The above is in contrast with the $pK_a°$ lowering of 0.7 pK_a unit by the same substitution in the pyridinolyses of DNPA and DNPTA ($pK_a°$ = 7.3 and 6.6, respectively).[5b,8] This result was attributed to a greater "push" to expel the amine exerted by DNPO in $T^{\pm}$ compared to that by DNPS in the analogous $T^{\pm}$.[8] The discrepancy could be due to the higher instability of the $T^{\pm}$ formed in the trinitro derivatives in respect to the dinitro compounds, which results in a smaller sensitivity of the nature of the leaving group of the trinitro substrates on the rate of amine expulsion from $T^{\pm}$.

Apparently, there is also a small $pK_a°$ decrease in going from the reactions of alicyclic secondary amines with DNPA ($pK_a°$ = 9.1)[4] to the reactions of the same amines with DNPTA ($pK_a°$ = 8.9).[8,24] This is consistent with the fact that the $T^{\pm}$ intermediates formed with alicyclic amines are much more unstable than those formed with pyridines.[3,4,8]

The fact that a concerted process takes place in the reactions of alicyclic secondary amines with DNPTC,[9] whereas a stepwise mechanism seems to be operating in the pyridinolysis of TNPMC, is consistent with the finding that alicyclic amines are much better nucleofuges from $T^{\pm}$ than isobasic pyridines.[3,4,8] The "intermediate" formed in the thiocarbonate aminolysis would be so unstable that it would not have a finite lifetime due to the larger nucleofugality of the alicyclic amines compared to pyridines, in spite of the fact that $TNPO^-$ should leave $T^{\pm}$ faster than does $DNPS^-$ from the corresponding $T^{\pm}$.

The stepwise reactions of alicyclic secondary amines with DNPA[4] can be explained through stabilization of the $T^{\pm}$ formed in these reactions compared to the hypothetical "intermediate" in the same aminolysis of DNPTC.[9] This stabilization arises from two sources: (i) The replacement of DNPS by DNPO, which should result in a slower nucleofugality of $DNPO^-$ than $DNPS^-$ from the intermediates since the basicities of the anions are 4.1 and 3.4, respectively[8,17] (although this should be partly compensated by the faster leaving of aryloxide ions than isobasic arylthiolate ions).[22] (ii) The substitution of ethoxy by methyl as the "acyl" group in $T^{\pm}$, which should retard the leaving of both the amine and the aryloxide ion from the latter $T^{\pm}$, compared to the nucleofugalities of the amine and arylthiolate ion from the former $T^{\pm}$.[3,5,7,16,18,19]

In order to verify whether the substitution of alicyclic amines for pyridines produces a destabilization of $T^{\pm}$ and could enforce a concerted mechanism, we are at present investigating the reactions of alicyclic amines with the two substrates that are the subject of this study.

Acknowledgment. We thank "Fondo Nacional de Desarrollo Científico y Tecnológico" (FONDECYT) for financial support.

Registry No. 2,4,6-Trinitrophenyl acetate, 7614-96-2; 2,4,6-trinitrophenyl methyl carbonate, 138835-54-8; 3-cyanopyridine, 100-54-9; 4-cyanopyridine, 100-48-1; 3-chloropyridine, 626-60-8; 3-pyridinecarboxamide, 98-92-0; pyridine, 110-86-1; 3-methylpyridine, 108-99-6; 4-methylpyridine, 108-99-6; 3,4-dimethylpyridine, 583-58-4; 4-aminopyridine, 504-24-5; 4-(dimethylamino)pyridine, 1122-58-3; picric acid, 88-89-1; methyl chloroformate, 79-22-1.

Supplementary Material Available: Table S1 with the experimental conditions and k_{obsd} values of the reactions and ^1H ^{13}C NMR and IR data of TNPMC (5 pages). Ordering information is given on any current masthead page.

(24) Although this $pK_a°$ difference is within experimental error.

Acid-Catalyzed Isomerization of 3-Indolyl Sulfides to 2-Indolyl Sulfides: First Synthesis of 3-Unsubstituted 2-(Arylthio)indoles. Evidence for a Complex Intermolecular Process

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The acid-catalyzed isomerization of 3-indolyl sulfides **1** to the corresponding 2-indolyl sulfides **4** provides the first synthesis of 3-unsubstituted 2-(arylthio)indoles, a hitherto unattainable class of compounds. When catalyzed by trifluoroacetic acid, the isomerization proceeds mainly via an intermolecular mechanism involving initial disproportionation to a 2,3-indolyl bis-sulfide **5** and an unsubstituted counterpart **6** followed by further interaction of these species to yield the rearranged isomer **4**. A mechanism is proposed involving a role for the acid in the sulfenyl-transfer steps. This type of process also occurs, to a lesser extent, in the polyphosphoric acid catalyzed isomerization.

Introduction

Rearrangements of 3-(carbon-substituted) indoles to 2-substituted indoles under acidic conditions have been known since Fischer's work on the indole synthesis which bears his name,[1a] and a number of workers have reported examples since those pioneering years.[1b,c,e] The inverse isomerization of 2-acetylindoles to 3-acetylindoles has also been documented.[2] In all of these examples, the process has been shown to be intramolecular in nature,[1b-d,2] i.e., the migrating group shifts to the alternate position on the same molecule. An interesting sulfide migration was observed by Nagarajan et al.[3] upon cyclization of 3-(3-indolylthio)propionic acid **1a**: when P_2O_5 in refluxing

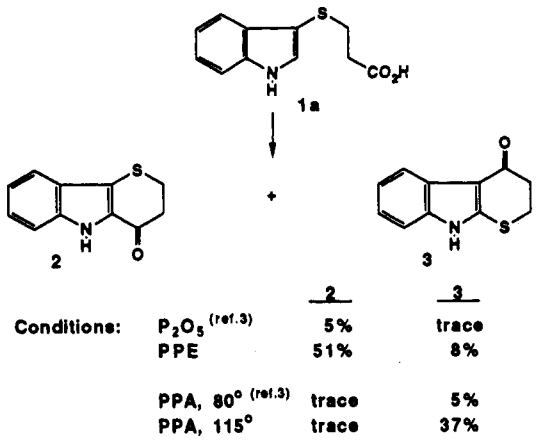
(1) (a) Fischer, E.; Schmitt, T., *Chem. Ber.* **1888**, *21*, 1071 and 1811. (b) Buu-Hoi, N. P.; Jacquignon, P. *Bull. Soc. Chim. Fr.* **1967**, *1104*. (c) Kost, A. N.; Budylin, V. A.; Matveeva, E. D.; Sterligov, D. O. *Zh. Org. Khim.* **1970**, *6*, 1503. (d) Jackson, A. H.; Smith, P. *Tetrahedron* **1968**, *24*, 2227. (e) Galons, H.; Girardeau, J. F.; Farnoux, C. C.; Miocque, M. *J. Heterocycl. Chem.* **1981**, *18*, 561.

(2) Chastrette, F. *Bull. Soc. Chim. Fr.* **1970**, 1151.

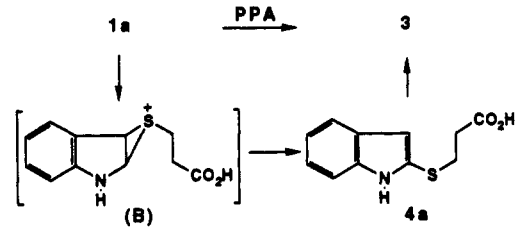
(3) Nagarajan, K.; Arya, V. P.; Parthasarathy, T. N.; Shenoy, S. J.; Shah, R. K.; Kulkarni, Y. S. *Ind. J. Chem.* **1981**, *20B*, 672.

0022-3263/92/1957-2694$03.00/0

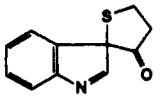
Scheme I



Scheme II



benzene was used as the cyclization medium, the expected ketone **2** (Scheme I) was obtained as the major cyclized product (ca. 5% yield); however, in polyphosphoric acid (PPA) at 80 °C, the major product (ca. 5% yield) was the isomeric ketone **3**, which they presumed was formed via a spiro intermediate (**A**). By performing the cyclization



(A)

of **1a** using polyphosphate ester (PPE) in $CHCl_3$ at room temperature, we were able to substantially increase the yield of **2** to 51% (along with 8% of **3**). We were also able to enhance the yield of **3** to 37% by raising the temperature of the PPA to 115 °C.

However, our interest was aroused when close monitoring of the latter reaction by TLC revealed the transient formation of an intermediate which, in a separate experiment done at a lower temperature (70 °C), was isolated in 15% yield. This substance was identified as 3-(2-indolylthio)propionic acid (**4a**) (Scheme II); on treatment of **4a** with PPE or PPA, the cyclized ketone **3** was obtained. We postulated that the formation of **3**, in PPA or PPE, could result from an initial isomerization of **1a** to **4a** which then cyclized to afford **3**. To explain this migration we proposed the formation of a transient episulfonium species **B**, which can open from the opposite side to afford the isomerized 2-indolyl sulfide **4a**.

As we were exploring the scope of this previously undocumented acid-catalyzed isomerization of 3-indolyl sulfides to 2-indolyl sulfides, Plate and Ottenheijm[4] reported on such a rearrangement catalyzed by trifluoroacetic acid (TFA) at room temperature. In their paper, the authors also suggested a putative episulfonium species as the intermediate in an intramolecular migration of the sulfide moiety.

(4) Plate, R.; Ottenheijm, H. C. J. *Tetrahedron* **1986**, *42*, 4511.

Scheme III

Table I. Acid-Catalyzed Isomerization of 3-Indolyl Sulfides to 2-Indolyl Sulfides

$$1 \xrightarrow[\text{or TFA, rt}]{\text{PPA, 100 °C}} 4$$

			yield (%) of 4[a]	
compd	R_1	R_2	PPA (h)	TFA (h)
b	H	Me	45 (1)	15 (2)[b]
c	H	Et	46 (1.5)	22 (3)[b]
d	H	$(CH_2)_2CO_2Me$	20 (1.5)	43 (2)
e	H	Ph	35 (1.5)	56 (4)
f	H	4-ClPh	66 (4)	67 (4)
g	H	2-MePh	32 (2)	69 (3)
h	H	4-MeOPh	39 (1)	47 (1.5)
i	H	3-NO_2Ph	85 (1.5)	38 (3)[c]
j	Me	Me	94 (3)	53 (72)
k	Me	Ph	69 (2.5)	91 (1.5)
l	CH_2Ph	Me	82 (2.5)	71 (18)
m	H	2-naphthyl	0 (1.5)[d]	67 (1.5)
n	Me	2-naphthyl	44 (1.5)[d]	87 (1.5)
o	H	1-naphthyl	17 (1)[d]	60 (1.5)
p	H	3-MeOPh	8 (0.5)[d]	53 (2.5)
q	H	2,5-Me_2Ph	31 (3.5)[d]	64 (2)

[a] Isolated yields. [b] Lit.[4] yield 85%. [c] Heating is required for this rearrangement to occur; after 3 h at reflux some **1i** remains, and further heating leads to decomposition. [d] In PPA a different type of isomerization leads to 2-(2-aminophenyl)benzothiophenes.[6]

However, upon performing a comparative study of the two methods of isomerization, we uncovered evidence of a complex, intermolecular mechanism for the transformation,[5] which is in contrast to the proposed intramolecular migration. We have explored the scope of this process, which provides the first synthesis of 3-unsubstituted 2-(arylthio)indoles, a previously unknown class of compounds.

Results and Discussion

Since we had applied our isomerization conditions (PPA, 100 °C) to a broader series of substrates than that of Plate and Ottenheijm,[4] we elected to perform a comparative study by submitting our substrates to the conditions described in their paper (TFA, rt). Either process (Scheme III) can be utilized to provide a variety of 2-(arylthio)-indoles in good to excellent yields. In particular, 3-unsubstituted 2-(arylthio)indoles, previously unknown, are easily obtained by this isomerization procedure. Examples representative of the scope of the process are listed in Table I. The table shows some notable differences in the yields of isomerized product depending on the method used. The two methods complement each other in that in several cases one method affords appreciably higher yields than the other. In cases where the arylthio moiety is electron-rich, a concomitant isomerization to 2-(2-aminophenyl)benzothiophenes can occur when PPA is used.[6]

As we were performing the TFA-catalyzed rearrangements, we unexpectedly uncovered evidence indicating that the isomerization actually occurs preferentially via a much more complex process than the simple intramolecular

(5) Hamel, P.; Girard, Y.; Atkinson, J. G. *J. Chem. Soc., Chem. Commun.* **1989**, 63.
(6) Hamel, P.; Girard, Y.; Atkinson, J. G.; Bernstein, M. A. *J. Chem. Soc., Chem. Commun.* **1990**, 1072.

Scheme IV

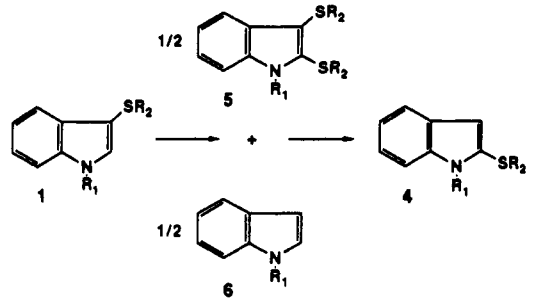


Table II. Stepwise Conversion of 1 to 4 in TFA at rt

Isolation of Disproportionation Products: 1 → 5 + 6					
compd	R_1	R_2	time (min)	%, 5[a]	% 6[a,b]
b	H	Me	5	25	c
e	H	Ph	4	69	55
j	Me	Me	2	63	74
k	Me	Ph	4	85	72
Recombination of Disproportionation Products: 5 + 6 → 4					
compd	R_1	R_2	time (h)	% 4[d]	
b	H	Me	40	19	
e	H	Ph	3.5	67	
j	Me	Me	24	52	
k	Me	Ph	18	86	

[a] Yield based on 0.5 molecule expected. [b] As mixture of monomer and dimer. [c] Monomer and dimer detected by TLC in complex reaction mixture. [d] Yield based on two molecules of 4 expected.

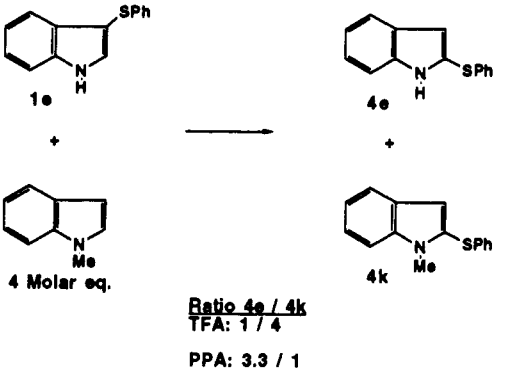
migration of the sulfide fragment as suggested by Plate and Ottenheijm.[4]

Thus, in all the cases studied, TLC monitoring of the rearrangement in TFA revealed the following surprising sequence of events: there was initial rapid (~minutes) disappearance of the starting 3-indolyl sulfide **1** with formation of an intermediate species which was subsequently transformed in a slower process to the isomerized indolyl sulfide **4** (Scheme IV). Rapid quenching of several reaction mixtures allowed the isolation and characterization of these intermediate entities, which were shown to be 2,3-indolyl bis-sulfides **5**. The formation of such species suggested that a disproportionation had occurred, and thus a nonsubstituted counterpart was sought. Indoles that have no substituent in the 2- and 3-positions are known to suffer reversible dimerization in strongly acidic media,[7] and indeed these "hidden" indoles were subsequently isolated from several of our reaction mixtures and characterized. The top half of Table II demonstrates how rapid quenching of the TFA reaction leads to the isolation of the two components resulting from the disproportionation step.

The following experiment led us to understand the subsequent events. When equimolar mixtures of 2,3-indolyl bis-sulfides **5** and the corresponding 2,3-unsubstituted counterparts **6** were stirred in TFA at room temperature, 3-unsubstituted 2-indolyl sulfides **4** were isolated in yields that indicated that interaction had occurred between the two components to afford *two* molar equivalents of **4**. The lower half of Table II lists four examples of such provoked interactions in TFA. The low yields of **5b** and **4b** in this table are compatible with the overall yield of **4b** reported in Table I for the rearrangement in TFA. Bis-sulfides **5** submitted to the same conditions in the absence of the corresponding **6** afford much lower yields of **4** after much longer reaction times.

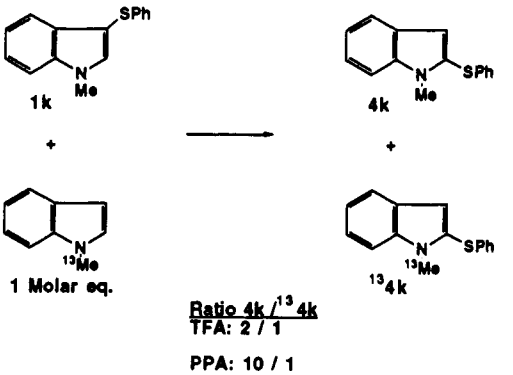
(7) For a review of indole dimerization see: Smith, G. G. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R.; Ed.; Academic Press: New York, 1963; Vol. 2, pp 300–309.

Scheme V. Crossover Experiments[a]



[a] Conditions: TFA, rt, 2 h; PPA, 100 °C, 1.5 h.

Scheme VI. Crossover Experiments[a]



[a] Conditions: TFA, rt, 2 h; PPA, 100 °C, 1.5 h.

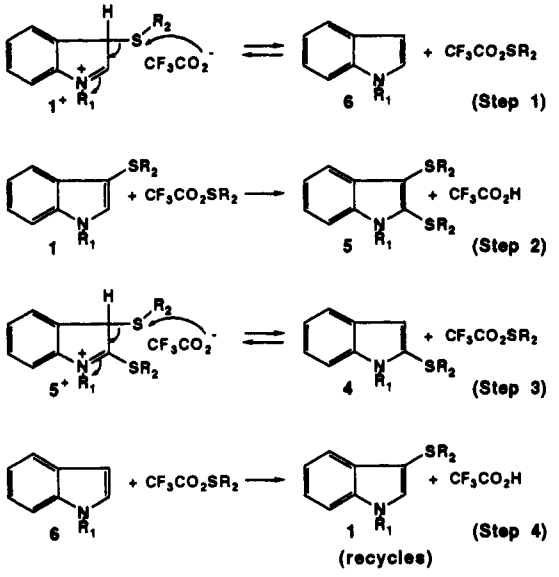
These data strongly refute the proposal of an exclusive intramolecular shift for the isomerization. Indeed, the process appears to be mostly intermolecular in nature, with the major pathway of the reaction occurring as outlined in Scheme IV.

The major difference in rates of the two steps of the isomerization in TFA allowed us to observe that the species **5** and **6** are indeed intermediates in the process. In the PPA-catalyzed isomerization, there is not such a marked difference in the reaction rates, and the 2,3-disubstituted species **5** did not stand out as distinct intermediates, although minor amounts of **5** were isolated as side-products of the reaction in all cases, lending support to the proposal that similar events occur in the PPA-catalyzed process.

A striking demonstration of the bimolecularity of the process was provided by the experiment outlined in Scheme V. When a 1:4 molar ratio of **1e** and *N*-methylindole was stirred in TFA at room temperature for 2 h, a mixture of **4e** and **4k** in a ratio of 1:4 (overall yield 48%) was obtained, thus demonstrating that a crossover process had indeed occurred. A similar crossover experiment performed in PPA at 100 °C for 1.5 h led to an opposite ratio of **4e**/**4k** (3.3:1). Scheme VI shows a more rigorous crossover experiment in which the sulfenyl-donating indole and the sulfenyl-receiving indole share the same N-substituent differentiated only by a ^{13}C isotope label. In TFA, there is once again extensive intermolecular transfer of the sulfenyl group, whereas in PPA a majority of the isomerization appears to be intramolecular.

These experiments indicate clearly that the major pathway for the rearrangement of **1** to **4** in TFA involves the disproportionation shown in Scheme IV rather than a simple migration of the sulfide moiety within the same

Scheme VII. Proposed Mechanism



molecule. An opposite scenario appears to prevail in the PPA-catalyzed isomerization; the higher viscosity of the PPA reaction medium may be a factor which disfavors intermolecular interactions.

The overall process involves two successive sulfenyl transfers: an initial transfer accounts for the disproportionation step; the subsequent process most likely involves a selective desulfenylation of the disubstituted species **5** at position 3 to afford the end product **4**, with the unsubstituted indole **6** acting as the recipient of the lost sulfenyl moiety which would be expected to enter in the most reactive 3-position to regenerate **1** which is recycled through the process.

In control experiments, several end-products **4** were recovered unchanged after 24 h at room temperature in TFA, thus demonstrating that the isomerized product behaves as the "sink" of the process. As pointed out by Chastrette,[2] in such an acid-catalyzed rearrangement, the equilibrium favors the side of the most basic indole isomer. In the case of alkyl-, aryl-, and the present sulfenyl-substituted indoles, this would be the 2-isomer;[15] in the case of acyl substituents, Chastrette has shown that the 3-isomer (obtained by acid-catalyzed isomerization of the 2-isomer) is more basic than the 2-isomer.

Scheme VII outlines the mechanism which we favor as an explanation for the overall process in TFA. In an initial event (step 1), the indolenium cation resulting from protonation of the 3-indolyl sulfide (1^+) suffers attack by trifluoroacetate anion, leading to desulfenylation and formation of an unsubstituted indole **6**, with concomitant generation of an acyloxy sulfide. Such substances have been described, and their sulfenylating properties have been demonstrated.[8] This acyloxy sulfide sulfenylates (step 2) the nonprotonated **1** to afford the 2,3-disubstituted **5** via direct introduction into the 2-position or 3,3-disubstitution followed by migration.[9] As mentioned previously, this initial disproportionation step is quite rapid. Once formed, the disubstituted species **5** also can be protonated and as such suffer desulfenylation through the action of trifluoroacetate anion (step 3), leading to the formation of the 2-indolyl sulfide **4**, and again generation of an acyloxy sulfide. Although the 2-indolyl sulfide **4** is susceptible to sulfenylation, the acyloxy sulfide can be trapped by unsubstituted indole **6** to regenerate starting 3-indolyl sulfide **1** (step 4) which is recycled through the whole process until the transformation to **4** is complete.

By analogy, such a process occurring in PPA calls for the generation of putative phosphorous analogues of acyloxy sulfides [$(HO)_2P(O)O$–SR_2]. Although there is no precedent for such substances in the literature, our experimental results strongly suggest their existence.

That the nonprotonated indoles **1** and **6** could conceivably act as the nucleophile responsible for the desulfenylation steps, by direct attack on the protonated forms of **1** and **5**, respectively, cannot be completely ruled out. However, we have further indirect evidence of the formation of acyloxy or phosphoryloxy sulfides. Acyloxy sulfides have been shown to degrade to the corresponding disulfides,[8] presumably by a thermal free-radical sequence. In the experiments described above, where bis-sulfides **5** were stirred in TFA in the absence of the corresponding **6**, a slow process led to low yields of **4** but near-quantitative yields of the corresponding disulfides were obtained. Under these conditions, although the equilibrium of the reaction strongly disfavors the desulfenylation, the eventual decomposition of the acyloxy sulfides leads to the slow formation of **4** and disulfides. When the 2,3-unsubstituted **6** are present, they trap the acyloxy sulfide, thus greatly accelerating the overall process. In all the examples listed in Table I, in either PPA or TFA, detectable quantities of disulfides were produced, which could originate from decomposition of the acyloxy or phosphoryloxy sulfides.

The strength of the acid appears to be a determining factor in the isomerization process. Acetic acid appears too weak to cause protonation of the indole and thus no reaction occurs after 20 h at room temperature. In contrast, methanesulfonic acid and trifluoromethanesulfonic acid lead to rapid disproportionation, but no 2-indolyl sulfide is formed on further reaction at room temperature possibly due to excessive decomposition of the unsubstituted indole. In a substrate-related observation, it was found that the *N*-acetyl derivative of **1b** was unchanged after several hours in TFA, reflecting the reduced basicity of the indole nucleus.

Conclusion

The acid-catalyzed isomerization of 3-indolyl sulfides is a general, efficient process affording 3-unsubstituted 2-indolyl sulfides in good to excellent yields, and in particular, it provides access to the previously unknown 3-unsubstituted 2-(arylthio)indoles. Our data clearly demonstrate that the isomerization does not proceed solely via an intramolecular migration of the sulfide moiety. Indeed, in TFA the major pathway involves an initial disproportionation to a 2,3-disubstituted species and a 2,3-unsubstituted counterpart, followed by subsequent sulfenyl transfer to afford the isomerized product. This type of sequence occurs to a lesser extent in the PPA-catalyzed isomerization.

Experimental Section

All reactions were carried out under N_2 atmosphere, although this may not be necessary. Reagents and solvents of commercial sources were used without further purification or drying. Melting points were recorded using a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 681 spectrophotometer, while a Bruker AM 250 instrument afforded 250-MHz proton NMR data which are reported in ppm relative to TMS. Elemental

(8) (a) Barton, D. H. R.; Nakano, T.; Sammes, P. G. *J. Chem. Soc. C* **1968**, *322*. (b) Morishita, T.; Furukawa, N.; Oae, S. *Tetrahedron* **1981**, *37*, 3115. (c) Haas, A.; Lieb, M.; Zhang, Y. *J. Fluorine Chem.* **1985**, *29*, 297.

(9) Plate, R.; Nivard, R. J. F.; Ottenheijm, H. C. J. *Tetrahedron* **1986**, *42*, 4503.

analyses were performed by Guelph Chemical Laboratories Ltd, Guelph, Ontario.

Cyclization of 3-(3-indolylthio)propionic acid (1a): 2,3,4,5-tetrahydrothiopyrano[3,2-*b*]indol-4-one (2) and 2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indol-4-one (3).

A. In PPE. To a solution of 120 g of PPE[16] in 120 mL of $CHCl_3$ was added 12 g of **1a**,[3] and the mixture was stirred at room temperature for 1 h. It was then poured onto 1.2-L of ice-cold water and extracted four times with ether. The combined organic extracts were washed 4 times with water, dried, and evaporated. The residue was triturated with CH_2Cl_2 and filtered to afford 1.72 g of **2** as a tan solid. Chromatography of the filtrate material on silica gel, eluting with 5% EtOAc in CH_2Cl_2, afforded a further 3.91 g of **2** for a total of 5.63 g (51%), mp 150–152 °C (lit.[3] 147 °C). There was also obtained 865 mg of **3** (8%).

B. In PPA. To 30 g of PPA (Aldrich) preheated to 115 °C was added 1 g of **1a**, and the mixture was stirred for 15 min and then allowed to cool down. The mixture was triturated with 300 mL of water and extracted three times with ethyl acetate. The combined extracts were washed several times with water, dried, and evaporated to a residue which was triturated with ether and filtered. This crude solid was chromatographed on silica gel, eluting with a 1:1 mixture of ethyl acetate and hexane, to afford 347 mg of **3** (37%) as a beige solid, mp 220–221 °C (lit.[3] mp 228 °C).

A trace of **2** was detected in the crude product but it was not isolated.

C. Isolation of 3-(2-Indolylthio)propionic Acid (4a). To 60 g of PPA preheated to 70 °C was added 1.5 g of **1a**, and the mixture was stirred for 30 min. After being cooled, the mixture was triturated with ice-cold water and extracted three times with ether. These combined extracts were washed three times with water and then extracted three times with 10% aqueous $NaHCO_3$. The aqueous basic extracts were washed with EtOAc and then acidified with 1 N aqueous HCl and extracted twice with ether to afford 550 mg of an oil which solidified. This crude **4a** was esterified with ethereal CH_2N_2, and the mixture was chromatographed on silica gel, eluting with 10% EtOAc in hexane, to afford 245 mg of methyl ester **4d** (15% overall).

This ester was hydrolyzed at room temperature in a mixture of 5 mL of MeOH and 5 mL of 1 N aqueous NaOH for 1 h. Usual workup afforded **4a** as a straw colored solid, mp 115–117 °C: IR (KBr) 3370 (NH), 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.68 and 3.04 (2t, $2CH_2$), 6.69 (s, H_3), 7.11 and 7.22 (2t, H_5 and H_6), 7.34 (d, J = 8 Hz, H_7), 7.57 (d, J = 7.6 Hz, H_4), 8.32 (br, NH). Anal. Calcd for $C_{11}H_{11}NO_2S$: C, 59.70; H, 5.01; N, 6.33; S, 14.49. Found: C, 59.97; H, 5.07; N, 6.29; S, 14.34.

Cyclization of 4a. In PPE. To a solution of 2 mL of PPE and 2 mL of $CHCl_3$ was added 150 mg of **4a**, and the mixture was stirred at room temperature for 1.5 h. Quenching with water, extraction with EtOAc, and chromatography afforded 54 mg of **3** (39%).

In PPA. To 10 g of PPA preheated to 85 °C was added 150 mg of **4a**, and the mixture was stirred for 1 h. Usual workup and chromatography afforded 40 mg of **3** (29%).

Starting Materials. 3-Indolyl sulfides 1b,[10] c,[10] e–i,[11] k,[12] m,[10] and p[10] were prepared by published procedures.

Methyl 3-(3-indolylthio)propionate (1d) was obtained by esterification (CH_2N_2) of the corresponding acid **1a**:[3] mp 45–46 °C (toluene–hexane); IR (KBr) 3390 (NH), 1729 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.55 (t, J = 7.4 Hz, CH_2), 2.93 (t, J = 7.3 Hz, CH_2), 3.63 (s, CH_3), 7.2–7.4 (m, 4 H, arom), 7.77 (d, J = 7.8 Hz, H_4), 8.36 (br, NH). Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95; S, 13.63. Found: C, 61.38; H, 5.55; N, 5.89; S, 13.64.

1-Methyl-3-(methylthio)indole (1j) was prepared in 93% yield by N-methylation of **1b** using NaH/MeI in DMF. The compound is an oil: ^1H NMR ($CDCl_3$) δ 2.35 and 3.77 (2s, $2CH_3$), 7.17 (s, H_2), 7.19–7.32 (m, 3 H, arom), 7.76 (d, J = 7 Hz, H_4). Anal. Calcd for $C_{10}H_{11}NS$: C, 67.75; H, 6.26; N, 7.90; S, 18.09. Found: C, 67.85; H, 6.30; N, 8.20; S, 17.73.

1-Benzyl-3-(methylthio)indole (1l) was prepared similarly from **1b** using benzyl bromide: mp 93–94 °C; ^1H NMR ($CDCl_3$) δ 2.37 (s, CH_3), 5.29 (s, CH_2), 7.14–7.30 (m, 9 H, arom), 7.78 (d, J = 7.5 Hz, H_4). Anal. Calcd for $C_{16}H_{15}NS$: C, 75.84; H, 5.97; N, 5.53; S, 12.66. Found: C, 75.69; H, 5.92; N, 5.52; S, 12.75.

1-Methyl-3-(2-naphthylthio)indole (1n) was obtained in 89% yield by treatment of **1m** with MeI using NaH in DMF: mp 129–131 °C; IR (KBr) 1618, 1572, 1508, 1496 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.89 (s, CH_3), 7.13 (m, 1 H, arom), 7.25–7.48 (m, 7 H, arom), 7.55–7.74 (m, 4 H, arom). Anal. Calcd for $C_{19}H_{15}NS$: C, 78.85; H, 5.22; N, 4.84; S, 11.08. Found: C, 78.83; H, 5.36; N, 4.80; S, 11.15.

3-(1-Naphthylthio)indole (1o) was prepared by the procedure described in ref 11: mp 91–3 °C (Et_2O–hexane); IR (KBr) 3420 (NH) 1505, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.95 (dd, J = 1 and 7.5 Hz, 1 H, arom), 7.15 (m, 2 H, arom), 7.27 (m, 1 H, arom), 7.44–7.60 (m, 6 H, arom), 7.83 (d, J = 7.6 Hz, H_4), 8.46 (d, J = 8.4 Hz, 1 H, arom), 8.48 (br, NH). Anal. Calcd for $C_{18}H_{13}NS$: C, 78.51; H, 4.76; N, 5.09; S, 11.65. Found: C, 78.60; H, 5.08; N, 5.14; S, 11.52.

3-[(2,5-Dimethylphenyl)thio]indole (1q) was prepared in the same manner: mp 75–77 °C (ether–hexane); IR (KBr) 3400 (NH) 1592, 1452 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 and 2.45 (2s, $2CH_3$), 6.56 (s, 1 H, arom), 6.78 (d, J = 7.5 Hz, 1 H, arom), 7.02 (d, J = 7.6 Hz, 1 H, arom), 7.16 (m, 1 H, arom), 7.27 (m, 1 H, arom), 7.45 (m, 2 H, arom), 7.60 (d, J = 8.3 Hz, H_4), 8.45 (br, NH). Anal. Calcd for $C_{16}H_{15}NS$: C, 75.84; H, 5.97; N, 5.53; S, 12.66. Found: C, 76.07; H, 5.89; N, 5.68; S, 12.79.

Representative Examples of Isomerization of 3-Indolyl Sulfides to 2-Indolyl Sulfides. Isomerization of 3-(Phenylthio)indole (1e) to 2-(Phenylthio)indole (4e) in PPA. To 40 g of PPA (Aldrich) preheated to 100 °C was added 800 mg of **1e**, and the mixture was stirred at 100 °C for 1.5 h. After being cooled, the mixture was triturated with water and the resulting solid filtered. This crude material was chromatographed on a column of silica gel, eluting with a 5:1 mixture of hexane and ethyl acetate to afford 112 mg of diphenyl disulfide and 286 mg (35%) of **4e**. Crystallized from hexane as white needles: mp 74–76 °C; IR (KBr) 3410 (NH), 1435 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.95 (d, J = 1.2 Hz, H_3), 7.18–7.35 (m, 7 H, arom), 7.40 (d, J = 7.8 Hz, H_7), 7.70 (d, J = 7.9 Hz, H_4), 8.17 (br, NH). Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22; S, 14.23. Found: C, 74.74; H, 4.68; N, 6.25; S, 14.28.

Also obtained was 60 mg of 2,3-bis(phenylthio)indole (**5e**).[14]

Isomerization of 1e to 4e in TFA. A mixture of 675 mg of **1e** in 6 mL of TFA was stirred at room temperature for 4 h; the TFA was evaporated away without applying heat, and the residue was dissolved in ether; the solution was washed several times with water, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a column of silica gel, eluting with a 9:1 mixture of hexane/ethyl acetate to afford 80 mg of diphenyl disulfide and 383 mg of **4e** (56%).

Characterization Data on Other 2-Indolyl Sulfides. 4b,[4] c,[4] j,[13] and l[13] conform with published results.

Methyl 3-(2-indolylthio)propionate (4d): mp 41–43 °C; IR (neat on NaCl disk) 3380 (NH), 1730 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65 and 3.05 (2t, $(CH_2)_2$), 3.69 (s, CH_3), 6.68 (s, H_3), 7.10 and 7.20 (2t, J = 7 Hz, H_5 and H_6), 7.34 (d, J = 8 Hz, H_7), 7.56 (d, J = 7.7 Hz, H_4), 8.44 (br, NH). Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95; S, 13.63. Found: C, 60.94; H, 5.38; N, 5.75; S, 13.74.

2-[(4-Chlorophenyl)thio]indole (4f): mp 105–106 °C (ether–hexane); IR (KBr) 3380 (NH) 1471 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.87 (s, H_3), 7.06–7.27 (m, 6 H, arom), 7.32 (d, J = 8.0 Hz, H_7), 7.62 (d, J = 7.8 Hz, H_4), 8.10 (br, NH). Anal. Calcd for $C_{14}H_{10}ClNS$: C, 64.73; H, 3.88; N, 5.39; S, 12.35; Cl, 13.65. Found: C, 65.01; H, 4.13; N, 5.62; S, 12.32; Cl, 13.59.

2-[(2-Methylphenyl)thio]indole (4g): mp 105–106 °C (ether–hexane); IR (KBr) 3401 (NH), 1582 cm^{-1}; ^1H NMR ($CDCl_3$)

(10) Tomika, K.; Terada, A.; Tachikura, R. *Heterocycles* **1976**, *4*, 729.
(11) Atkinson, J. G.; Hamel, P.; Girard, Y. *Synthesis* **1988**, 480.
(12) Jackson, A. H.; Johnston, D. N.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1024.
(13) Baudin, J.-B.; Bekhazi, M.; Julia, S. A.; Ruel, O. *Synthesis* **1985**, 956.
(14) Anzai, K. *J. Heterocycl. Chem.* **1979**, *16*, 567.
(15) (a) Hinman, R. L.; Lang, J. *J. Am. Chem. Soc.* **1964**, *86*, 3796. (b) Jackson, A. H.; Smith, A. E. *J. Chem. Soc.* **1964**, 5510.
(16) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley and Sons: New York, 1967; Vol. 1, p 892.

δ 2.42 (s, CH_3), 6.83 (s, H_3), 6.91 (d, J = 7.7 Hz, 1 H, arom), 6.99–7.25 (m, 5 H, arom), 7.31 (d, J = 8 Hz, H_7), 7.61 (d, J = 8 Hz, H_4), 8.05 (br, NH). Anal. Calcd for $C_{15}H_{13}NS$: C, 75.27; H, 5.47; N, 5.85; S, 13.40. Found: C, 75.39; H, 5.67; N, 5.85; S, 13.47.

2-[(4-Methoxyphenyl)thio]indole (4h): mp 68–70 °C (hexane); IR (KBr) 3438 (NH), 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (s, CH_3), 6.75 (s, H_3), 6.82 (dd, J = 6.8 and 2.0 Hz, 2 H, arom), 7.07–7.30 (m, 5 H, arom), 7.58 (d, J = 7.7 Hz, H_4), 8.02 (br, NH). Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.56. Found: C, 70.86; H, 5.36; N, 5.52; S, 12.76.

2-[(3-Nitrophenyl)thio]indole (4i): mp 96–98 °C; IR (KBr) 3390 (NH), 1522 and 1345 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.97 (d, J = 2 Hz, H_3), 7.15–7.39 (m, 5 H, arom), 7.67 (d, J = 8 Hz, H_4), 7.97 (m, 1 H, arom), 8.02 (s, 1 H, H_2[1]), 8.19 (br, NH). Anal. Calcd for $C_{14}H_{10}N_2O_2S$: C, 62.20; H, 3.73; N, 10.37; S, 11.86. Found: C, 62.06; H, 3.79; N, 10.23; S, 11.85.

1-Methyl-2-(phenylthio)indole (4k): mp 71–73 °C (hexane); IR (KBr) 2940, 1462 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69 (s, CH_3), 6.95 (s, H_3), 7.03–7.34 (m, 8 H, arom), 7.49 (d, J = 7.9 Hz, H_4). Anal. Calcd for $C_{15}H_{13}NS$: C, 75.27; H, 5.47; N, 5.85; S, 13.40. Found: C, 75.22; H, 5.74; N, 6.03; S, 13.46.

2-(2-Naphthylthio)indole (4m): mp 117–119 °C (hexane); IR (KBr) 3400 (NH) 1445, 1337 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.92 (s, H_3), 7.12–7.34 (m, 4 H, arom), 7.43 (m, 2 H, arom), 7.64–7.79 (m, 5 H, arom), 8.15 (br, NH). Anal. Calcd for $C_{18}H_{13}NS$: C, 78.51; H, 4.76; N, 5.09; S, 11.65. Found: C, 78.66; H, 5.06; N, 5.00; S, 11.63.

1-Methyl-2-(2-naphthylthio)indole (4n): mp 85–87 °C (hexane); IR (KBr) 1450, 1319 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69 (s, CH_3), 7.01 (s, H_3), 7.14–7.48 (m, 7 H, arom), 7.62–7.73 (m, 4 H, arom). Anal. Calcd for $C_{19}H_{15}NS$: C, 78.85; H, 5.22; N, 4.84; S, 11.08. Found: C, 79.02; H, 5.41; N, 4.85; S, 11.18.

2-(1-Naphthylthio)indole (4o): mp 96–98 °C (ether–hexane); IR (KBr) 3380 (NH), 1340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.88 (s, H_3), 7.09–7.35 (m, 5 H, arom), 7.57 (m, 3 H, arom), 7.73 (dd, J = 2 and 7 Hz, 1 H, arom), 7.86 (dd, J = 2 and 7 Hz, 1 H, arom), 8.15 (br, NH), 8.41 (d, J = 7.8 Hz, 1 H, arom). Anal. Calcd for $C_{18}H_{13}NS$: C, 78.51; H, 4.76; N, 5.09; S, 11.65. Found: C, 78.73; H, 4.85; N, 5.17; S, 11.45.

2-[(3-Methoxyphenyl)thio]indole (4p): mp 71–73 °C; IR (KBr) 3380 (NH) 1588, 1472 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (s, CH_3), 6.72 (m, 3 H, arom), 6.87 (s, H_3), 7.11–7.34 (m, 4 H, arom), 7.63 (d, J = 8 Hz, H_4), 8.12 (br, NH). Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.56. Found: C, 70.50; H, 5.09; N, 5.46; S, 12.51.

2-[(2,5-Dimethylphenyl)thio]indole (4q): mp 126–128 °C; IR (KBr) 3380 (NH) 1478, 1432 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 and 2.38 (2s, $2CH_3$), 6.80 (m, 2 H, 1 arom and H_3), 6.85 (d, J = 7.6 Hz, 1 H, arom), 7.05–7.26 (m, 4 H, arom), 7.61 (d, J = 7.7 Hz, H_4), 8.05 (br, NH). Anal. Calcd for $C_{16}H_{15}NS$: C, 75.84; H, 5.97; N, 5.53; S, 12.66. Found: C, 75.88; H, 6.14; N, 5.45; S, 12.53.

Typical Isolation of Disproportionation Products: Disproportionation of 1-Methyl-3-(phenylthio)indole in TFA. To 15 mL of TFA was added 717 mg of 1-methyl-3-(phenylthio)indole (**1k**), and the mixture was stirred at room temperature for 4 min and then quenched with 100 mL of water. The mixture was extracted twice with ether, and the extracts were washed twice with water, with aqueous $NaHCO_3$ until the washings were slightly basic, and then with water and dried over Na_2SO_4. The crude product from evaporation of this organic phase was chromatographed on a column of silica gel eluting with a 25:1 mixture of hexane and ethyl acetate to afford 59 mg of 1-methyl-2-(phenylthio)indole (**4k**), 89 mg of *N*-methylindole, and 444 mg of 1-methyl-2,3-bis(phenylthio)indole (**5k**) (85%). **5k** was crystallized from ether–hexane as cream prisms, mp 107–108 °C (lit.[12] mp 107 °C).

There was also obtained 53 mg of the dimer of *N*-methylindole. Total yield of *N*-methylindole and its dimer was 72%.

2,3-Bis(phenylthio)indole (5e) was prepared as described[14] for comparison. Other 2,3-indolyl bis-sulfides were synthesized as follows to provide authentic samples.

2,3-Bis(methylthio)indole (5b). To a solution of dimethyl disulfide (1.13 g, 12 mmol) in 1,2-dichloroethane (20 mL) at rt was added sulfuryl chloride (1.49 g, 11 mmol), and the resulting yellow solution, after stirring for 20 min, was added dropwise to a cooled (0 °C) solution of indole (1.17 g, 10 mmol) in DMF (15 mL). After 45 min at 0 °C, the mixture was quenched with water. The dichloroethane was evaporated off and the residue partitioned between H_2O–ether. The crude product from the organic phase was chromatographed on silica gel, eluting with 1:5 ethyl acetate–hexane, to afford **5b** (1.7 g, 81%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 2.36 and 2.52 (2s, $2CH_3$), 7.15–7.33 (m, 3 H, arom), 7.71 (d, J = 7.6 Hz, H_4), 8.32 (br, NH). Anal. Calcd for $C_{10}H_{11}NS_2$: C, 57.37; H, 5.30; N, 6.69; S, 30.64. Found: C, 57.30; H, 5.25; N, 6.96; S, 30.32.

1-Methyl-2,3-bis(methylthio)indole (5j) was obtained in 84% yield by *N*-methylation of **5b** using NaH/MeI in DMF. The compound was an oil: ^1H NMR ($CDCl_3$) δ 2.36 and 2.38 (2s, $2CH_3$), 3.84 (s, CH_3), 7.14–7.28 (m, 3 H, arom), 7.75 (d, J = 7.9 Hz, H_4). Anal. Calcd for $C_{11}H_{13}NS_2$: C, 59.18; H, 5.87; N, 6.28; S, 28.67. Found: C, 59.58, H, 5.82; N, 6.60; S, 28.72.

Typical Recombination of Disproportionation Products in TFA: 4k from 5k and *N*-Methylindole. A mixture of 87 mg (0.25 mmol) of 1-methyl-2,3-bis(phenylthio)indole (**5k**) and 33 mg of *N*-methylindole (0.25 mmol) in 2.5 mL of TFA was stirred at room temperature. By TLC it was seen that *N*-methylindole was rapidly transformed into the corresponding dimer. After being stirred at room temperature overnight (18 h), the mixture was quenched with 20 mL of water and extracted twice with ether. These extracts were washed with water, 0.5 N NaOH, and then water, dried over Na_2SO_4, and evaporated to a residue which on chromatography on silica gel, eluting with a 19:1 mixture of hexane–ethyl acetate, afforded 103 mg of 1-methyl-2-(phenylthio)indole (**4k**) (86%).

Crossover Experiments in TFA. (A) To a solution of 524 mg of *N*-methylindole (4 mmol) in 5 mL TFA at rt was added 225 mg of 3-(phenylthio)indole (**1e**) (1 mmol), and the mixture was stirred at rt for 2 h. The TFA was evaporated (bath temperature ~30 °C), and the residue was dissolved in ether; the solution was washed with water, aqueous $NaHCO_3$ and again water, dried over Na_2SO_4, and evaporated to a residue which was chromatographed on silica gel, eluting with a 3:1 mixture of hexane–toluene to afford 92 mg of 1-methyl-2-(phenylthio)indole (**4k**) (38.5%) and 22 mg of 2-(phenylthio)indole (**4e**) (9.8%) for a molar ratio (**4e**/**4k**) of 1:4.

(B) *N*-[^{13}C]Methylindole was prepared from indole and [^{13}C]methyl iodide (99.3% enriched) using NaH in DMF. When a 1:1 molar mixture of **1k** and *N*-[^{13}C]methylindole was stirred in TFA at room temperature for 2 h and then worked up as above, ^1H NMR analysis of the **4k** obtained (74% yield) showed a $^{12}C/^{13}C$ ratio of 2:1 while the recovered *N*-methylindole had a $^{12}C/^{13}C$ ratio of 1:1.

Crossover Experiments in PPA. (A) To 25 g of PPA (Aldrich) preheated to 100 °C was added 1.048 g of *N*-methylindole (8 mmol) and 450 mg of 3-(phenylthio)indole (**1e**) (2 mmol). The mixture was stirred at 100 °C for 1.5 h and then cooled. It was triturated with water and extracted three times with ethyl acetate. These extracts were washed three times with water, dried over Na_2SO_4, and evaporated to a residue which was chromatographed on silica gel, eluting with a 3:1 mixture of hexane/toluene to afford 203 mg of 2-(phenylthio)indole (**4e**) (45%) and 66 mg of 1-methyl-2-(phenylthio)indole (**4k**) (13.8%) for a **4e**/**4k** ratio of 3.3:1.

(B) When a 1:1 molar ratio of **1k** and *N*-[^{13}C]methylindole was stirred in PPA at 100 °C for 1.5 h and worked up as above, ^1H NMR analysis of the **4k** obtained (61% yield) showed a $^{12}C/^{13}C$ ratio of 10:1 and the recovered *N*-methylindole had a $^{12}C/^{13}C$ ratio of 1:2.

Registry No. **1a**, 80412-20-0; **1b**, 40015-10-9; **1c**, 1484-16-8; **1d**, 139461-60-2; **1e**, 54491-43-9; **1f**, 32884-73-4; **1g**, 116757-18-7; **1h**, 116757-20-1; **1i**, 72496-79-8; **1j**, 116442-14-9; **1k**, 63955-67-9; **1l**, 139461-61-3; **1m**, 116757-22-3; **1n**, 130128-84-6; **1o**, 139461-62-4; **1p**, 116757-19-8; **1q**, 130128-85-7; **2**, 105532-78-3; **3**, 80412-21-1; **4a**, 139461-63-5; **4b**, 13637-43-9; **4c**, 15936-38-6; **4d**, 139461-64-6; **4e**, 120517-31-9; **4f**, 139493-28-0; **4g**, 139461-65-7; **4h**, 139461-66-8; **4i**, 139461-67-9; **4j**, 13637-44-0; **4k**, 120517-32-0; **4l**, 104501-77-1; **4m**, 130128-87-9; **4n**, 130128-89-1; **4o**, 130128-91-5; **4p**, 130128-93-7; **4q**, 130128-96-0; **5b**, 120517-33-1; **5e**, 70291-88-2; **5j**, 120517-34-2; **5k**, 63955-64-6; **6e**, 120-72-9; **6j**, 603-76-9.