Cyclization of 2- and 3-Indolylthioalkanoic Acids to Novel Indole-containing Tricyclic Ring Systems

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A series of 2- and 3-indolylthioalkanoic acids of various chain lengths were cyclized under dehydrative conditions affording tricyclic indole-containing ring systems wherein the third ring contains a sulfur atom attached to the 2- or 3-position of the indole ring. This methodology affords entry into the novel thiepino[3,2-*b*]indole, thiocino[2,3-*b*]indole and thiocino[3,2-*b*]indole ring systems.

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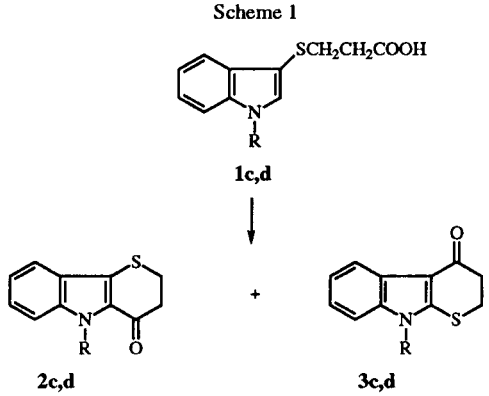
Introduction.

Several approaches have been used to elaborate linear tricyclics incorporating an indole ring, wherein the third ring consists of a sulfur-containing heterocycle with the heteroatom linked to either the 2- or 3-position of the indole ring. For example, the thiopyrano[2,3-*b*]indole system may be constructed by Fisher indolization using tetrahydrothiopyran-3-one [1], or by intramolecular Grignard reaction on the mesylate of a 2-(3-hydroxypropylthio)indole [2], as well as by several other approaches. In a more recent paper [3], the thieno[2,3-*b*]indole system was elaborated by an annulation reaction of a 2-chloroindole-3-carbaldehyde with methyl thioglycolate. Although 3-indolylthioalkanoic acids are easily attainable, examples of their use in dehydrative cyclizations to yield indole-containing tricyclic rings are very scarse. One example is the Friedel-Crafts cyclization of 3-(3-indolylthio)propionic acid **1c** reported by Nagarajan [4], (Scheme 1), where the use of phosphorus pentoxide in benzene at 80° led to a low yield (5%) of the expected thiopyrano[3,2-*b*]indol-4-one **2c**, while treatment with polyphosphoric acid at 80° led to an equally low yield of the isomeric thiopyrano[2,3-*b*]indol-4-one **3c**, result of an unexpected rearrangement. More recently, we reported [5] on improved conditions for these cyclizations (Scheme 1), and these studies led to the conclusion that the unexpected **3c** results from initial isomerization of the 3-(3-indolylthio)propionic acid **1c** to 3-(2-indolylthio)propionic acid **4c**, with subsequent cyclization. To our knowledge, no reports exist on cyclizations of indolylthioalkanoic acids of other chain lengths.

Scheme 1



c) R = H	PPA, 80° (ref 4)	**2c**	(0%)	**3c**	(5%)
	P_2O_5, C_6H_6, 80° (ref 4)		(5%)		(0%)
	PPA, 115° (ref 5)		traces		(37%)
	PPE, rt (ref 5)		(51%)		(8%)
d) R = CH_3	PPA, 100°	**2d**	(2%)	**3d**	(33%)
	PPE, rt		(67%)		(5%)

In this paper we wish to present cyclization studies on 2- and 3-indolylthioalkanoic acids of various chain lengths (1, 2, 3 and 4 methylene units) leading to the elaboration of several novel tricyclic indole-containing ring systems.

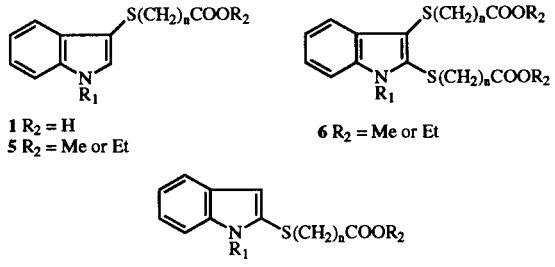
Materials and Methods.

Several methods were used to prepare the different 2- and 3-indolylthioalkanoic acids used in this study. The 3-indolylthioacetic acid **1a** was obtained by a modification of the method of Bourdais and Lorre [6], *via* alkylation of *in situ* generated 3-indolethiolate with ethyl bromoacetate, affording intermediate ester **5a**, followed by basic hydrolysis. A similar process using ethyl 3-bromopropionate led to ester **5c** and 3-(3-indolylthio)propionic acid **1c**. The *N*-methyl analog **1b** was obtained by monosulfenylation [7] of *N*-methylindole with the sulfenyl halide generated from dimethyl dithiodiglycolate and sulfuryl chloride, leading to ester **5b** which was hydrolyzed. Double methylation of 3-indolylthiopropionic acid **1c** using sodium hydride and methyl iodide in *N,N*-dimethylformamide led to ester **5d**, which gave *N*-methylated acid **1d** on hydrolysis. The 3-indolylthiobutyric and pentanoic acids **1e** and **1g** were obtained by initial monosulfenylation of indole with the appropriate sulfenyl halides, with subsequent hydrolysis of the resulting esters, while the *N*-methyl analog **1f** was obtained by *N*-methylation of ester **5e** followed by hydrolysis.

The 2-indolylthioalkanoic acids of type **4** were generally arrived at by initial bis sulfenylation [5,7] of indole,

using excess sulfenyl chloride, leading to 2,3-bis((carbalkoxyalkyl)thio)indoles **6**, followed by non-reductive, regioselective desulfenylation [8] at the 3-position, leading to esters of type **7** which were hydrolyzed. The *N*-methyl-2-indolylthioacetic acid **4b** was best obtained by initial polyphosphoric acid-catalyzed isomerization [5] of the *N*-methyl-3-indolylthioacetate **5b**, affording ester **7b** which was hydrolyzed.

INSERT



Example	R_1	n
a	H	1
b	Me	1
c	H	2
d	Me	2
e	H	3
f	Me	3
g	H	4

Cyclizations of the 2- and 3-indolylthioalkanoic acids were generally effected in hot, neat polyphosphoric acid or with polyphosphate ester in methylene chloride or chloroform (1:1) solution. Attempts at the preparation of acid chlorides of the indolylthio alkanoic acids led to decomposition.

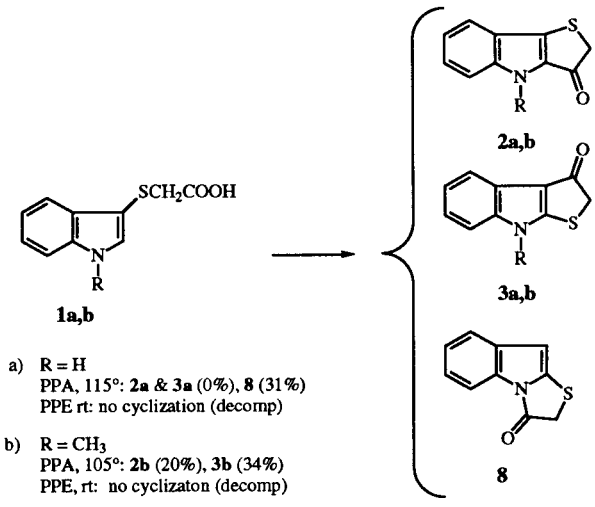
Results and Discussion.

Cyclization of (2- and 3-Indolylthio)acetic Acids.

Attempted cyclization of 3-indolylthioacetic acid **1a** (Scheme 2) using polyphosphoric acid at 100° did not lead to either thieno[3,2-*b*]indol-3-one **2a** or the isomeric thieno[2,3-*b*]indol-3-one **3a**. The only cyclized product obtained, in 31% yield, was the angular derivative 2,3-dihydrothiazolo[3,2-*a*]indol-3-one **8**, most likely resulting from initial isomerization of **1a** to 2-indolylthioacetic acid **4a** followed by preferential amide formation with the indole nitrogen. Reaction at lower temperatures were not successful. Attempted cyclization using the milder conditions of polyphosphate ester in methylene chloride solution did not lead to any cyclized products, only to decomposition products.

When a methyl substituent was placed on the indole nitrogen, **1b**, the amide formation was prevented and heating in polyphosphoric acid led to a mixture of the two linear thienoindolones **2b** (20%) and **3b** (34%). Again, attempted ring closure using polyphosphate ester led only to decomposition products.

Scheme 2



4a —R = H, PPE, rt, 18 hours→ **8** (65%), no **3a** formed

4b —R = Me, PPE, neat, 60°→ **3b** (53%)

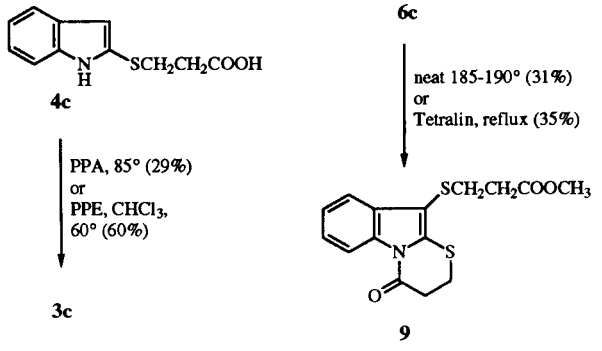
When 2-indolylthioacetic acid **4a** was treated with polyphosphate ester in methylene chloride solution at room temperature it slowly cyclized to the angular tricyclic amide **8** in 65% yield, with no formation of the linear product **3a**. The *N*-methylated 2-indolylthioacetic acid **4b** could be brought to cyclize to the thieno[2,3-*b*]-indol-3-one **3b** in neat polyphosphate ester at 60°, in fair yield (53%).

Cyclization of 3-(2- and 3-Indolylthio)propionic Acids.

We have reported [5] on improved conditions for the cyclization of 3-(3-indolylthio)propionic acid **1c** to either the thiopyrano[3,2-*b*]indol-4-one **2c** or the isomeric thiopyrano[2,3-*b*]indol-4-one **3c** (Scheme 1). The presence of a methyl substituent on the indole nitrogen of **1d** did not improve the yield (33%) of the corresponding thiopyrano [2,3-*b*]indol-4-one **3d**, whereas the polyphosphate ester-catalyzed ring closure of **1d** led to an acceptable yield (67%) of thiopyrano[3,2-*b*]indol-4-one **2d**. As an alternate approach to the thiopyrano-[2,3-*b*]indol ring system (Scheme 3), ring closure of 3-(2-indolylthio)propionic acid **4c** to **3c** is sluggish in hot polyphosphoric acid (29%) but cleaner when done in polyphosphate ester (60%).

In contrast to the facile formation of the angular tricyclic **8** from 2-indolylthioacetic acid **4a**, no corresponding angular tricyclic analog was obtained from **4c**. The [1,3]thiazino[3,2-*a*]indole ring could not be obtained alternatively from ester **7c**, either thermally or by cyclization of the indolyl anion (sodium hydride in

Scheme 3

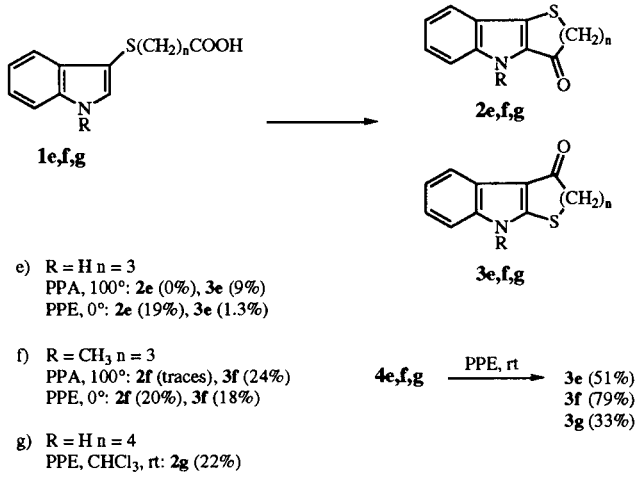


N,N-dimethylformamide). However, thermal dehydration of the bis thiopropionate **6c**, neat at 185-190° or in refluxing decalin, led to the angular tricyclic **9** in moderate yield.

Cyclization of 4-(2- and 3-Indolylthio)butyric Acids.

The cyclization of 4-(3-indolylthio)butyric acid **1e** in hot polyphosphoric acid (Scheme 4) led only to the rearranged thiepino[2,3-*b*]indol-5-one **3e**, in low yield (9%). In polyphosphate ester at 0°, a mixture of **3e** (1.3%) and the expected thiepino[3,2-*b*]indol-5-one **2e** (19%) resulted. With a methyl substituent on the indole nitrogen, cyclization of **1f** in polyphosphoric acid led to **3f** in modest yield (24%) while treatment with polyphosphate ester at 0° led to equal amounts (*ca* 20%) of the two isomeric tricyclic ketones **2f** and **3f.** To our knowledge, compounds **2e** and **2f** represent the first examples in the hitherto unknown thiepino[3,2-*b*]indol ring system.

Scheme 4



The 4-(2-indolylthio)butyric acids **4e** and **4f** were readily cyclized to the thiepino[2,3-*b*]indol-5-ones **3e** and **3f** in polyphosphate ester at room temperature in fair yield.

Cyclization of 5-(2- and 3-Indolylthio)pentanoic Acids.

Our study was extended to include cyclizations of acids having **4** methylene units. Thus cyclization of 5-(3-indolylthio)pentanoic acid **1g** (Scheme 4) with polyphosphate ester at room temperature led to the thiocino[3,2-*b*]-indol-6-one derivative **2g**, albeit in low yield (22%). Similar treatment of 5-(2-indolylthio)pentanoic acid **4g** afforded a modest yield of the isomeric thiocino[2,3-*b*]-indol-6-one **3g**. These compounds also represent the first examples in novel ring systems.

As can be seen by the results, the polyphosphoric acid-catalyzed cyclizations of the 3-indolylthioalkanoic acids invariably led to a major product which resulted from initial isomerization to the corresponding 2-indolylthioalkanoic acid prior to cyclization, as had been observed previously with 3-(3-indolylthio)propionic acid **1c** [4,5]. This isomerization, promoted by the strongly acidic conditions [5], is less prevalent when the milder conditions of polyphosphate ester are used. The failure to obtain compounds **2a** and **3a** from **1a** may be due in part to ring strain in the cyclized product, thus favoring, in the polyphosphoric acid-catalyzed process, preferential *in-situ* isomerization to the 2-indolylthioacetic acid **4a** which prefers to cyclize on the indole nitrogen affording the angular tricyclic **8**. This preference is also demonstrated by the exclusive formation of **8** on treatment of **4a** with polyphosphate ester, whereas all of the other 2-indolylthioalkanoic acids in the study led to the expected linear tricyclics in fair yields under the same conditions. Although in several cases the yields of cyclized products are low, this method of obtaining indole-containing tricyclic ring systems offers the advantage of easy accessibility of the required 2- and 3-indolylthioalkanoic acid precursors. Where mixtures of the two isomeric ketones of type **2** and **3** were obtained, they were easily separable by column chromatography, the type **3** being the more polar component. Structural assignments were based on the presence of a doublet at low field (*ca* 8.2 ppm) in type **3** ketones, corresponding to the H-4 proton on the indole ring, and also by the unambiguous cyclization of type **4** acids to type **3** ketones.

Conclusion.

Cyclization of easily available 2- and 3-indolylthioalkanoic acids of various chain lengths constitutes an easy and attractive approach to tricyclic indole-containing ring systems wherein the third ring is a sulfur-containing heterocycle. Novel ring systems such as thiepino[3,2-*b*]indole and thiocino[2,3-*b*] and [3,2-*b*]indole are now attainable by this methodology.

EXPERIMENTAL

Commercial reagents and solvents were used without further purification. Melting points were recorded in open-end capil-

lairies and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 681 spectrophotometer, as potassium bromide pellets, and the values reported correspond to the largest or most characteristic absorptions. The 400 MHz proton and ^{13}C nmr spectra were recorded using a Bruker instrument. Elemental analyses were performed by Guelph Chemical Laboratories Ltd, Guelph, Ontario, Canada. The required dithiodialkanoic esters were prepared by oxidation of the corresponding thiols using iodine in ethanolic solution.

Ethyl (3-Indolylthio)acetate (**5a**) and (3-Indolylthio)acetic Acid (**1a**).

A modification of the method of Boudrais and Lorre [6] was used. A 0.2 *M* solution of potassium triiodide was prepared by stirring 49.8 g (300 mmoles) of potassium iodide and 50.8 g of iodine (200 mmoles) together in 1 liter of water at rt for 24 hours. To a solution of 5.85 g (50 mmoles) of indole and 4.19 g of thiourea (60 mmoles) in 150 ml of methanol was added slowly 300 ml (60 mmoles) of the potassium triiodide solution and the mixture was stirred at rt for 30 minutes. After filtration the filtrate was concentrated to one half of its volume. To this mixture was added 20 ml of 10 *N* aqueous sodium hydroxide and the mixture was heated at 95° for 30 minutes under a nitrogen atmosphere. The resulting suspension was filtered while hot and the solids washed with water. The filtrate, an aqueous solution of sodium 3-indolylthiolate, was cooled down to room temperature and treated with a solution of 8.35 g (50 mmoles) of ethyl bromoacetate in 75 ml of ether. The resulting 2-phase mixture was stirred vigorously at rt for 45 minutes. The organic phase was collected and evaporated to a residue of crude ester **5a** which was hydrolyzed as such (see below). The aqueous phase was extracted with ether twice, then acidified with 1 *N* hydrochloric acid, affording after filtration a first crop of 3.20 g of acid **1a**.

The crude ester from the original organic phase was dissolved in 50 ml of ethanol, there was added 50 ml of 5 *N* aqueous sodium hydroxide and the mixture was stirred at rt for 30 minutes. After dilution with 250 ml of water, the mixture was extracted twice with ether, then acidified with 6 *N* hydrochloric acid and extracted 3 times with ether. These extracts were washed with water 3 times, dried and evaporated to afford crude acid **1a** as a solid which was triturated in hexane and filtered to yield a second crop of 5.6 g of **1a**, bringing the total yield to 8.8 g (85%). A sample of **1a** was crystallized from toluene, affording tan crystals, mp 108-110° (lit mp 110° [6]).

Anal. Calcd for $C_{10}H_9NO_2S$: C, 57.95; H, 4.38; N, 6.76; S, 15.47. Found: C, 57,98; H, 4.41; N, 6.77; S, 15.50.

Ethyl 3-(3-Indolylthio)propionate (**5c**) and 3-(3-Indolylthio)propionic Acid (**1c**).

A similar procedure was followed, using ethyl 3-bromopropionate as alkylating agent, to afford crude ester **5c** which was hydrolyzed in the same fashion to acid **1c** in 72% overall yield. A sample of **1c** was crystallized from toluene to afford cream-colored crystals, mp 135-136° (lit mp 176° [4]).

Anal. Calcd for $C_{11}H_{11}NO_2S$: C, 59.70; H. 5.01; N, 6.33; S, 14.49. Found: C, 59.73; H, 5.07; N, 6.40; S, 14.38.

Methyl (1-Methyl-3-indolylthio)acetate (**5b**).

To a solution of 1.65 g of dimethyl dithiodiglycolate (7.84 mmoles) in 10 ml of 1,2-dichloroethane at room temperature there was added 0.97 g of sulfuryl chloride (7.17 mmoles) and the mixture was stirred at room temperature for 20 minutes. This yellow solution was added slowly to a solution of 1.81 g of 1-methylindole (13.8 mmoles) in 8 ml of DMF. The resulting mixture was stirred at room temperature for 1 hour then quenched with saturated aqueous sodium bicarbonate, diluted with water and extracted with ethyl acetate. The extracts were washed several times with water, dried and evaporated to a residue which was stirred in a small volume of ether for 30 minutes and filtered to afford 2.9 g (89%) of **5b** as a light yellow solid, mp 88-89°; ir (potassium bromide): 1730, 1505, 1285, 1125 cm^{-1}; ^1H nmr (acetone-d_6): δ 3.38 (s, 2H), 3.56 (s, 3H), 3.84 (s, 3H), 7.15 (t, 1H), 7.22 (t, 1H), 7.42 (d, 1H), 7.43 (s, 1H), 7.66 (d, 1H).

Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95; S, 13.63. Found: C, 61.34; H, 5.61; N, 5.91; S, 13.63.

A similar procedure was followed to prepare the following esters **5**.

Methyl 4-(3-Indolylthio)butyrate (**5e**) was obtained in 92% crude yield and it was used as such for hydrolysis.

Ethyl 5-(3-Indolylthio)pentanoate (**5g**).

The product was obtained in 63% yield as a white solid, mp 43-44°; ir (potassium bromide): 3400 (br), 2950, 1750 cm^{-1}; ^1H nmr (acetone-d_6): δ 1.16 (t, 3H), 1.54 (m, 2H), 1.70 (m, 2H), 2.25 (t, 2H), 2.68 (t, 2H), 4.04 (q, 2H), 7.09-7.18 (m, 2H), 7.45 (m, 2H), 7.68 (d, 1H), 10.45 (br, NH).

Anal. Calcd. for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05; S, 11.56. Found: C, 65.14; H, 7.01; N, 5.03; S, 11.75.

(1-Methyl-3-indolylthio)acetic Acid (**1b**).

To a solution of 2.3 g of ester **5b** (9.8 mmoles) in 10 ml of tetrahydrofuran and 10 ml of methanol was added 10 ml of 1 *N* aqueous sodium hydroxide. The mixture was stirred at room temperature for 5.5 hours, the organic solvents were evaporated and the residue was diluted with water and acidified with 10% aqueous hydrochloric acid, then extracted with ethyl acetate. The extracts were washed with water, dried and evaporated, and the residue was stirred in a small volume of ether for 2 hours and filtered to afford 1.95 g (91%) of acid **1b** as a yellow solid, mp 102-103°; ir (potassiuim bromide): 3300-2700 (br), 1705, 1510, 1408 cm^{-1}; ^1H nmr (acetone-d_6): δ 3.41 (s, 2H), 3.84 (s, 3H), 7.14 (t, 1H), 7.22 (t, 1H), 7.42 (d, 1H), 7.44 (s, 1H), 7.71 (d, 1H), 10.78 (br, 1H).

Anal. Calcd. for $C_{11}H_{11}NO_2S$: C, 59.71; H. 5.01; N, 6.33; S, 14.49. Found: C, 59.67; H, 5.08; N, 6.31; S, 14.37.

A similar hydrolysis procedure was followed to prepare the following acids **1** from the appropriate esters.

4-(3-Indolylthio)butyric Acid (**1e**).

The product was obtained, in 91% overall yield, as a white solid, mp 80-81° (ether-hexane); ^1H nmr (acetone-d_6): δ 1.80 (m, 2H), 2.44 (t, 2H), 2.72 (t, 2H), 7.09-7.18 (m, 2H), 7.45 (d, 1H), 7.48 (s, 1H), 7.68 (d, 1H), 10.46 (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, 61.13; H, 5.61; N, 5.91; S, 13.77.

5-(3-Indolylthio)pentanoic Acid (**1g**).

The compound was obtained in 95% yield as a beige solid, mp 94-95°; ir (potassium bromide): 3400 (br), 1700 cm^{-1}; ^1H nmr (acetone-d_6): δ 1.57 (m, 2H), 1.72 (m, 2H), 2.26 (t, 2H), 2.69 (t, 2H), 7.09-7.17 (m, 2H), 7.45 (m, 2H), 7.68 (d, 1H), 10.46 (br, NH).

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.63; H, 6.06; N, 5.62; S, 12.86. Found: C, 62.38; H, 6.06; N, 5.56; S, 12.79.

Methyl 3-(1-Methyl-3-indolylthio)propionate (**5d**) and 3-(1-Methyl-3-indolylthio)propionic Acid (**1d**).

To a suspension of 1.44 g (60 mmoles) of 97% sodium hydride in 120 ml of *N,N*-dimethylformamide, at 0° there was added slowly 4.42 g of acid **1c** [4] (20 mmoles) and the mixture was stirred in the cold until gas evolution ceased. There was added 8.52 g of iodomethane (60 mmoles) and the mixture was stirred at room temperature overnight. After quenching with saturated aqueous ammonium chloride the mixture was partitioned between ether and water. The product from the organic phase, crude **5d**, was dissolved in 150 ml of methanol, and there was added 50 ml of 2.5 *N* aqueous sodium hydroxide. After stirring for 3 hours the mixture was diluted with water and extracted with ether. The aqueous fraction was acidified with 6*N* hydrochloric acid and extracted with ether 3 times, the combined extracts were washed 4 times with water, dried and evaporated to yield 3.97 g (84%) of **1d** as a cream-colored solid, mp 106-108°; ^{1}H nmr (acetone-d_6): δ 2.51 (t, 2H), 2.85 (t, 2H), 3.86 (s, 3H), 7.14 (t, 1H), 7.22 (t, 1H), 7.42 (s, 1H), 7.43 (d, 1H), 7.69 (d, 1H).

Anal. Calcd. for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95; S, 13.63. Found: C, 61.19; 11, 5.59; N, 6.01; S, 13.88.

The same 2-step procedure was followed to prepare, *via* ester **5f**, 4-(1-methyl-3-indolylthio)butyric acid (**1f**) in 92% overall yield, as a beige solid, mp 93-95.5°; ^{1}H nmr (acetone-d_6): δ 1.80 (m, 2H), 2.44 (t, 2H), 2.71 (t, 2H), 3.83 (s, 3H), 7.13 (t, 1H), 7.21 (t, 1H), 7.40 (s, 1H), 7.41 (d, 1H), 7.67 (d, 1H), 10.49 (br, OH).

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.63; H, 6.06; N, 5.62; S, 12.86. Found: C, 62.25; H, 6.10; N, 5.55; S, 13.10.

2,3-bis(Carbomethoxymethylthio)indole (**6a**).

To a solution of 4.2 g of dimethyl dithiodiglycolate (20 mmoles) in 20 ml of 1,2-dichloroethane was added 2.37 g of sulfuryl chloride (17.5 mmoles) and the resulting yellow solution was stirred at room temperature for 10 minutes. It was added slowly to a cold (0°) solution of 1.638 g (14 mmoles) of indole in 20 ml of *N,N*-dimethylformamide. After the addition, the mixture was allowed to warm up to room temperature and stirred for 1 hour. The mixture was quenched with 10 ml of water and the dichloroethane was evaporated off. The residue was partitioned between ether and water, the product from the organic phase was chromatographed on silica gel, eluting with a 1:3 mixture of ethyl acetate and hexane, to afford **6a** as an oil which solidified. The solid was triturated with hexane and filtered to give 3.53 g (78%) of **6a**, mp 78-81°; ^{1}H nmr (acetone-d_6): δ 3.45 (s, 2H), 3.55 (s, 3H), 3.69 (s, 3H), 3.82 (s. 2H), 7.13 (t, 1H), 7.20 (t, 1H), 7.42 (d, 1H), 7.63 (d, 1H), 10.78 (br, NH).

Anal. Calcd. for $C_{14}H_{15}NO_4S_2$: C, 51.68; H, 4.65; N, 4.30; S, 19.71. Found: C, 51.90; H, 4.65; N, 4.31; S, 19.75.

The same procedure was followed to prepare the following 2,3-bis((carbalkoxyalkyl)thio)indoles **6**.

2,3-bis[(2-Carbomethoxyethyl)thio]indole (**6c**) has been previously reported by us [8].

2,3-bis[(3-Carbomethoxypropyl)thio]indole (**6e**).

The product was obtained as a colorless oil in 91% yield; ^{1}H nmr (deuteriochloroform): δ 1.80 (m, 2H), 1.94 (m, 2H), 2.49 (m, 4H), 2.78 (t, 2H), 2.96 (t, 2H), 3.61 (s, 3H), 3.70 (s, 3H), 7.11-7.22 (m, 4H), 7.36 (d, 1H), 7.68 (d, 1H), 8.99 (br, NH).

Anal. Calcd. for $C_{18}H_{23}NO_4S_2$: C, 56.67; H, 6.08; N, 3.67; S, 16.81. Found: C, 56.75; H, 6.09; N, 3.60; S, 16.74.

2,3-bis[(3-Carbomethoxypropyl)thio]-1-methylindole (**6f**).

The compound was obtained as a colorless oil in 74% yield; ^{1}H nmr (deuteriochloroform): δ 1.80 (m, 4H), 2.48 (t, 4H), 2.77 (t, 2H), 2.86 (t, 2H), 3.61 (s, 3H), 3.62 (s, 3H), 3.87 (s, 3H), 7.18 (t, 1H), 7.28 (m, 2H), 7.71 (d, 1H).

Anal. Calcd. for $C_{19}H_{25}NO_4S_2$: C, 57.70; H, 6.37; N, 3.54; S, 16.21. Found: C, 58,01; H, 6.50; N, 3.66; S, 16.56.

2,3-bis((4-Carbethoxybutyl)thio)indole (**6g**).

The compound was obtained as a light yellow oil in 65% yield; ir (potassium bromide): 3300, 2400, 1700 cm^{-1}; ^{1}H nmr (acetone-d_6): δ 1.17 (m, 6H), 1.50-1.78 (m, 8H), 2.27 (m, 4H), 2.75 (t, 2H), 3.03 (t, 2H), 4.04 (m, 4H), 7.08-7.17 (m, 2H), 7.36 (d, 1H), 7.72 (d, 1H), 10.66 (br, NH).

Anal. Calcd. for $C_{22}H_{31}NO_4S_2$: C, 60.38; H, 7.14; N, 3.20; S, 14.65. Found: C, 60.47; H, 7.14; N, 3.21; S, 14.67.

Methyl (2-Indolylthio)acetate (**7a**) by Selective Desulfenylation [8] of **6a**.

A mixture of 2.6 g of **6a** (8 mmoles) and 2.47 g of thiosalicylic acid (16 mmoles) in 30 ml of trifluoroacetic acid was stirred at 60° for 1.5 hours.

After evaporation of the trifluoroacetic acid the residue was partitioned between ether and water, with excess sodium bicarbonate added to neutralize the residual acid. The organic phase was washed with water, dried and evaporated, and the crude mixture was chromatographed on silica gel (5% ethyl acetate in toluene) to afford 1.08 g (61%) of **7a** as a yellow oil which slowly solidified. The solid was triturated with hexane and filtered to give 770 mg of yellow solid, mp 48-50°; ^{1}H nmr (acetone-d_6): δ 3.65 (s, 3H), 3.69 (s, 2H), 6.62 (s, 1H), 7.01 (t, 1H), 7.11 (t, 1H), 7.37 (d, 1H), 7.50 (d, 1H), 10.36 (br, NH).

Anal. Calcd. for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01; N, 6.33; S, 14.49. Found: C, 59.94; H, 5.11; N, 6.23; S, 14.56.

The same procedure was followed to afford the following **7**.

Methyl 3-(2-indolylthio)propionate (**7c**) has been previously reported by us [8].

Methyl 4-(2-indolylthio)butyrate (**7e**).

Refluxing for 3 hours was necessary to obtain the product as cream-colored crystals in 89% yield, mp 53-55° (ether-hexane); ^{1}H nmr (deuteriochloroform): δ 1.95 (m, 2H), 2.47 (t, 2H), 2.82 (t, 2H), 3.68 (s, 3H), 6.63 (s, 1H), 7.08 (t, 1H), 7.18 (t, 1H), 7.34 (d, 1H), 7.54 (d, 1H), 8.40 (br, NH).

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06; N, 5.62; S, 12.86. Found: C, 62.75; H, 6.28; N, 5.69; S, 12.89.

Methyl 4-(1-Methyl-2-indolylthio)butyrate (**7f**).

Refluxing for 1.5 hours was necessary to obtain the product as a yellow oil in 81% yield; ^{1}H nmr (deuteriochloroform): δ 1.90 (m, 2H), 2.44 (t, 2H), 2.78 (t, 2H), 3.64 (s, 3H), 3.79 (s, 3H), 6.66 (s, 1H), 7.08 (t, 1H), 7.20 (t, 1H), 7.28 (d, 1H), 7.53 (d, 1H).

Anal. Calcd. for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32; S, 12.17. Found: C, 63.73; H, 6.49; N, 5.34; S, 12.03.

Ethyl 5-(2-Indolylthio)pentanoate (**7g**).

Refluxing for 4 hours was necessary to obtain the product as a white solid in 75% yield, mp 66-67°; ir (potassium bromide): 3450, 2950, 1725 cm^{-1}; ^{1}H nmr (acetone-d_6): δ 1.17 (t, 3H), 1.60-1.77 (m, 4H), 2.29 (t, 2H), 2.91 (q, 2H), 4.04 (q, 2H), 6.55 (s, 1H), 6.99 (t, 1H), 7.08 (t, 1H), 7.33 (d, 1H), 7.48 (d, 1H), 10.34 (br, NH).

Anal. Calcd. for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05; S, 11.56. Found: C, 64.85; H. 7.00; N, 4.95; S, 11.88.

Methyl (1-Methyl-2-indolylthio)acetate (**7b**) by Isomerization [5] of Methyl (1-Methyl-3-indolylthio)acetate (**5b**).

A mixture of 470 mg of **5b** and 12 g of commercial polyphosphoric acid was heated at 90° for 10 minutes. The mixture was cooled down, triturated with water and extracted with ethyl acetate. The extracts were washed several times with water, dried and evaporated, and the crude product chromatographed on silica gel (1:5 ethyl acetate-hexane) to afford 411 mg of **7b** (87%) as a yellow oil; ^{1}H nmr (acetone-d_6): δ 3.62 (s, 3H), 3.63 (s, 2H), 3.85 (s, 3H), 6.73 (s, 1H), 7.04 (t, 1H), 7.20 (t, 1H), 7.38 (d, 1H), 7.52 (d, 1H).

Anal. Calcd. for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95; S, 13.63. Found: C, 61.28; H, 5.57; N, 5.96; S, 13.87.

(2-Indolylthio)alkanoic Acids **4**.

The method for basic hydrolysis described above in the preparation of **1b** was applied to hydrolyze the esters **7** to afford the following acids **4**.

(2-Indolylthio)acetic Acid (**4a**).

The product was obtained as a yellow solid in 74% yield, mp 73-76° dec; ^{1}H nmr (acetone-d_6): δ 3.70 (s, 2H), 6.62 (s, 1H), 7.01 (t, 1H), 7.11 (t, 1H), 7.37 (d, 1H), 7.49 (d, 1H), 10.37 (br, NH).

Anal. Calcd. for $C_{10}H_9NO_2S$: C, 57.96; H, 4.38; N, 6.76; S, 15.47. Found: C, 58.06; H, 4.38; N, 6.51; S, 15.69.

(1-Methyl-2-indolylthio)acetic Acid (**4b**).

The product was obtained as a light yellow solid in 86% yield, mp 94-96°; ^{1}H nmr (acetone-d_6): δ 3.64 (s, 2H), 3.86 (s, 3H), 6.74 (s, 1H), 7.03 (t, 1H), 7.18 (t, 1H), 7.38 (d, 1H), 7.51 (d, 1H).

Anal. Calcd for $C_{11}H_{11}NO_2S$: C, 59.70; H, 5.01; N, 6.33; S, 14.49. Found: C, 60.07; H, 5.07; N, 6.32; S, 14.54.

3-(2-Indolylthio)propionic acid (**4c**) has been previously reported by us [5]. The product was obtained as a straw-colored solid in 58% yield.

4-(2-Indolylthio)butyric Acid (**4e**).

The product was obtained as a tan solid in 80% yield, mp 99-101°; ^{1}H nmr (deuteriochloroform): δ 1.94 (m, 2H), 2.51 (t, 2H), 2.86 (t, 2H), 6.63 (s, 1H), 7.07 (t, 1H), 7.16 (t, 1H), 7.30 (d, 1H), 7.54 (d, 1H), 8.19 (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, 60.92; H, 5.85; N, 5.77; S, 13.84.

4-(1-Methyl-2-indolylthio)butyric Acid (**4f**).

The product was obtained as a white solid in 91% yield, mp 114-116°; ^{1}H nmr (deuteriochloroform): δ 1.90 (m, 2H), 2.50 (t, 2H), 2.79 (t, 2H), 3.79 (s, 3H), 6.67 (s, 1H), 7.08 (t, 1H), 7.19-7.28 (m, 2H), 7.53 (d, 1H).

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.63; H, 6.06; N, 5.62; S, 12.86. Found: C, 62.36; H, 6.16; N, 5.70; S, 12.75.

5-(2-Indolylthio)pentanoic Acid (**4g**).

The product was obtained as a beige solid in 88% yield, mp 68-69°; ^{1}H nmr (acetone-d_6): δ 1.63-1.77 (m, 4H), 2.31 (t, 2H), 2.92 (t, 2H), 6.56 (s, 1H), 6.99 (t, 1H), 7.08 (t, 1H), 7.33 (d, 1H), 7.47 (d, 1H), 10.35 (br, NH); hrms: Calcd. for $C_{13}H_{15}NO_2S$+ H 250.0918. Found 250.0901.

Cyclization of (3-Indolylthio)alkanoic Acids. Typical Procedures.

Cyclization of **1d**. 4-Methyl-2,3-dihydrothiopyrano[3,2-*b*]indol-4(5*H*)-one (**2d**) and 9-Methyl-2,3-dihydrothiopyrano[2,3-*b*]-indol-4(9*H*)-one (**3d**).

A mixture of 470 mg of **1d** and 24 g of polyphosphoric acid was heated at 100° for 15 minutes. After cooling, the mixture was triturated with water and extracted 3 times with ethyl acetate, the extracts were washed several times with water, dried and evaporated. Chromatography on silica gel (2:1 ethyl acetate-hexane) afforded: 10 mg (2%) of **2d** (see below) and 145 mg (33%) of **3d** as a tan solid, mp 166-167°; ^{1}H nmr (acetone-d_6): δ 2.74 (t, 2H), 3.50 (t, 2H), 3.75 (s, 3H), 7.17-7.24 (m, 2H), 7.42 (d, 1H), 8.13 (d, 1H).

Anal. Calcd. for $C_{12}H_{11}NOS$: C, 66.33; H, 5.10; N, 6.45; S, 14.75. Found: C, 66,69; H, 5.34; N 6.42; S, 14.36.

To 8 ml of a 1:1 mixture of polyphosphate ester [9] and chloroform there was added 470 mg of **1d**, and the mixture was stirred at room temperature for 1.5 hours. After quenching with water the mixture was extracted 3 times with ethyl acetate, and the extracts were washed with water several times, dried and evaporated. Chromatography on silica gel (2:1 ethyl acetate-hexane) afforded 291 mg (67%) of **2d** as a beige solid, mp 99-101°; ^{1}H nmr (acetone-d_6): δ 2.88 (t, 2H), 3.39 (t, 2H), 4.08 (s, 3H), 7.14 (t, 1H), 7.44 (t, 1H), 7.50 (d, 1H), 7.56 (d, 1H).

Anal. Calcd. for $C_{12}H_{11}NOS$: C, 66.33; H, 5.10; N, 6.45; S, 14.75. Found: C, 65.98; H, 5.19; N,6.49; S, 14.47.

The same procedures were used to effect the following ring closures.

Cyclization of **1a**: 2,3-Dihydrothiazolo[3,2-*a*]indol-3-one (**8**).

Cyclization at 115° for 1.5 hours in polyphosphoric acid gave after workup and chromatography on silica gel (1:3 ethyl acetate-hexane) only **8** in 31% yield, as a light orange solid, mp 141-143°; ^{1}H nmr (acetone-d_6): δ 4.42 (s, 2H), 6.40 (s, 1H), 7.20-7.28 (m, 2H), 7.45 (d, 1H), 8.03 (d, 1H); ^{13}C nmr (deuteriochloroform): δ 166.5, 136.7, 135.6, 131.9, 124.8, 122.9, 119.5, 112.9, 100.3, 38.3.

Anal. Calcd. for $C_{10}H_7NOS$: C, 63.46; H, 3.73; N, 7.40; S, 16.95. Found: C, 63.81; H, 3.71; N, 7.30; S, 16.77.

In polyphosphate ester-chloroform (1:1) at rt, no cyclized products were obtained, only decomposition products.

Cyclization of **1b**. 4-Methyl-3,4-dihydro-2*H*-thieno[3,2-*b*]indol-3(4*H*)-one (**2b**) and 8-Methyl-3,4-dihydro-2*H*-thieno[2,3-*b*]-indol-3(8*H*)-one (**3b**).

In polyphosphoric acid the reaction at 105° for 30 hours afforded **2b** as a beige solid in 20% yield, mp 155-156°; ^{1}H nmr (acetone-d_6): δ 3.93 (s, 3H), 4.15 (s, 2H), 7.19 (t, 1H), 7.49 (t, 1H); 7.54 (d, 1H); 7.69 (d, 1H); ^{13}C nmr (deuteriochloroform): δ 187.0, 145.3, 142.1, 131.8, 128.2, 121.8, 121.6, 120.3, 111.1, 44.9, 29.8.

Anal. Calcd. for C_9H_9NOS: C, 65.00; H, 4.46; N, 6.89; S,15.77. Found: C, 65.18; H, 4.39; N, 6.84; S, 16.11.

There was also obtained **3b** in 34% yield as a beige solid, mp 189-190°; ^{1}H nmr (acetone-d_6): δ 3.79 (s, 3H), 4.16 (s, 2H), 7.20-7.29 (m, 2H), 7.45 (d, 1H), 7.73 (d, 1H); ^{13}C nmr (deuteriochloroform): δ 186.9, 166.2, 143.2, 123.0, 122.6, 122.5, 119.6, 113.6, 109.2, 46.1, 31.0.

Anal. Calcd. for C_9H_9NOS: C, 65.00; H, 4.46; N, 6.89; S,15.77. Found: C, 65.38; H, 4.48; N, 6.92; S, 16.08.

In polyphosphate ester-methylene chloride (1:1), under these conditions, at room temperature, **1b** yielded no cyclized products; forced conditions led to decomposition.

Cyclization of **1c.** 2,3-Dihydrothiopyrano[3,2-*b*]indol-4(5*H*)-one (**2d**) and 2,3-Dihydrothiopyrano[2,3-*b*]indol-4(9*H*)-one (**3d**).

We have previously described these cyclizations [5], affording 37% of **3c** and traces of **2c** in polyphosphoric acid at 115° and 51% of **2c** and 8% of **3c** in polyphosphate ester-chloroform (1:1) at rt.

Cyclization of **1e**. 3,4-Dihydro-2*H*-thiepino[3,2-*b*]indol-5(6*H*)-one (**2e**) and 3,4-Dihydro-2*H*-thiepino[2,3-*b*]indol-5(10*H*)-one (**3e**).

In polyphosphoric acid the reaction at 100° for 3 hours afforded after chromatography (4:1 ethyl acetate-hexane) **3e** in 9% yield as a cream-colored solid, mp 189-190°; ^{1}H nmr (acetone-d_6): δ 2.25 (m, 2H), 2.91 (t, 2H), 3.20 (t, 2H), 7.12-7.22 (m, 2H), 7.36 (d, 1H), 8.22 (d, 1H), 11.1 (br, NH); ^{13}C nmr (deuteriochloroform): δ 196.2, 145.5, 135.6, 127.1, 123.7, 122.6, 121.6, 118.7, 110.1, 42.0, 36.9, 27.8.

Anal. Calcd for $C_{12}H_{11}NOS$: C, 66.33; H, 5.10; N, 6.45; S, 14.75. Found: C, 66.53; H, 5.21; N, 6.66; S, 14.42. No **2e** was formed.

In polyphosphate ester-methylene chloride at 0° for 4 hours these conditions yielded **2e** in 19% yield as a cream-colored solid, mp 170-171°; ^{1}H nmr (acetone-d_6): δ 2.26 (m, 2H), 3.00 (t, 2H), 3.05 (t, 2H), 7.15 (t, 1H), 7.37 (t, 1H), 7.53 (d, 1H), 7.67 (d, 1H), 10.8 (br, NH); ^{13}C nmr (deuteriochloroform): δ 192.7, 135.9, 134.9, 128.2, 127.1, 123.6, 121.5, 120.8, 112.2, 41.3. 36.9. 28.2.

Anal. Calcd. for $C_{12}H_{11}NOS$: C, 66.33; H, 5.10; N, 6.45; S, 14.75. Found: C, 66.05; H. 5.05; H, 6.57; S, 14.60.

There was also obtained a 1.3% yield of **3e**.

Cyclization of **1f**. 6-Methyl-3,4-dihydro-2*H*-thiepino[3,2-*b*]-indol-5(6*H*)-one (**2f**) and 10-Methyl-3,4-dihydro-2*H*-thiepino[2,3-*b*]indol-5(10*H*)-one (**3f**).

In polyphosphoric acid cyclization at 100° for 15 minutes afforded **3f** in 24% yield as a cream-colored solid, mp 167-168°; ^{1}H nmr (acetone-d_6): δ 2.26 (m, 2H), 2.91 (t, 2H), 3.21 (t, 2H), 3.84 (s, 3H), 7.18 (t, 1H), 7.24 (t, 1H), 7.41 (d, 1H), 8.27 (d, 1H).

Anal. Calcd. for $C_{13}H_{13}NOS$: C, 67.50; H. 5.66; N, 6.06; S, 13.86. Found: C, 67.37; H, 5.71; N, 6.08; S, 13.51.

In polyphosphate ester-chloroform (1:1) the reaction at 0° for 4 hours gave **2f** in 20% yield as a beige solid, mp 97-99°; ^{1}H nmr (acetone-d_6): δ 2.25 (m, 2H), 2.98-3.05 (m, 4H), 4.03 (s, 3H), 7.18 (t, 1H), 7.41 (t, 1H), 7.52 (d, 1H), 7.69 (d, 1H).

Anal. Calcd. for $C_{13}H_{13}NOS$: C, 67.50;, H, 5.66; N, 6.06; S, 13.86. Found: C, 67.70; H, 5.76; N, 6.22; S, 13.60.

There was also obtained 18% of **3f**.

Cyclization of **1g**: 3,4,5,6-tetrabydro-2*H*-thiocino[3,2-*b*]indol-6(7*H*)-one (**2g**).

In polyphosphate ester-chloroform (1:1) at room temperature for 2 hours the cyclization yielded **2g** in 22% yield as a white solid, mp 168-169°; ir (potassium bromide): 3400, 1700, 1500, 1330 cm^{-1}; ^{1}H nmr (acetone-d_6): 1.69 (m, 2H), 1.91 (m, 2H), 2.82 (t, 2H), 3.52 (m, 2H), 7.19 (t, 1H), 7.36 (t, 1H), 7.59 (d, 1H), 7.82 (d, 1H), 11.11 (br, NH); ^{13}C nmr (deuteriochloroform): δ 193.5, 140.3, 137.5, 131.5, 127.0, 122.1, 121.7, 113.6, 109.9, 39.7, 32.3, 24.5, 24.3.

Anal. Calcd. for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06; S, 13.86. Found: C, 67.70; H, 5.79; N, 6.05; S, 13.85. No **3g** was observed.

Cyclization of 2-(Indolylthio)alkanoic Acids.

Cyclization of **4a**.

In polyphosphate ester-methylene chloride (1:1) at room temperature for 18 hours, only **8** was obtained in 65% yield. No trace of **3a** was detected.

Cyclization of **4b**.

In neat polyphosphate ester at 60° for 1 hour a 53% yield of **3b** was obtained.

Cyclization of **4c**.

In polyphosphoric acid at 95° for 1 hour [5] a 29% yield of **3c** was obtained. In polyphosphate ester-chloroform (1:1) at 60° for 4 hours there was obtained a 60% yield of **3c**.

Cyclization of **4e**.

In polyphosphate ester-methylene chloride (1:1) at room temperature for 5 hours a 51% yield of **3e** was obtained.

Cyclization of **4f**.

In polyphosphate ester-methylene chloride (1:1) at room temperature for 4.5 hours a 79% yield of **3f** was obtained.

Cyclization of **4g**. 3,4,5,6-Tetrahydro-2*H*-thiocino[2,3-*b*]indol-6(11*H*)-one (**3g**).

In polyphosphate ester-chloroform (1:1) at room temperature for 5.5 hours a 33% yield of **3g** was obtained. The product was a white solid, mp 230-232°; ir (potassium bromide): 3450, 2950, 1750, 1635 cm^{-1}; ^{1}H nmr (acetone-d_6): δ 1.75-1.91 (m, 4H), 2.98 (t, 2H), 3.37 (t, 2H), 7.22 (m, 2H), 7.44 (d, 1H), 8.43 (d, 1H), 11.09 (br, NH); ^{13}C nmr (deuteriochloroform): δ 197.7, 135.2, 133.7,127.5, 124.3, 122.9, 122.8, 110.4, 39.7, 33.0, 24.4, 24.0.

Anal. Calcd. for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06; S, 13.86. Found: C, 67.50; H, 5.65; N, 6.07; S, 14.08.

Thermal Cyclization of **6c**. 10-(2-Carbomethoxyethylthio)-3,4-dihydro-2*H*-[1,3]thiazino[3,2-*a*]indol-4-one (**9**).

The starting material **6c** was heated neat at 185-190° under mild vacuum for 6 hours. The crude product was chromatographed on silica gel (1:3 ethyl acetate-hexane) to afford compound **9** in 31% yield as a beige solid, mp 74-76°; ^{1}H nmr (acetone-d_6): δ 2.56 (t, 2H), 2.99 (t, 2H), 3.21 (t, 2H), 3.42 (t, 2H), 3.55 (s, 3H), 7.27-7.34 (m, 2H), 7.57 (d, 1H), 8.39 (d, 1H).

Anal. Calcd. for $C_{15}H_{15}NO_3S_2$: C, 56.05. H, 4.70; N, 4.36; S, 19.95. Found: C, 56.00; H, 4.67; N, 4.37; S, 20.27.

A similar cyclization in refluxing tetralin (206°) for 6 hours afforded a 35% yield of **9**.

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