Cyclization of 2- and 3-Indolylthiobenzoic, Phenylacetic and Nicotinic Acids and Esters to Novel Indole-Containing Tetracyclic Ring Systems.

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A series of 2- and 3-indolylthio benzoic, phenylacetic and nicotinic acids or esters were cyclized under dehydrative conditions affording several tetracyclic indole-containing ketones, several of which constitute the first reported examples of novel ring systems, such as the [1]benzothiepino[2,3-*b*] and [3,2-*b*]indole and the pyrido[3'2':5,6] and [3'4':5,6]thiopyrano[2,3-*b*] and [3,2-*b*]indole as well as the [3'2':5,6] and [3'4':5,6][1,3]thiazino[3,2-*a*]indole ring systems.

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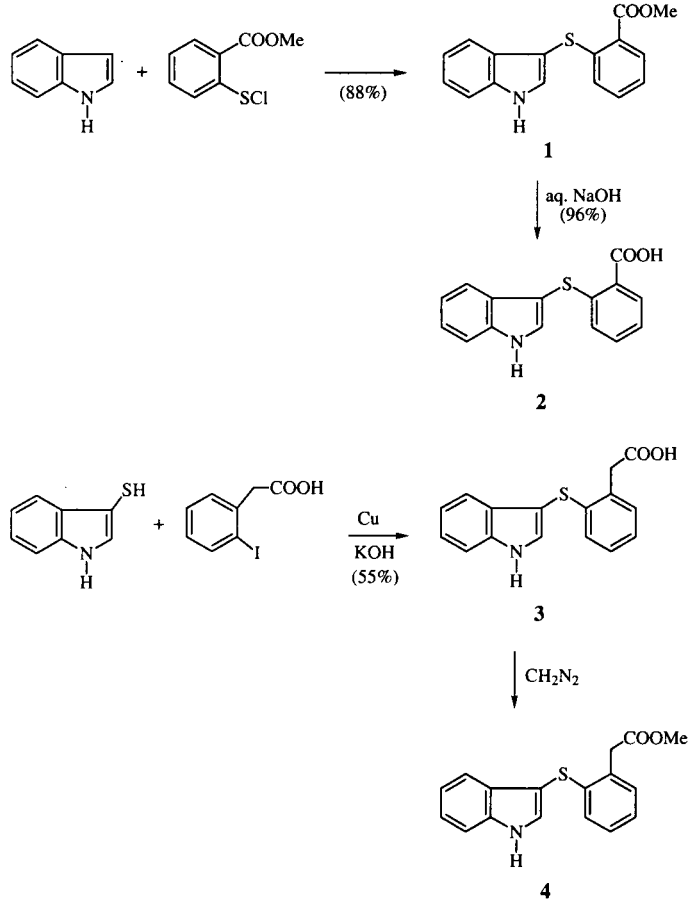
Introduction.

In a recent publication [1], we reported on the cyclization, under dehydrative conditions, of a series of readily available 2- and 3-indolylthioalkanoic acids of various chain lengths (1-4 methylene units) to novel indole-containing tricyclic ring systems. This methodology afforded entry into the hitherto unreported thiepino[3,2-*b*]indole, thiocino[2,3-*b*]indole and thiocino[3,2-*b*]indole ring systems. We have now expanded the same process to include the cyclization of 2-(2- and 3-indolylthio)benzoic and phenylacetic acids, leading to [1]benzothiopyrano[2,3-*b*] and [3,2-*b*]indole as well as the novel [1]benzothiepino[2,3-*b*] and [3,2-*b*]indole ring systems. In a further extension, we have also synthesized 2- and 4-(2- and 3-indolylthio)nicotinic acids which on cyclization led to novel linear and angular pyridine-containing tetracyclic ring systems. In some cases, the corresponding esters were used directly to afford the same cyclized products.

Materials and Methods.

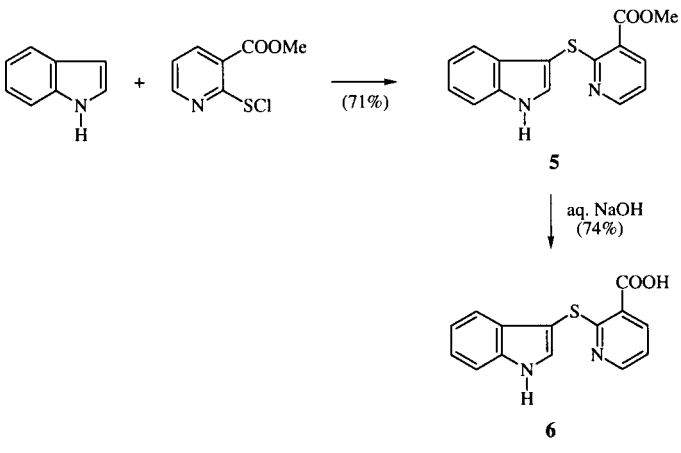
The various 2- and 3-indolylthiobenzoic, phenylacetic and nicotinic acid substrates were obtained *via* a variety of methods. Sulfenylation [2] of indole (Scheme 1) with slightly less than 1 equivalent of *o*-carbomethoxybenzenesulfenyl chloride, prepared *in situ* by reaction of sulfuryl chloride on *o*-carbomethoxyphenyl disulfide, led to the 2-(3-indolylthio)-benzoate **1** which on basic hydrolysis afforded the corresponding acid **2** in 84% overall yield. Since the preparation *o*-(carbomethoxymethyl)phenyl disulfide proved to be tedious, an alternate approach involving copper-catalyzed alkylation of 3-mercaptoindole [3] with *o*-iodophenylacetic in aqueous potassium hydroxide provided an acceptable yield (55%) of the homologated 2-(3-indolylthio)phenyl-acetic acid **3**, which was esterified using diazomethane to the ester **4**. Synthesis of 2-(3-indolylthio)nicotinic acid **6** was readily accomplished (Scheme 2) *via* sulfenylation of indole with 3-carbomethoxypyridine-2-sulfenyl chloride, derived from the corresponding disulfide and sulfuryl chloride, leading to ester **5** which was hydrolyzed to the acid **6** in 74% yield. The isomeric 4-(3-indolylthio)nicotinic acid **7** resulted

Scheme 1

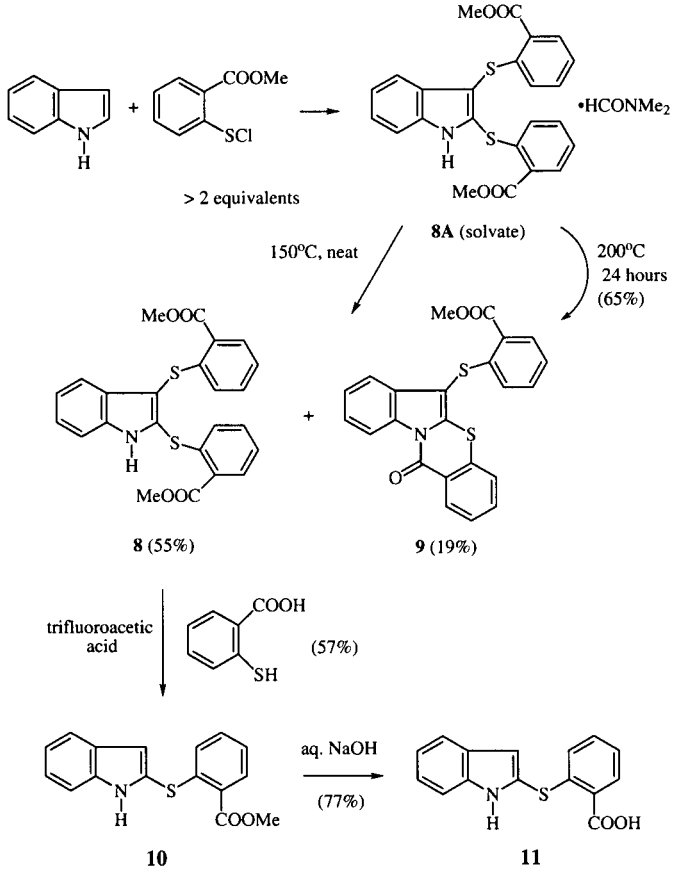


from copper-catalyzed alkylation of 3-mercaptoindole with 4-chloronicotinic acid [4] in aqueous sodium hydroxide. The corresponding 2-indolylthio analogs of the above substrates were prepared as follows. Double sulfenylation [2] of indole with *o*-carbomethoxybenzenesulfenyl chloride (Scheme 3) in the usual solvent mixture of dimethylformamide and 1,2-dichloroethane led to the 2,3-indolyl bis sulfide which

Scheme 2

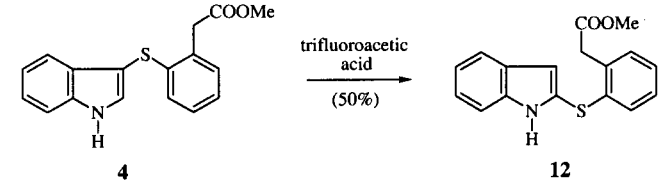


Scheme 3

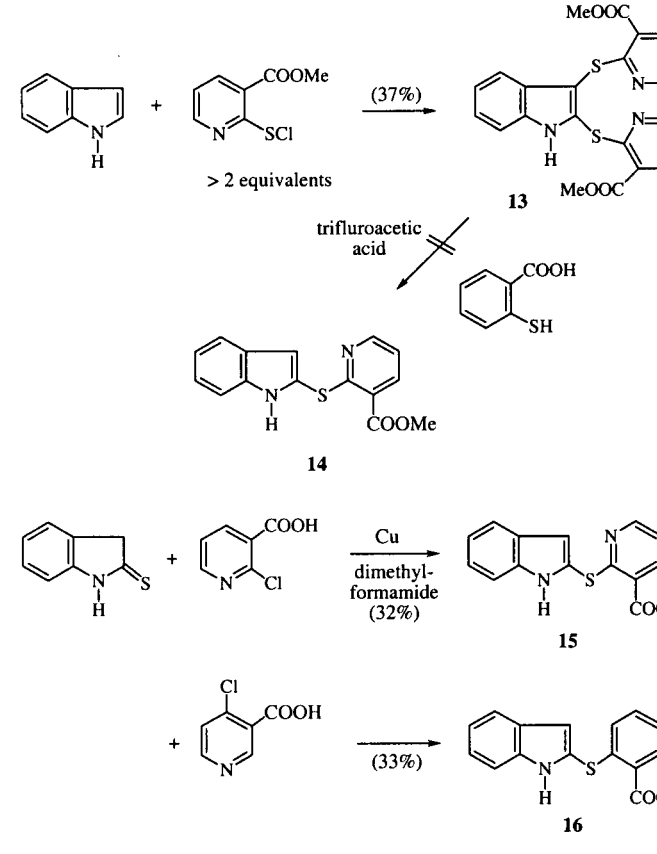


retained one molecule of dimethylformamide (**8A**) as was observed by proton nmr and elemental analysis. Even on crystallization from ethyl acetate-hexane or toluene, this solvate remained unchanged. It was possible to remove the trapped dimethylformamide by prolonged heating at 150° under vacuum, affording the pure bis sulfide **8** in 55% yield. As a side-product in this pyrolysis, the angular cyclized product **9** was obtained in 19% yield, resulting from cyclization on the indole nitrogen with loss of methanol. A superior yield of 65% of compound **9** was obtained by heating the solvate

Scheme 4



Scheme 5



8A at 200° for 24 hours. Selective desulfenylation [5] at the 3-position of the indole ring of **8** in trifluoroacetic acid in the presence of thiosalicylic acid afforded in 57% yield the 2-sulfide ester **10** which on basic hydrolysis provided 2-(2-indolylthio)benzoic acid **11**. Trifluoroacetic acid-catalyzed isomerization [6a,b] of 2-(3-indolylthio)phenylacetate **4** (Scheme 4) led to a moderate yield (50%) of the 2-indolylthio isomer **12**.

In an initial attempt (Scheme 5) at the preparation of

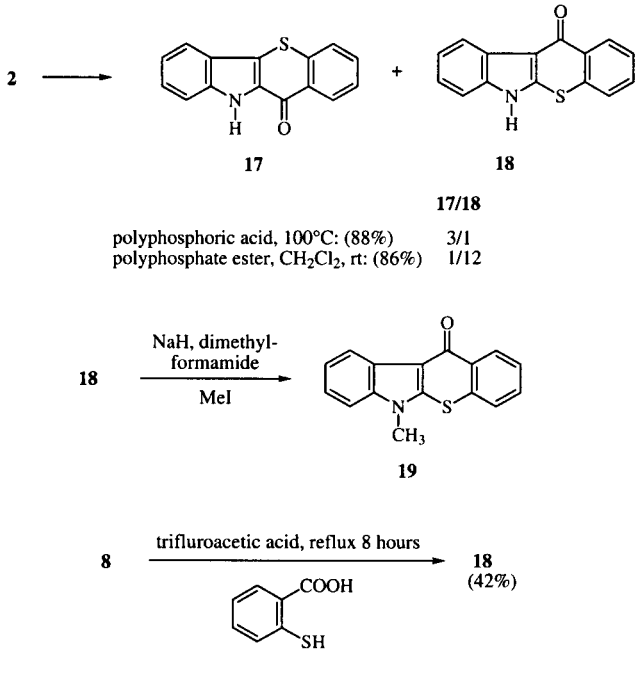
2-(2-indolylthio)nicotinic acid **15**, double sulfenylation of indole led to a 37% yield of the 2,3-bis sulfide **13**. When this material was subjected to selective desulfenylation at the 3-position, the desired 2-(2-indolylthio)nicotinate **14** was not obtained and only a dimeric product was produced. The desired acid **15** was alternatively obtained in modest yield (32%) *via* copper-catalyzed alkylation of 2-thioindole [7] with 2-chloronicotinic acid in dimethylformamide at 110°. The same approach, using 4-chloronicotinic acid, led to the isomeric 4-(2-indolylthio)nicotinic acid **16** in 33% yield. Cyclizations of the 2- and 3-indolylthio acids were effected in hot, neat polyphosphoric acid or in polyphosphate ester [8] as a 50% solution in methylene chloride or chloroform, at room temperature or with heating. In some cases, esters were cyclized directly without need for hydrolysis to the corresponding acids.

Results and Discussion.

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

Heating 2-(3-indolylthio)benzoic acid **2** in neat polyphosphoric acid at 100° for 45 minutes (Scheme 6) led to an excellent yield (88%) of a mixture of two cyclized products, in 3:1 ratio as determined by proton nmr. The compounds could not be separated by chromatography due to their low solubility, but heating in tetrahydrofuran allowed the isolation of the least soluble component in 32% yield. This compound was assigned structure **17** based on the presence of a doublet at 8.40 ppm in the proton nmr of the minor isomer **18**, corresponding to the H-4 proton of the indole ring, which is expected to appear at lower field than in compound **17** based on our studies of tricyclic analogs [1]. Although compound **18** has been previously reported [9] no nmr data was presented. When the cyclization was effected in 50% polyphosphate ester in methylene chloride at room temperature for 24 hours, the ratio of cyclized isomers was reversed and a 86% yield of a 12:1 mixture favoring isomer **18** was produced, from which **18** was isolated in 53% yield by crystallization from tetrahydrofuran. The structure of compound **18** was confirmed by transforming it into its *N*-methyl derivative **19**, which is a known compound [10]. These results were the opposite of what we had expected, since in our previous study of the cyclization of 2- and 3-indolylthioalkanoic acids [1] the major compounds resulting from polyphosphoric acid-catalyzed cyclizations had invariably resulted from initial isomerization [6a,b] to the corresponding 2-indolylthioalkanoic acids, leading to the cyclized isomer in which the sulfur atom of the third ring is attached to the 2-position of the indole ring. In the polyphosphate ester-catalyzed ring closures, the opposite trend had been observed. The possibility of rearrangement of **18** to **17** needed to be addressed in light of the observations of Bates and Habib [10] who reported on the acid-catalyzed isomerization of the *N*-methyl derivative of **18** (compound **19**) to the *N*-methyl derivative of **17**, presumably *via* a spirocyclic intermediate. In control experiments, we subjected both **17** and **18** to the conditions of cyclization, and did not observe any detectable isomerization in either case. At this time we cannot offer a formal explanation for the anomalous results of the cyclizations. As a working hypothesis, we speculate that the strongly acidic polyphosphoric acid leads to activation of the carboxylic acid as well as protonation of the indole ring, the latter being the first step in the proposed mechanisms leading to isomerization [6a,b]. If activation of the acid predominates, the steric hindrance caused by the presence of the phenyl ring, as well as the viscous reaction medium, all represent factors which could favor cyclization at the 2-position of the indole ring over the rearrangement. In contrast, the lesser acidity of the polyphosphate ester-methylene chloride solution may be sufficient to cause protonation of the indole ring in preference to acylium ion formation. The less viscous reaction medium would favor isomerization to the 2-indolylthio analog prior to cyclization, especially if the isomerization occurs *via* a complex intermolecular process [6a].

Scheme 6



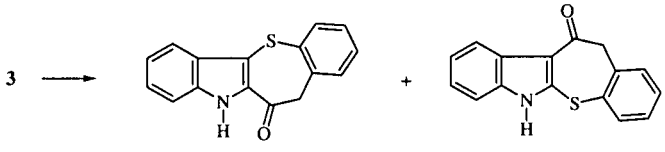
In an alternative approach, product **18** can be obtained directly in 42% yield by prolonged heating of bis-sulfide **8** in trifluoroacetic acid in the presence of thiosalicylic acid. In this case, selective desulfenylation leads *in situ* to the intermediate **10** which cyclizes to **18**. This last result was judged satisfactory enough to render unnecessary the study of the cyclization of 2-(2-indolylthio)benzoic acid **11** as an approach to compound **18**, since the combined yield for the transformation of **8** to **11** *via* ester **10** is only 44%.

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

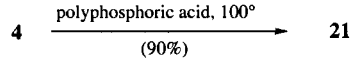
Submitting 2-(3-indolylthio)phenylacetic acid **3** to our dehydrative cyclization conditions led to results which were in line with our previous study [1] (Scheme 7). Thus, in hot

polyphosphoric acid, cyclized products **20** and **21** were produced in 15% and 21% yields respectively, while in 50% polyphosphate ester in methylene chloride at room temperature, only compound **20** was isolated in 65% yield, with traces of **21** detected in the crude product. Compounds **20** and **21** represent the first examples of the [1]benzothiepino-[3,2-*b*] and [2,3-*b*]indole ring systems. As mentioned in the materials and methods section, methyl 2-(2-indolylthio)-phenylacetate **12** was obtained in modest yield (50%) by isomerization of the 3-indolyl isomer **4**. However, when **4** was heated in polyphosphoric acid at 100° for a prolonged period (8.5 hours), an excellent yield of cyclized compound **21** (90%) was isolated, indicating that isomerization to **12** had occured followed by cyclization.

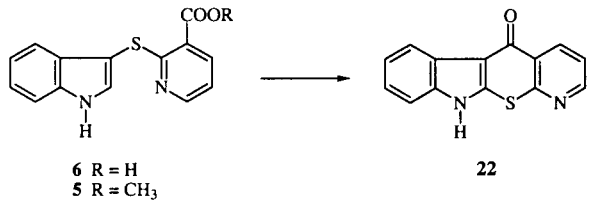
Scheme 7



	20	**21**
polyphosphoric acid, 100°:	15%	21%
polyphosphate ester, CH_2Cl_2:	65%	trace



Scheme 8

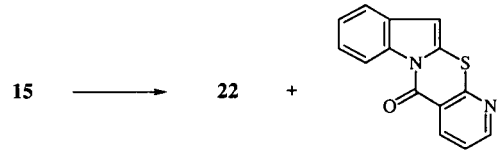


6 R = H
5 R = CH_3

22

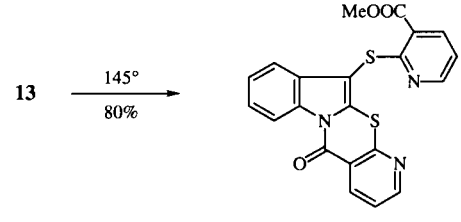
R = H: polyphosphoric acid, 90°C, 68%; polyphosphate ester, $CHCl_3$, rt, 42%

R = CH_3: polyphosphoric acid, 90°C, 92%



15 → **22** + **23**

	22	**23**
polyphosphoric acid, 90°:	44%	trace
polyphosphate ester, $CHCl_3$, 60°C:	12%	41%



13 → (145°, 80%) **24**

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

Treatment of 2-(3-indolylthio)nicotinic acid **6** with either polyphosphoric acid at 90° or 50% polyphosphate ester in chloroform at room temperature led to modest yields of only one cyclized compound (Scheme 8). This made the structural assignment difficult for lack of comparison of spectral data with the isomeric product. We have assigned the structure **22** to the isolated compound, the first example of the pyrido[3',2':5,6]thiopyrano[2,3-*b*]indole ring system, with the sulfur atom of the third ring attached to the 2-position of the indole ring, based on the result obtained in the cyclization of the isomeric 2-(2-indolylthio)nicotinic acid **15** in hot polyphosphoric acid. These conditions led to a 44% yield of the same compound, along with small amounts of minor components, one of which was the angular compound **23** described below. Since acid-catalyzed rearrangements of 2-indolyl sulfides to 3-indolyl sulfides have never been observed in previous studies [6a,b] we were confident in our assignment of the structure **22** to the compound resulting from polyphosphoric acid-catalyzed cyclization of **15**. The structure of compound **22** was formally confirmed by single crystal X-ray crystallography (ORTEP drawing, Figure 1, details in experimental section and Tables 1-3). Alternatively, 2-(3-indolylthio)nicotinate ester **5** could be cyclized directly to **22** in excellent yield (92%) in hot polyphosphoric acid.

In the polyphosphate ester-catalyzed ring closure of **15** at 60°, a mixture of compound **22** (12%) and a less polar component (41%) was obtained. This product was identified as the angular tetracyclic derivative **23** based on the presence of a singlet at 7.12 ppm in the proton nmr spectrum, corresponding to the H-3 proton of the indole ring. Compound **23** is the first isolated example of the pyrido[3',2':5,6][1,3]-thiazino[3,2-*a*]indole ring system. Another example of a derivative of this novel ring system was obtained when bis-sulfide **13** was pyrolyzed at 145° for 20 minutes, leading to the substituted analog **24** in 80% yield.

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

In the ring closure of 4-(3-indolylthio)nicotinic acid **7** (Scheme 9), once again only one cyclized compound was isolated, whether polyphosphoric acid (52%) or polyphosphate ester (56%) were used. The same reasoning as above led us to assign structure **25** to this product, the first example of the pyrido[3':4':5,6]thiopyrano[2,3-*b*]indole ring system, again based on the results obtained in the cyclization of the isomeric 4-(2-indolylthio)nicotinic acid **16**. In polyphosphoric acid at 90°, **16** afforded a 64% yield of the

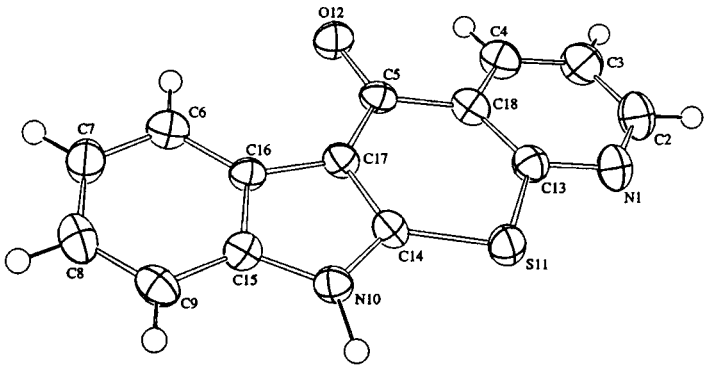


Figure 1. Perspective view of **22** with 50% thermal probability ellipsoids (except hydrogens which are at an arbitrary size).

Table 1

Crystallographic Experimental Quantities

compound	**22**
formula	$C_{14}H_8N_2OS$
fw	252.297
a	12.327(3) Å
b	8.031(4) Å
c	23.017(3) Å
α	90°
β	109.34(1)°
γ	90°
Z	8
V	2150(2) Å^3
D_x	1.559 g/cm^3
space group	Monoclinic C2/c
radiation (λ)	Cu
temperature(K)	294°
reflections measured	2107
reflections used	2107
refinement type	F^2 (SHELXL-93)
parameters varied	163
R	0.053 [a]
GOF	1.12
residual peak (eÅ^{-3})	0.26

[a] Based on 1283 reflections with $I > 2\sigma(I)$.

same compound **25** along with traces of the angular tetracyclic **26,** the first representative of the pyrido[3',4':5,6]-[1,3]thiazino[3,2-*a*]indole ring system. In 50% polyphosphate ester in chloroform yields of **25** and **26** were 14% and 56% respectively.

The results of the cyclizations of compounds **6** and **7**, leading to single cyclized isomers **22** and **25** in which the sulfur atom of the third ring is attached to the 2-position of the indole ring, seem to indicate that isomerization to the 2-indolylthio analogs (**15** and **16** respectively) occured prior to cyclization. Why such an isomerization should be favored under these conditions is not clear. Two mechanisms previously reported for this type of rearrangement propose an initial protonation of the indole ring followed by either an intramolecular migration of the sulfide group [6b] or a more complex intermolecular process [6a]. In the cases at hand, the sulfide group bears a pyridine ring which could itself get protonated, thus potentially disfavoring the isomerization. However, protonation of the pyridine ring would also be expected to disfavor the activation of the carboxylic acid *via* formation of an acylium ion species,

Table 2

Selected Bond Lengths (Å) and Angles (degrees)

S11—C14	1.721(4)	C5—C18	1.480(5)
S11—C13	1.752(4)	C6—C7	1.374(6)
O12—C5	1.251(5)	C6—C16	1.406(5)
N1—C2	1.340(6)	C7—C8	1.396(6)
N1—C13	1.343(5)	C8—C9	1.372(6)
N10—C14	1.359(5)	C9—C15	1.388(6)
N10—C15	1.389(5)	C13—C18	1.387(6)
C2—C3	1.377(7)	C14—C17	1.400(5)
C3—C4	1.375(6)	C15—C16	1.393(5)
C4—C18	1.399(5)	C16—C17	1.443(5)
C5—C17	1.428(5)		
C14—S11—C13	100.1(2)	N10—C14—C17	110.2(3)
C2—N1—C13	116.6(4)	N10—C14—S11	122.4(3)
C14—N10—C15	108.4(3)	C17—C14—S11	127.3(3)
N1—C2—C3	123.6(4)	C9—C15—N10	128.7(4)
C4—C3—C2	118.4(5)	C9—C15—C16	122.7(4)
C3—C4—C18	120.4(4)	N10—C15—C16	108.6(3)
O12—C5—C17	121.2(4)	C15—C16—C6	119.2(4)
O12—C5—C18	121.2(4)	C15—C16—C17	107.2(3)
C17—C5—C18	117.6(3)	C6—C16—C17	133.6(4)
C7—C6—C16	118.2(4)	C14—C17—C5	124.2(4)
C6—C7—C8	121.3(4)	C14—C17—C16	105.5(3)
C9—C8—C7	121.6(4)	C5—C17—C16	130.3(3)
C8—C9—C15	117.0(4)	C13—C18—C4	116.0(4)
N1—C13—C18	124.9(4)	C13—C18—C5	125.0(4)
N1—C13—S11	110.0(3)	C4—C18—C5	119.0(4)
C18—C13—S11	125.1(3)		

Estimated standard deviations are in parentheses.

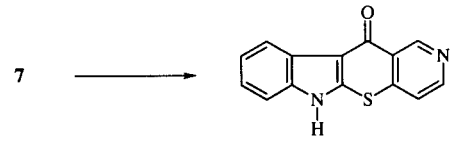
Table 3

Fractional Atomic Coordinates and Isotropic Displacement Parameters (Å^2)

Atom	x	y	z	Ueq
S11	0.71588(9)	0.05908(14)	0.38135(5)	0.0357(3)
O12	1.0415(2)	0.3082(4)	0.49880(14)	0.0390(7)
N1	0.7555(3)	0.2403(5)	0.2999(2)	0.0405(9)
N10	0.7453(3)	-0.0400(4)	0.4979(2)	0.0312(7)
C2	0.8074(4)	0.3595(6)	0.2779(2)	0.0467(12)
C3	0.9000(4)	0.4503(7)	0.3140(2)	0.0491(12)
C4	0.9434(4)	0.4146(6)	0.3759(2)	0.0391(10)
C5	0.9473(3)	0.2466(5)	0.4670(2)	0.0287(8)
C6	0.9965(4)	0.1241(5)	0.6120(2)	0.0362(9)
C7	0.9918(4)	0.0525(6)	0.6653(2)	0.0407(10)
C8	0.9030(4)	-0.0560(6)	0.6649(2)	0.0428(10)
C9	0.8168(4)	-0.0959(5)	0.6113(2)	0.0366(10)
C13	0.7987(3)	0.2104(5)	0.3606(2)	0.0322(9)
C14	0.7840(3)	0.0543(5)	0.4598(2)	0.0302(8)
C15	0.8210(3)	-0.0220(5)	0.5576(2)	0.0316(9)
C16	0.9086(3)	0.0863(5)	0.5566(2)	0.0265(8)
C17	0.8856(3)	0.1362(5)	0.4934(2)	0.0279(8)
C18	0.8950(4)	0.2876(5)	0.4009(2)	0.0320(9)

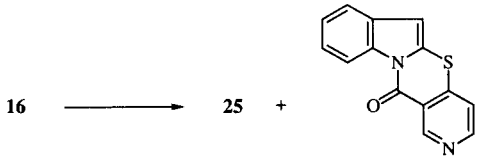
Ueq is given by one-third of the trace of Uij.

Scheme 9



25

polyphosphoric acid, 90°C 52%
polyphosphate ester, $CHCl_3$, 60°C 56%



26

	25	26
polyphosphoric acid, 90°:	64%	trace
polyphosphate ester, $CHCl_3$, 60°;	14%	56%

since it would lead to a positively charged substituent on a ring already bearing such a charge. In the light of the observed results it would appear that the isomerization represents the "least disfavored" of the two processes.

In all of the cyclizations presented in this report, the yields of cyclized products vary from modest to fair, although all of the starting materials have been consumed. Where lower yields are obtained, losses are attributed to the formation of decomposition products. In some cases separation and/or purification of cyclized products are complicated by their low solubility in organic solvents, as exemplified by compounds **17** and **18**. It is likely that transformation to more soluble derivatives, such as *N*-substituted analogs, would facilitate separation of the isomers.

Conclusion.

Cyclization of 2- and 3-indolylthiobenzoic, phenylacetic and nicotinic acids or esters provides access to a series of indole-containing tetracyclic ring systems. In particular, the [1]benzothiepino[3,2-*b*] and [2,3-*b*]indole, the pyrido-[3',2':5,6] and [3',4':5,6]thiopyrano[2,3-*b*] and [3,2-*b*]-indole as well as the [3',2':5,6] and [3',4':5,6][1,3]thiazino-[3,2-*a*]indole ring systems become attainable for the first time by this methodology.

EXPERIMENTAL

Commercial reagents and solvents were used without further purification. Melting points were recorded in open-end capillairies and are uncorrected. Infrared spectra of cyclized products 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 provided by Oneida Research Services, Inc. Whitesboro, N. Y. and Laboratoire d'analyse élémentaire, Université de Montréal. Thin layer chromatography was done using commercial silica gel plates and chromatographic separations were performed using flash silica gel columns.

Methyl 2-(3-Indolylthio)benzoate (**1**).

To a solution of 1.20 g of (2-carbomethoxyphenyl)disulfide (3.6 mmoles) in 15 ml of 1,2-dichloroethane was added 459 mg of sulfuryl chloride (3.4 mmoles), and the resulting green-purple solution was stirred at room temperature for 5 minutes. This solution was added slowly to a cold (0°) solution of 936 mg (8 mmoles) of indole in 15 ml of dimethylformamide. The mixture was stirred in the cold for 1 hour, then it was quenched with 15 ml of water. The 1,2-dichloroethane was evaporated, and the residual solution was diluted with 100 ml of water, precipitating an oil which solidified on further stirring. After filtration, the dry solid was crystallized from ether affording 1.69 g (88%) of **1** as a cream-colored solid, mp 156-158° (lit 160-162° by another method [11]).

2-(3-Indolylthio)benzoic Acid (**2**).

A mixture of 1.5 g of ester **1**, 15 ml of methanol and 10 ml of 2.5*N* aqueous sodium hydroxide was refluxed for 20 minutes. The cooled solution was diluted with 50 ml of water and acidified with 6*N* aqueous hydrochloric acid, precipitating a solid which was filtered to afford 1.37 g (96%) of acid **2** as a white solid, mp 254-256° dec; ^1H nmr (acetone-d_6): δ 6.83 (d,1H), 7.08-7.15 (m, 2H), 7.19-7.25 (m, 2H), 7.42 (d, 1H), 7.56 (d, 1H), 7.67 (s, 1H), 8.05 (d, 1H), 10.8 (br, NH).

Anal. Calcd. for $C_{15}H_{11}NO_2S$: C, 66.90; H, 4.12; N, 5.20; S, 11.90. Found: C, 67.24; H, 4.15; N, 5.40; S, 11.99.

2-(3-Indolylthio)phenylacetic Acid (**3**) and Methyl 2-(3-Indolylthio)phenylacetate (**4**).

A mixture of 1.49 g of 3-mercaptoindole [3] (10 mmoles), 2.49 g of 2-iodophenylacetic acid (9.5 mmoles), 794 mg of copper powder (12.5 mmoles), 6 ml of 8*N* aqueous potassiun hydroxide (48 mmoles) and 50 ml of water was refluxed for 18 hours. The cooled mixture was filtered and the filtrate was acidified with 1*N* aqueous hydrochloric acid, then extracted 3 times with ether. The crude product from the extracts was stirred with 20 ml of ether at room temperature for 30 minutes and filtered to yield a first crop of 692 mg of **3** as a cream-colored solid, mp 175-177°. The filtrate was evaporated and the residue was stirred with 25 ml of 1:1 ether-hexane for 30 minutes at room temperature and filtered, affording a second crop of 854 mg of **3**, bringing the yield to 1.546 g (55%); ^1H nmr (acetone-d_6): δ 3.95 (s, 2H), 6.84 (d, 1H), 6.97-7.09 (m, 3H), 7.18-7.22 (m, 1H), 7.26 (d, 1H), 7,47 (d, 1H), 7.52 (d, 1H), 7.69 (s, 1H), 10.77 (br, NH).

Anal. Calcd. for $C_{16}H_{13}NO_2S$: C, 67.82; H, 4.62; N, 4.94; S, 11.31. Found: C, 67.53; H, 4.61; N, 4.91; S, 11.13.

The filtrate material of the second filtration was esterified with ethereal diazomethane, and the crude ester chromatographed, eluting with 1:3 ethyl acetate-hexane to yield 187 mg (6%) of ester **4** as a cream-colored solid, mp 115-117°; ^1H nmr (acetone-d_6): δ 3.72 (s, 3H), 3.95 (s, 2H), 6.85 (d, 1H), 6.99-7.11 (m, 3H), 7.19 (m, 1H), 7.24 (d, 1H), 7.45 (d, 1H), 7.52 (d, 1H), 7.69 (s, 1H), 10.77 (br, NH).

Anal. Calcd. for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71; S, 10.78. Found: C, 68.39; H, 5.08; N, 4.77; S, 10.69.

Methyl 2-(3-Indolylthio)nicotinate (**5**).

To a suspension of 2.29 g of 2-(3-carbomethoxypyridine) disulfide (6.82 mmoles) in 20 ml of 1,2-dichloroethane was added 857 mg of sulfuryl chloride (6.35 mmoles). The mixture was stirred at room temperature for 5 minutes, then filtered through a plug of glass wool into a solution of 1.71 g of indole (14.6 mmoles) in 20 ml of dimethylformamide. After stirring at room temperature for 2 hours the 1,2-dichloroethane was evaporated, and the residue was diluted with 100 ml of water. The resulting suspension was extracted 3 times with ethyl acetate. The insoluble solid at the interface was filtered, affording a first crop of 1.4 g of **5** as a light yellow solid. The extracts were evaporated and the residue was stirred with 20 ml of ethyl acetate for 2 hours at room temperature and filtered, yielding an additional 1.56 g, bringing the total yield of **5** to 2.96 g (71%), mp 207-209°; ^{1}H nmr (acetone-d_6): δ 3.97 (s, 3H), 7.04 (t, 1H), 7.16 (m, 2H), 7.38 (d, 1H), 7.49 (d, 1H), 7.56 (s, 1H), 8.25 (m, 2H), 10.65 (br, NH).

Anal. Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85; S, 11.28. Found: C, 63.18; H, 4.27; N, 9.72; S, 11.33.

2-(3-Indolylthio)nicotinic Acid (**6**).

A mixture of 500 mg of ester **5**, 7.5 ml of methanol, 7.5 ml of tetrahydrofuran and 7.5 ml of 1*N* aqueous sodium hydroxide was heated for a few minutes on a steam bath until a solution was obtained.The cooled mixture was diluted with water and acidified with 1*N* aqueous hydrochloric acid. The precipitate was filtered to give 350 mg (74%) of **6** as a yellow solid, mp 135° (dec) which was shown to be a hydrate; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 6.99 (t, 1H), 7.12 (m, 2H), 7.25 (m, 1H), 7.44 (d, 1H), 7.57 (s, 1H), 8.18 (d, 1H), 8.25 (m, 1H). The NH proton was not observed.

Anal. Calcd. for $C_{14}H_{10}N_2O_2S{\cdot}H_2O$: C, 58.32; H, 4.20; N, 9.72; S, 11.12. Found: C, 58.54; H, 3.79; N, 9.63; S, 11.16.

4-(3-Indolylthio)nicotinic Acid (**7**).

A solution of sodium 3-indolylthiolate was prepared as follows, by the method of Bourdais [3]. To a solution of 936 mg of indole (8 mmoles) and 608 mg of thiourea (8 mmoles) in 40 ml of methanol was added 0.2*M* aqueous iodine-potassium iodide complex until the color of iodine remained. The mixture was concentrated to remove most of the methanol and 40 ml of 2.5*N* aqueous sodium hydroxide was added. The cloudy mixture was heated at 100° under a nitrogen atmosphere for one hour. A mixture of 945 mg of 4-chloronicotinic acid [4] (6 mmoles) and 445 mg of copper metal (7 mmoles) was added and the mixture was refluxed for 24 hours. The cooled mixture was filtered, the filtrate was acidified to *p*H 5 and the resulting precipitate was filtered. This solid was partitioned between ethyl acetate and 10% aqueous sodium bicarbonate. The aqueous fraction was acidified to *p*H 5 and extracted three times with ethyl acetate, the extracts were washed twice with brine, dried and evaporated to a yellow solid which was stirred in a small volume of ether for one hour. Filtration yielded 763 mg (47%) of **7** as a yellow solid, mp 190° dec; ^{1}H nmr (acetone-d_6): δ 6.72 (d, 1H), 7.13 (t, 1H), 7.26 (t, 1H), 7.41 (d, 1H), 7.59 (d, 1H), 7.73 (s, 1H), 8.15 (d, 1H), 9.04 (s, 1H), 10.95 (br, NH).

Anal. Calcd. for $C_{14}H_{10}N_2O_2S{\cdot}H_2O$: H, 4.20; N, 9.72; S, 11.12. Found: H, 4.15; N, 9.56; S, 11.15.

2,3-bis(2-Carbomethoxyphenylthio)indole (**8**) and 6-(2-Carbomethoxyphenylthio)indolo[2,1-*b*][1,3]benzothiazin-12-one (**9**).

To a solution of 2.10 g of 2-carbomethoxyphenyl disulfide (6.3 mmoles) in 30 ml of 1,2-dichloroethane at room temperature was added 810 mg of sulfuryl chloride (6 mmoles). The resulting gray-purple solution was stirred for 5 minutes then added to a solution of 585 mg of indole (5 mmoles) in 15 ml of dimethylformamide. The resulting amber solution was stirred overnight at room temperature. The 1,2-dichloroethane was evaporated and the residual solution was diluted with water, precipitating an oil which solidified on further stirring. The supernatant was decanted and the solid was stirred with 100 ml of 1:1 ether-hexane for 30 minutes and filtered, affording 2.14 g of a tan solid (**8A**) which was shown to be a dimethylformamide solvate of **8**. Crystallization from ethyl acetate-hexane led to 1.66 g of crystalline product, mp 137-139°, which was still the same solvate; ^{1}H nmr (deuteriochloroform): δ 2.86 (s, 3H), 2.93 (s, 3H), 3.93 (s, 6H), 6.76 (d, 1H), 6.85 (d, 1H), 7.03-7.21 (m, 5H), 7.30 (t, 1H), 7.42 (d, 1H), 7.55 (d, 1H), 7.91 (d, 1H), 7.98 (m, 2H), 8.89 (br, NH).

Anal. Calcd. for $C_{24}H_{19}NO_4S_2{\cdot}C_7H_3NO$: C, 62.05; H, 5.01; N, 5.36; S, 11.90. Found: C, 61.94; H, 5.14; N, 5.34; S, 11.90.

A sample crystallized from toluene also gave the same solvate. The crystalline product (1.33 g) was heated at 150° under mild vacuum for 5 hours, whereupon all the dimethylformamide had been removed, and a mixture of two compounds was obtained. Separation by chromatography eluting with a 1:3 mixture of ethyl acetate and hexane afforded, as least polar component, 225 mg (19%) of compound **9** as a fluffy yellow solid, mp 215-216°; ^{1}H nmr (deuteriochloroform): δ 4.01 (s, 3H), 6.76 (d, 1H), 7.13 (m, 2H), 7.38-7.48 (m, 4H), 7.54-7.60 (m, 2H), 8.06 (d, 1H), 8.62 (d, 1H), 8.90 (d, 1H); ^{13}C nmr (deuteriochloroform): δ 166.9, 159.8, 140.5, 136.3, 135.3, 133.5, 133.2, 132.7, 131.7, 131.3, 130.4, 126.63, 126.56, 125.8, 125.7, 125.3, 124.5, 124.3, 123.3, 117.9, 117.3, 103.6, 52.3; ir: 1710, 1688, 1438, 1135 cm^{-1}.

Anal. Calcd. for $C_{23}H_{15}NO_3S_2$: C, 66.17; H, 3.62; N, 3.35; S, 15.36. Found: C, 65.98; H, 3.80; N, 3.43; S, 14.98.

Further elution provided 710 mg (55%) of **8** as a light yellow solid, mp 171-173°; ^{1}H nmr (deuteriochloroform): δ 3.93 (s, 6H), 6.75 (d, 1H), 6.85 (d, 1H), 7.02-7.21 (m, 5H), 7.30 (t, 1H), 7.42 (d, 1H), 7.55 (d, 1H), 7.90 (d, 1H), 7.98 (d, 1H), 8.90 (br, NH).

Anal. Calcd. for $C_{24}H_{19}NO_4S_2$: C, 64.12; H, 4.26; N, 3.12; S, 14.26. Found: C, 63.90; H, 4.33; N, 3.25; S, 13.91.

Improved Yield of Compound **9** by Prolonged Pyrolysis of Dimethylformamide Complex **8A**.

A 200 mg sample of compound **9** was heated neat at 190-200° under light vacuum for 24 hours. A small amount of **8** remained. The cooled mixture was chromatographed, eluting with 25% ethyl acetate in hexane, with methylene chloride used to dissolve the mixture, to afford 103 mg of compound **9** (65%) as a yellow fluffy solid.

Methyl 2-(2-indolylthio)benzoate (**10**).

A mixture of 550 mg of compound **8** (1.225 mmoles) and 378 mg of thiosalicylic acid (2.45 mmoles) in 7 ml of trifluoroacetic acid was refluxed for 2 hours. The acid was evaporated and the residue was partitioned between ethyl acetate and 1*N* aqueous sodium hydroxide. The crude product from the organic phase was chromatographed, eluting with a 1:5 mixture of acetone and hexane, to yield 198 mg (57%) of **10** as an oil which solidified. Crystallization from ether-hexane led to 110 mg of off-white crystals, mp 98-100°; ^{1}H nmr (acetone-d_6): δ 3.94 (s, 3H), 6.79 (d, 1H), 6.90 (s, 1H), 7.10 (t, 1H), 7.22 (m, 2H), 7.35 (t, 1H), 7.45 (t, 1H), 7.65 (d, 1H), 7.98 (d, 1H), 10.56 (br, NH).

Anal. Calcd. for $C_{16}H_{13}NO_2S$: C, 67.82; H, 4.62; N, 4.94; S, 11.32. Found: C, 68.19; H, 4.55; N, 4.65; S, 11.07.

2-(2-Indolylthio)benzoic Acid (**11**).

Ester **10** was hydrolyzed as in the preparation of compound **6**. The crude acid was stirred in a small volume of 1:3 ether-hexane for 10 minutes and filtered to yield 88 mg (77%) of acid **11** as a white solid, mp 195° dec; ^{1}H nmr (acetone-d_6): δ 6.77 (d, 1H), 6.90 (s, 1H), 7.10 (t, 1H), 7.22 (m, 2H), 7.35 (t, 1H), 7.44 (d, 1H), 7.64 (d, 1H), 8.06 (d, 1H), 10.55 (br, NH).

Anal. Calcd. for $C_{15}H_{11}NO_2S$: C, 66.90; H, 4.12; N, 5.20; S, 11.90. Found: C, 66.55; H, 4.08; N, 5.01; S, 11.70.

Methyl 2-(2-Indolylthio)acetate (**12**) by Isomerization of Methyl 2-(3-Indolylthio)acetate (**4**).

A solution of 300 mg of compound **4** in 4 ml of trifluoroacetic acid was stirred at room temperature for 24 hours. The mixture was poured onto 50 ml of water and extracted twice with ethyl acetate. The combined organic fractions were washed with water, aqueous sodium bicarbonate and water, dried and evaporated. The residue was chromatographed, eluting with a 1:5 mixture of ethyl acetate and hexane to afford 150 mg (50%) of **12** as a cream-colored solid, mp 98-100°; ^{1}H nmr (acetone-d_6): δ 3.67 (s, 3H), 3.92 (s, 2H), 6.76 (s, 1H), 7.03 (t, 1H), 7.10-7.22 (m, 4H), 7.31 (d, 1H), 7.36 (d, 1H), 7,57 (d, 1H), 10.43 (br, NH).

Anal. Calcd. for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71; S, 10.78.Found: C, 68.57; H, 4.98; N, 4.72; S, 10.88.

2,3-bis(3-Carbomethoxypyridyl-2-thio)indole (**13**).

The preparation of 3-carbomethoxypyridine-2-sulfenyl chloride was accomplished as described above in the synthesis of compound **5**, using 2.16 g of 2-(3-carbomethoxypyridine) disulfide (6.3 mmoles) and 810 mg of sulfuryl chloride (6 mmoles) in 30 ml of 1,2-dichloroethane. The solution was added to a solution of 585 mg of indole (5-mmoles) in 15 ml of dimethylformamide, and the resulting mixture was stirred at room temperature overnight. After evaporation of the dichloroethane the residual solution was diluted with 150 ml of water and a small amount of disulfide starting material was filtered. The filtrate was basified with 1*N* aqueous sodium hydroxide, leading to precipitation of a light orange solid which was filtered. This solid was boiled with 40 ml of ethanol for 20 minutes, the suspension was cooled, left at room temperature for 3 hours and filtered, affording 844 mg (37%) of **13** as a cream-colored solid, mp 145° dec; ^{1}H nmr (acetone-d_6): δ 3.89 (s, 6H), 7.23 (m, 3H), 7.40 (t, 1H), 7.50 (d, 1H), 7.64 (d, 1H), 8.25 (d, 2H), 8.36 (d, 2H), 9.30 (br, NH).

Anal. Calcd. for $C_{22}H_{17}N_3O_4S_2$: C, 58.52; H, 3.79; N, 9.31; S, 14.20. Found: C, 58.74; H, 3.86; N, 9.46; S, 14.32.

2-(2-Indolylthio)nicotinic Acid (**15**).

A mixture of 1.49 g of thioindole [7] (10 mmoles), 1.732 g of 2-chloronicotinic acid (11 mmoles) and 826 mg of copper powder (13 mmoles) in 25 ml of dimethylformamide was heated at 110° for 2.5 hours under nitrogen atmosphere. After cooling, the mixture was filtered and the insolubles were washed with dimethylformamide. The filtrate was diluted with 100 ml of water and stirred until a yellow solid was obtained. After filtration the solid was taken up in 50 ml of 1*N* aqueous sodium hydroxide and the mixture was filtered. The filtrate was acidified with 1*N* aqueous hydrochloric acid and extracted 4 times with ethyl acetate. The extracts were washed with water, dried and evaporated to a yellow solid, which was stirred in a small volume of ethyl acetate at room temperature for 30 minutes and filtered. This afforded 866 mg (32%) of **15** as a yellow solid, mp 203° dec; ^{1}H nmr (acetone-d_6): δ 6.74 (s, 1H), 7.03 (t, 1H), 7.15 (t, 1H), 7.25 (m, 1H), 7.41 (d, 1H), 7.57 (d, 1H), 8.34 (d, 1H), 8.38 (d, 1H), 10.45 (br, NH).

Anal. Calcd. for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36; S, 11.86. Found; C, 61.99; H, 3.77; N, 10.23; S, 12.17.

4-(2-Indolylthio)nicotinic Acid (**16**).

The same procedure as above for the preparation of compound **15** was followed, using 4-chloronicotinic acid [4] as starting material. After heating for 30 minutes the mixture was worked up in the same manner. The crude product was dissolved in hot acetone and the solution was decolorized with activated charcoal and filtered through celite. Concentration to a small volume led to separation of a yellow solid which was filtered to afford **16** in 33% yield, mp >300°; ^{1}H nmr (acetone-d_6): δ 6.68 (d, 1H); 6.95 (s, 1H), 7.13 (t, 1H), 7.25 (t, 1H), 7.48 (d, 1H), 7.68 (d, 1H), 8.40 (br s, 1H); 9.08 (br s, 1H); 10.70 (br, NH).

Anal. Calcd. for $C_{14}H_{10}N_2O_2S$; C, 62.21; H, 3.73; N, 10.36; S, 11.86. Found: C, 61.80; H, 3.77; N 10.23; S, 12.17.

Based on mp and nmr data the product appears to be in zwitterionic form.

Representative Procedures for the Cyclization Reactions.

Cyclization of **2**. [1]Benzothiopyrano[3,2-*b*]indol-11(10*H*)-one (**17**) and [1]Benzothiopyrano[2,3-*b*]indol-11(6*H*)-one (**18**).

a) in Polyphosphoric Acid.

To 25 g of polyphosphoric acid preheated to 100° was added 600 mg of **2** which slowly dissolved into a dark syrup. After 45 minutes the mixture was cooled down and triturated with 200 ml of water until a green solid was obtained. The solid was filtered, suspended in water and filtered again to afford 495 mg (88%) of crude product, shown to be a mixture of two compounds in a 3:1 ratio as determined by ^{1}H nmr. The solid was boiled in 40 ml of tetrahydrofuran for 10 minutes, the suspension was allowed to cool down and was stirred at room temperature overnight. Filtration afforded 180 mg (32%) of the major component **17** as a yellow solid, mp >300°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.25 (t, 1H), 7.51 (t, 1H), 7.64 (m, 2H), 7.77 (t, 1H), 7.92 (d, 1H), 8.03 (d, 1H), 8.61 (d, 1H), 12.75 (NH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 171.2, 138.2, 136.0, 131.3, 130.8, 128.8, 128.0 127.8, 127.6, 126.4, 123.1, 120.49, 120.47, 116.4, 113.3; ir: 3180, 1603, 1578, 723 cm^{-1}.

Anal. Calcd. for $C_{15}H_9NOS$: H, 3.61; N, 5.57; S, 12.76. Found: H, 3.56; N, 5.64; S, 12.91.

The filtrate material was a 1:1.5 mixture of **18** (see below) and **17**.

b) In Polyphosphate Ester.

To a solution of 6 g of polyphosphate ester [8] in 6 ml of dichloromethane was added 600 mg of **2**, and the mixture was stirred at room temperature for 21 hours. To the solution was added 15 ml of water, precipitating a solid which was filtered, affording 480 mg (86%) of a mixture of **17** and **18** in a 1:12 ratio as determined by ^{1}H nmr. Crystallization of the mixture from tetrahydrofuran afforded 298 mg (53%) of the major isomer **18** [9] as beige crystals, mp >300°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.28-7.37 (m, 2H), 7.55 (m, 1H), 7.63 (t, 1H), 7.73 (t, 1H), 7.95 (d, 1H), 8.40 (m, 1H), 8.57 (d, 1H), 12.51 (NH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 175.4, 141.1, 136.6, 132.3, 131.2, 130.8, 128.0, 127.4, 126.9, 125.0, 124.0, 121.7, 120.7, 111.2, 110.7; ir: 3150, 1595, 1568, 1460, 735 cm^{-1}.

Anal. Calcd. for $C_{15}H_9NOS$; : C, 71.69; H, 3.61; N, 5.57; S, 12.76. Found: C, 71.63; H, 3.52; N, 5.62; S, 12.46

The filtrate material was a 4:1 mixture of **17** and **18**.

N-Methylation of **18**. 6-Methyl-[1]benzothiopyrano[2,3-*b*]indol-11(6*H*)-one (**19**).

To a suspension of 12 mg of sodium hydride (80% suspension in oil, 0.23 mmole) in 1 ml of dimethylformamide was added 25 mg of compound **18** (0.1 mmole). The mixture was stirred at room temperature for 20 minutes, resulting in a yellow suspension to which an excess of iodomethane (0.2 ml) was added. After stirring for 2 hours the mixture was quenched with water and partitioned between ethyl acetate and water. From the organic phase was obtained 26 mg of a yellow solid, the ^{1}H nmr data of which corresponded to that reported for compound **19** [10].

Formation of **18** by Desulfenylation-cyclization of **8**.

A mixture of 403 mg of compound **8** (0.9 mmole) and 276 mg of thiosalicylic acid (1.79 mmoles) in 6 ml of trifluoroacetic acid was refluxed for 24 hours. The mixture was evaporated and the residue was stirred with 20 ml of ethyl acetate for 6 hours and filtered. The solid was then stirred with 20 ml of 1*N* aqueous sodium hydroxide for 2 hours, filtered and washed with water. A final swish with ethyl acetate provided 95 mg (42%) of compound **18** as a yellowish-brown solid, pure by nmr.

Cyclization of **3**. 11,12-Dihydro[1]benzothiepino[3,2-*b*]indol-11(10*H*)-one (**20**) and 11,12-Dihydro[1]benzothiepino[2,3-*b*]-indol-11(6*H*)-one (**21**).

a) In Polyphosphoric Acid.

The cyclization was accomplished at 100° for 45 minutes. The crude product was chromatographed, eluting with a 1:3 mixture of ethyl acetate and hexane, to afford as the least polar component 57 mg (15%) of compound **20** (see below) and as the more polar component 77 mg (21%) of compound **21** as a cream-colored solid, mp 283-285°; ^{1}H nmr (acetone-d_6): δ 4.19 (s, br, 2H), 7.16-7.30 (m, 3H), 7.41-7.47 (m, 2H), 7.55 (d, 1H), 7.70 (d, 1H), 8.28 (d, 1H), 11.40 (br, NH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 188.6, 141.2, 138.8, 135.0, 131.5, 131.4, 130.3, 130.0, 127.2, 126.7, 123.4, 122.0, 120.7, 114.8, 111.2, 51.4; ir: 3130, 1610, 1430, 750 cm^{-1}.

Anal. Calcd. for $C_{16}H_{11}NOS$: C, 72.43; H, 4.18; N, 5.28; S, 12.08. Found: C, 72.12; H, 4.19; N, 5.23; S, 11.77

b) In Polyphosphate Ester.

The cyclization in polyphosphate ester-dichloromethane was complete after 1.5 hours at room temperature. The crude product from the organic phase was chromatographed to afford 65% of **20** as a cream-colored solid, mp 234-236°; ^{1}H nmr (acetone-d_6): δ 7.20-7.32 (m, 2H), 7.40-7.48 (m, 2H), 7.56-7.60 (m, 2H), 7.77 (d, 1H), 7.86 (d, 1H), 11.05 (br, NH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 185.2, 137.8, 135.9, 135.0, 132.8, 131.0, 130.5, 129.4, 127.1, 126.7, 126.6, 120.7, 120.4, 117.6, 113.0, 50.5; ir: 3300, 1640, 1500, 1335, 742 cm^{-1}.

Anal. Calcd. for $C_{16}H_{11}NOS$: C, 72.43; H, 4.18; N, 5.28; S, 12.08. Found: C, 72.35; H, 4.11; N, 5.29; S, 12.00.

Minute traces of compound **21** were observed in the tlc of the crude mixture.

Formation of **21** by Polyphosphoric Acid-catalyzed Rearrangement-Cyclization of **4**.

A mixture of 162 mg of ester **4** and 7 g of polyphosphoric acid was heated at 100° for 8 hours. After cooling, the mixture was diluted with water and triturated. Filtration of the solid afforded 130 mg (90%) of crude **21** as a brown solid which was shown to be pure by nmr.

Cyclization of **6**. Pyrido[3',2':5,6]thiopyrano[2,3-*b*]indol-5(10*H*)-one (**22**).

a) In Polyphosphoric Acid.

After heating at 110° for 1.5 hours, the usual workup of water quench, trituration, filtration and ether swish afforded 68% of compound **22** as a yellow solid, mp >300°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.30-7.39 (m, 2H), 7.58 (d, 1H), 7.69 (m, 1H), 8.38 (d, 1H), 8.84 (m, 2H), NH not observed; ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 174.9, 154,7, 152.1, 141.6, 136.9, 136.4, 127.7, 124.7, 124.2, 122.5, 122.0, 120.7, 111.5, 110.8.

Anal. Calcd. for $C_{14}H_8N_2OS$: C, 66.65; H, 3.20; N, 11.10; S, 12.71. Found: C, 66.48; H, 3.05; N, 11.24; S, 12.59.

b) In Polyphosphate Ester.

The cyclization was accomplished in a 1:1 solution of polyphosphate ester and chloroform at room temperature for 28 hours. The crude product from the organic phase was shown to be exclusively compound **22** by ^{1}H nmr. Crystallization from dimethylformamide afforded 25 mg (42%) of crystalline **22**.

Compound **22** from Cyclization of Ester 5 in Polyphosphoric Acid.

To 11 g of polyphosphoric acid preheated to 90° was added 375 mg of ester **5**, and the mixture was heated for 1.5 hours. The mixture was quenched with 100 ml of water, triturated and filtered. The solid was washed with water and ethyl acetate to afford a crude yield of 320 mg (92%) of **22** as a greenish solid, shown to be a single entity by tlc and nmr.

Cyclization of **15**. Compound **22** and Pyrido[3',2':5,6]-[1,3]thiazino[3,2-*a*]indol-12-one (**23**).

a) In Polyphosphoric Acid.

Heating in polyphosphoric acid at 90° for 45 minutes, quenching with 50 ml of water and filtration gave a green solid which was dissolved in a 1:1 mixture of methanol and dichloromethane and adsorbed onto silica gel. The mixture was chromatographed, eluting with 10% ethanol in dichloromethane to yield 44% of compound **22**. In the crude mixture compound **23** (see below) was detected as a minor component.

b) In Polyphosphate Ester.

The cyclization was done in a 1:1 mixture of polyphosphate ester and chloroform at 60° for 1.5 hours. The usual workup gave a crude mixture which was chromatographed, eluting with a 1:2 mixture of ethyl acetate and hexane to afford 41% of compound **23** as a yellow solid, mp 191-193°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.12 (s, 1H), 7.37-7.43 (m, 2H), 7.59 (m, 1H), 7.66 (m, 1H), 8.68 (m, 1H), 8.74 (d, 1H), 8.80 (d, 1H); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 159.1, 154.9, 153.9, 138.5, 134.8, 129.0, 125.5, 124.8, 123.4, 121.8, 120.2, 119.4, 116.2, 105.0; ir: 1675, 1480, 1400, 1348 cm^{-1}.

Anal. Calcd. for $C_{14}H_8N_2OS$: C, 66.65; H, 3.20; N, 11.10; S, 12.71. Found: C, 66.27; H, 3.06; N, 10.97; S, 12.95.

Further elution of the column with 20% ethanol in ethyl acetate yielded 12% of compound **22**.

Pyrolysis of Indole bis-Sulfide **13**. 6-(3-Carbomethoxypyridyl-2-thio)pyrido[3',2':5,6][1,3]thiazino[3,2-*a*]indol-12-one (**24**).

A 400 mg sample of **13** was heated neat at 145-150° for 20 minutes with evolution of gas. The resulting brown solid was

stirred in 4 ml of ethyl acetate at room temperature for 30 minutes and filtered affording 297 mg (80%) of compound **24** as a gray-green solid, mp >250°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.93 (s, 3H), 7.28 (m, 1H), 7.38-7.48 (m, 3H), 7.63 (m, 1H), 8.33 (s, 1H), 8.34 (m, 1H), 8.75-8.83 (m, 3H); ^{13}C nmr (deuteriochloroform): δ 165.7, 160.1, 159.6, 156.2, 153.7, 152.5, 139.1, 138.8, 136.0, 133.9, 131.4, 125.2, 124.1, 123.1, 121.2, 120.7, 119.4, 118.2, 117.0, 105.3, 52.6; ir: 1715, 1688, 1440, 1400 cm^{-1}.

Anal. Calcd. for $C_{21}H_{13}N_3O_3S_2$: C, 60.13; H, 3.12; N, 10.02; S, 15.29. Found: C, 59.92; H, 3.11; N, 10.03; S, 15.39.

Cyclization of **7**. Pyrido[3',4':5,6][1,3]thiopyrano[2,3-*b*]indol-5(10*H*)-one (**25**).

a) In Polyphosphoric Acid.

The substrate **7** was cyclized in polyphosphoric acid at 90°. After 1.25 hours the mixture was quenched with 75 ml of water, triturated and filtered. This solid, possibly a phosphate salt, was stirred in 15 ml of 2*N* aqueous sodium hydroxide and 15 ml of ethyl acetate for 1 hour. The organic phase was collected and the insoluble solid in the aqueous phase was filtered and treated once more under the same conditions. The combined organic extracts were washed 3 times with water, dried and evaporated. The solid residue was triturated with 10 ml of ether and filtered to yield 146 mg (52%) of **25** as a yellow solid, mp >300°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.29-7.40 (m, 2H), 7.59 (d, 1H), 8.02 (d, 1H), 8.40 (d, 1H), 8.73 (d, 1H), 9.58 (s, 1H), 13.0 (br, NH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 174.9, 149.9, 149.3, 142.1, 140.1, 136.5, 125.2, 124.6, 124.3, 122.1, 121.6, 120.8, 120.5, 111.6.

Anal. Calcd. for $C_{14}H_8N_2OS$: H, 3.20; N, 11.10; S, 12,71. Found: H, 3.15; N, 10.92; S, 12.56.

b) In Polyphosphate Ester.

After refluxing for 1 hour in polyphosphate ester-chloroform the cooled mixture was diluted with water, stirred for 30 minutes and filtered. The solid was shaken with 2.5*N* aqueous sodium hydroxide and extracted several times with ethyl acetate until it had all dissolved. The crude product from the organic extracts was triturated with 10 ml of ether and filtered to afford a 56% yield of **25** as a yellow solid.

Cyclization of **16**. Compound **25** and Pyrido[3',4':5,6][1,3]-thiazino[3,2-*a*]indol-12-one (**26**).

a) In Polyphosphoric Acid.

After cyclization at 90° for 15 minutes the mixture was processed as described in the cyclization of **7** in polyphosphoric acid to yield 64% of **25** as a yellow solid. Traces of the angular product **26** (see below) were observed but not isolated.

b) In Polyphosphate Ester.

The substrate was heated at 60° for 1 hour in 1:1 polyphosphate ester-chloroform. Chromatography of the crude organic residue, eluting with 1:1 ethyl acetate-hexane afforded a 56% yield of compound **26** as a yellow solid, mp 177-179°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.15 (s, 1H), 7.41 (m, 2H), 7.68 (m, 1H), 7.79 (d, 1H), 8.69 (m, 1H), 8.70 (d, 1H), 9.43 (s, 1H); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 158.4, 151.7, 151.1, 143.2, 134.9, 128.6, 124.8, 124.7, 123.6, 119.7, 119.5, 118.3, 116.2, 105.4; ir: 1665, 1560, 1430, 1335 cm^{-1}.

Anal. Calcd. for $C_{14}H_8N_2OS$: C, 66.65; H, 3.20; N, 11.10; S, 12.71. Found: C, 66.57; H, 2.98; N, 10.93; S, 12.71.

From the aqueous fraction of the extractions a compound slowly crystallized and was filtered after 24 hours. This afforded 20 mg (14%) of compound **25** as a cream-colored solid.

X-Ray Crystallographic Analysis of **22**.

Suitable crystals of **22** ($C_{14}H_8N_2O_1S_1$) for X-ray analysis were obtained by slow evaporation from dimethylformamide. Data were collected on a Rigaku AFC5 diffractometer to a θ limit of 72.75° which yielded 2107 measured reflections. The structure was solved by direct methods (SHELXS-86) [12] and refined using full-matrix least-squares on F^2 (SHELXL93) [13]. The final model was refined using 163 parameters and all 2107 data.

Examination of the crystal packing in the unit cell shows one unique hydrogen bonding interaction between O12 and N10 of a neighboring molecule with a donor—H···acceptor distance of 2.80 Å. The carbonyl oxygen, O12, also points to an edge of a neighboring phenyl ring, ring-O-C angle of 172°, and a distance of 3.53 Å to the nearest atom. Stacking interactions between parallel molecules with interplanar distances ranging from 3.33 to 3.56 Å and dihedral angles ranging from 3.47 to 7.85° are also observed in the crystal lattice. Pertinent data are listed in Tables 1-3.

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