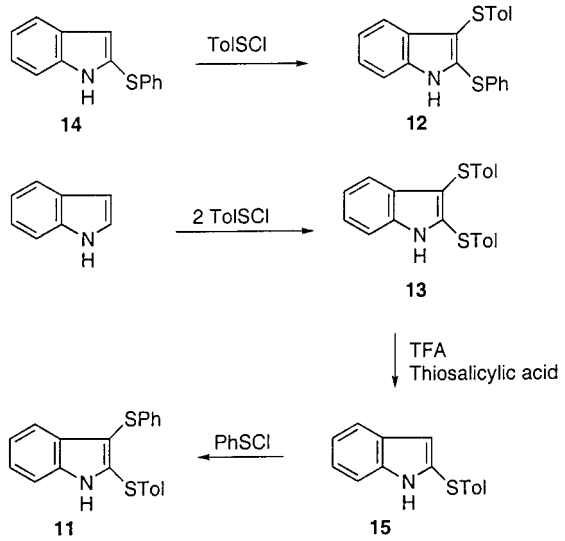
Scheme 5



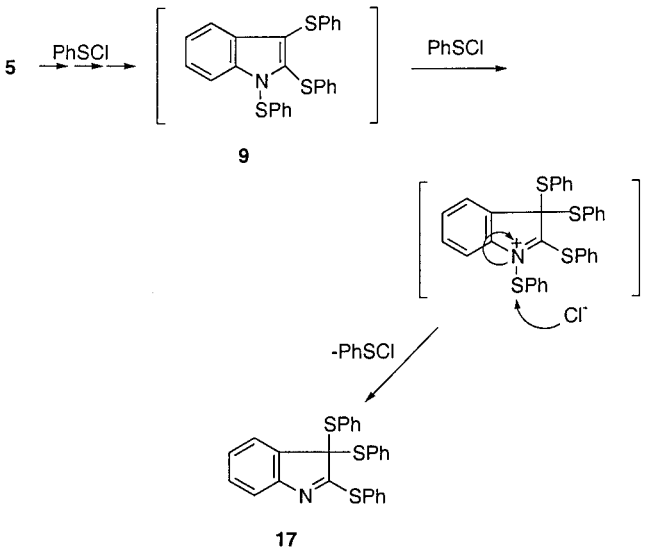
The generation of compounds **12** and **13** was quite puzzling, since they both bear a *p*-tolylthio group at the 3-position of the ring. This led us to suspect that sulfenylation with *p*-toluenesulfenyl chloride could have occurred at the 3-position of the indole ring at some point. We propose that the appropriate substrate for such a process would be intermediate *N*-sulfenyl-2,3-indolyl bis sulfide **10** (Scheme 4) and that a second sulfenylation occurs at the 3-position, leading to 2,3,3-tris-sulfide indolenium intermediate **16**. This would be followed by migration of one of the sulfide groups from the 3-position to the 2-position with concomitant expulsion of the phenylthio substituent already present. In the case where the *p*-tolylthio group migrates, this would lead after workup to compound **11**, whereas migration of the phenylthio group would afford compound **12**. A similar exercise on the *N*-sulfenyl intermediate of **12** would explain the formation of the 2,3-bis(*p*-tolylthio)indole **13**. Although 1 equiv of the *p*-toluenesulfenyl chloride was used in this experiment, it is assumed that the initial quaternization occurs slowly and thus that significant amounts of the sulfenyl chloride are available for the competing ring sulfenylations proposed above.

Although the results of this experiment failed to provide the desired information on the pathway of the migration of the sulfide, the proposed sulfenylation to afford intermediate **16** actually represents an extension of the concept of a second sulfenylation at the 3-position and thus provides additional support for the mechanistic proposal that is the subject of this paper.

Evidence that such a third sulfenylation can indeed occur was provided by a closer examination of the mixtures obtained when **5** was treated with benzenesulfenyl chloride. In the crude mixtures, a minor component was always observed in variable amounts but not isolated. In one experiment a 19% yield of this component was isolated, and its structure was established as being 2,3,3-tris-phenylthio-3*H*-indole **17** (Scheme 6). This compound is proposed to derive from sulfenylation of intermediate **9** at the 3-position, with subsequent eviction of the *N*-sulfenyl substituent as benzenesulfenyl chloride in a "retroquaternization" step.

The isolation of compounds such as **5** and **6** and the formation of compounds such as **11**−**13** and **17** demon-

Scheme 6



strate that in 3-indolyl sulfides the strong nucleophilic character of the 3-position of the indole ring is indeed retained, despite the presence of the sulfide substituent, allowing a second sulfenylation to occur at the same position.

Conclusion

We believe that the data presented herein and in our preceding papers strongly support the proposal that the mechanism of the second sulfenylation of indole, as was proposed by Ottenheijm et al., proceeds initially via a second sulfenylation at 3-position, leading to in situ formation of a 3,3-bis-substituted indolenium intermediate. Studies on an isolated 3*H*-indole 3,3-bis-sulfide demonstrate that the positive charge on the nitrogen atom of the 3,3-disubstituted indolenium species provides the driving force that initiates the migration of one of the sulfide groups to the 2-position. The intermediacy of a transient episulfonium species remains at this time a plausible scenario for this migration.

Experimental Section

Commercial reagents were used without further purification or drying. The DMF and 1,2-dichloroethane used had water content <50 ppm. The solvents used for chromatography were of HPLC grade. ^{1}H NMR spectra were recorded on a 500 MHz instrument in acetone-d_6 solution, and chemical shifts are reported in ppm. Elemental analyses were performed at the Laboratoire d'analyse elementaire, Universite de Montreal. High-resolution mass spectra at 10 000 resolution were obtained in-house using a JEOL HX110 mass spectrometer with electron impact source. Progress of the reactions was monitored on TLC silica gel plates, and purifications were carried out using flash silica gel chromatography.

Stock Solution of Benzenesulfenyl Chloride. In all experiments the benzenesulfenyl chloride was prepared immediately prior to its use by the following method: To a solution of 1.2 g of diphenyl disulfide (5.5 mmol) in 15 mL of 1,2-dichloroethane at room temperature was added 667 mg of sulfuryl chloride (0.40 mL, 5 mmol), the resulting yellow solution was stirred for 5 min, and then the volume was completed to 25 mL with 1,2-dichloroethane. The solution was used as such, assuming a concentration of 0.4 M benzenesulfenyl chloride. In some cases a 0.5 M solution was prepared. An attempt to obtain the sulfenyl chloride in pure form by distillation led to decomposition, so it was used as such in solution and considered to have the theoretical concentration corresponding to a complete conversion. A rough confirmation was provided by the following titration.

Titration of the Benzenesulfenyl Chloride Solution. A freshly prepared 0.4 M solution was titrated by using it in a sulfenylation experiment with 2-methylindole as substrate. To a solution of 131 mg of 2-methylindole (1 mmol) in 2.5 mL of DMF was added incremental amounts of the benzenesulfenyl chloride solution, until the complete disappearance of the starting material and clean formation of 2-methyl-3-phenylthioindole[3] had resulted, as indicated by TLC. Isolation of the product in 90% yield after chromatography indicated a concentration of at least 0.36 M. Taking into account probable small losses of material in the workup and chromatography, the concentration of this and other sulfenyl chloride solutions was considered to be close enough to the theoretical value to be used as such.

Isolation of 3,3-Bis(phenylthio)-3*H*-indole (5). To a solution of 2.25 g of 3-phenylthioindole **1a**[4,5] (10 mmol) in 20 mL of DMF at room temperature was added 1.21 g of triethylamine (1.67 mL, 12 mmol). The mixture was cooled to 0 °C and 25 mL of a freshly prepared 0.4 M solution of benzenesulfenyl chloride (10 mmol) was added slowly. The mixture was stirred at 0 °C for 1 h, then it was partitioned between ether and water. The crude product from the organic phase was chromatographed by eluting with a 1:9 mixture of ethyl acetate and hexane. After elution of residual diphenyl disulfide, 1.11 g (33%) of the product **5** was obtained as a white solid, followed by 1.25 g (55%) of recovered **1a**. Only a trace of 2,3-bis(phenylthio)indole **2a**[5] was observed by TLC.

Data for **5**: mp 114−116 °C; ^{1}H NMR δ 7.12−7.31 (m, 9H), 7.36−7.41 (m, 3H), 7.53 (d, J = 7.9 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.88 (s, 1H); HRMS calcd for $C_{20}H_{15}NS_2$ 333.0646, found 333.0648. Anal. Calcd: C, 72.04; H, 4.53; N, 4.20; S, 19.23. Found: C, 71.91; H, 4.57; N, 3.83; S, 19.11.

Isolation of 3-Phenylthio-3-(*p*-tolylthio)-3*H*-indole (6). Following the same procedure, using a freshly prepared solution of *p*-toluenesulfenyl chloride (from *p*-tolyl disulfide and sulfuryl chloride), a 27% yield of **6** was obtained: mp 112−114 °C; ^{1}H NMR δ 2.30 (s, 3H), 7.11−7.16 (m, 3H), 7.20−7.25 (m, 5H), 7.28 (d, J = 6.4 Hz, 2H), 6.36 (m, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.88 (s, 1H); HRMS calcd for $C_{21}H_{17}NS_2$ 347.03802, found 347.0800. Anal. Calcd: C, 72.58; H, 4.93; N, 4.03; S, 18.45. Found: C, 72.20; H, 4.90; N, 3.99; S, 18.64.

Rearrangement of 5 to 2,3-Bis(phenylthio)indole (2a) and Isolation of 2,3,3-Tris(phenylthio)-3*H*-indole (17). Variable results were obtained in several experiments. The best yield of **17** was obtained in the following experiment. To a solution of 166.5 mg of **5** (0.5 mmol) in 1.5 mL of DMF at room temperature was added 1.25 mL of a 0.4 M solution of benzenesulfenyl chloride in 1,2-dichloroethane (0.5 mmol). The resulting yellow solution was stirred for 5 h and quenched with water. The mixture was partitioned between ether and water, and the crude product from the organic phase was chromatographed by eluting with a 1:9 mixture of ethyl acetate and hexane, affording 43 mg (19%) of trisulfide **17** as an off-white solid: mp 101−103 °C; ^{1}H NMR δ 7.05 (d, J = 7.2 Hz, 2H), 7.13−7.30 (m, 14H), 7.45 (m, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H); HRMS calcd for $C_{26}H_{19}NS_3$ 441.0680, found 441.0695. Anal. Calcd: C, 70.71; H, 4.34; N, 3.17; S, 21.78. Found: C, 70.39; H, 4.44; N, 3.08; S, 21.67. Further elution yielded 84 mg of the rearranged 2,3-bis(phenylthio)-indole **2a**[1] (50.5%) as a beige solid.

Reaction of 5 with *p*-Toluenesulfenyl Chloride. To a solution of 113 mg of **5** (0.4 mmol) in 1.5 mL of DMF at room temperature was added 1 mL of a 0.4 M solution of *p*-toluenesulfenyl chloride in 1,2-dichloroethane. The resulting yellow solution was stirred for 2.5 h, quenched with water, and then partitioned between ether and water. The crude product from the organic phase was chromatographed by eluting with a 1:9 mixture of ethyl acetate and hexane, and 101 mg of the major product was obtained as a yellow-brown syrup. The complex proton NMR spectrum (in acetone-d_6) contained four signals between 2.22 and 2.44 ppm, attributable

to methyl groups on tolyl residues. Mass spectral analysis of the mixture revealed signals indicating molecular masses of 347 (**11** and/or **12**) and 361 (**13**) as well as 333 (**2a**).

2-Phenylthio-3-(*p*-tolylthio)indole (12). To a solution of 225 mg of 2-phenylthioindole[12,13] (**14,** 1 mmol) in 2 mL of DMF at room temperature was added 2.2 mL of a 0.5 M solution of *p*-toluenesulfenyl chloride in 1,2-dichloroethane (1.1 mmol), and the mixture was stirred for 30 min. The dichloroethane was evaporated off and the residual solution was partitioned between ether and water. The crude organic product was chromatographed by eluting with a 1:5 mixture of ethyl acetate and hexane to afford 290 mg of **12** (84%) as a colorless syrup; ^{1}H NMR δ 2.21 (s, 3H), 6.99 (s, 4H), 7.11 (m, 1H), 7.18−7.29 (m, 6H), 7.45 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 7.9 Hz, 1H), 11.05 (br, NH). HRMS calcd for $C_{21}H_{17}NS_2$ 347.0802, found 347.0800. Anal. Calcd: C, 72.58; H, 4.93; N, 4.03. Found: C, 72.70; H, 4.91; N, 4.04.

2,3-Bis(*p*-tolylthio)indole (13). To a solution of 234 mg of indole (2 mmol) in 4 mL of DMF was added at 0 °C 10 mL of a 0.5 M solution of *p*-toluenesulfenyl chloride in 1,2-dichloroethane (5 mmol), and the resulting mixture was stirred at 0 °C for 30 min and then at room temperature for 18 h. The 1,2-dichloroethane was evaporated away and the residue was partitioned between ether and water. The crude organic product was chromatographed by eluting with a 1:5 mixture of ethyl acetate and hexane to afford 736 mg of **13** (quant) as a yellow syrup: ^{1}H NMR δ 2.24 (s, 3H), 2.29 (s, 3H), 7.01 (s, 4H), 7.11−7.14 (m, 3H), 7.20 (d, J = 8.2 Hz, 2H), 7.24 (dd, J = 8.2 and 1.1 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 11.0 (br, NH); HRMS calcd for $C_{22}H_{19}NS_2$ 361.0959, found 361.0964. Anal. Calcd: C, 73.09; H, 5.30; N, 3.87. Found: C, 73.01; H, 5.20; N, 3.82.

2-(*p*-Tolylthio)indole (15). To a solution of 450 mg of **13** (1.25 mmol) in 5 mL of trifluoroacetic acid was added 384 mg of thiosalicylic acid (2.5 mmol) and the suspension was stirred at 60 °C for 30 min. The TFA was evaporated away and the residue was stirred with ethyl acetate and 1 N aqueous NaOH. The organic phase was washed several times with water, dried, and evaporated. The residue was chromatographed by eluting with a 1:7 mixture of ethyl acetate and hexane to afford 275 mg of **15** (92%) as a white solid: mp 61−64 °C; ^{1}H NMR δ 2.29 (s, 3H), 6.79 (s, 1H), 7.07 (m, 1H), 7.14 (s, 4H), 7.17 (m, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 10.55 (br, NH); HRMS calcd for $C_{15}H_{13}NS$ 239.0769, found 239.0761. Anal. Calcd: C, 75.27; H, 5.47; N, 5.85; S, 13.40. Found: C, 74.94; H, 5.45; N, 5.64; S, 13.45.

3-Phenylthio-2-(*p*-tolylthio)indole (11). To a solution of 80 mg of **15** (0.33 mmol) in 1 mL of DMF was added at 0 °C 0.8 mL of a 0.5M solution of benzenesulfenyl chloride in 1,2-dichloroethane (0.4 mmol). The resulting solution was stirred at 0 °C for 5 min and then at room temperature for 1 h. The mixture was worked up as in the preparation of compound **12**, and the product was purified by chromatography, eluting with a 1:7 mixture of ethyl acetate and hexane to afford 93 mg of **11** (81%) as a light yellow syrup:

^{1}H NMR δ 2.28 (s, 3H), 7.01−7.15 (m, 6H), 7.18−7.27 (m, 5H), 7.47 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 11.05 (br, NH); HRMS calcd for $C_{21}H_{17}NS_2$ 347.0802, found 347.0807. Anal. Calcd: C, 72.58; H, 4.93; N, 4.03. Found: C, 72.56; H, 4.84; N, 3.97.

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