

Paul C. Unangst*, David T. Connor and Steven R. Miller

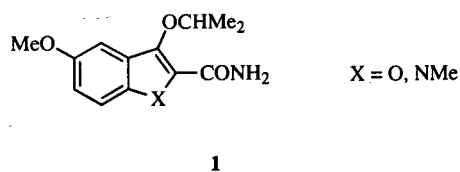
Department of Chemistry, Parke-Davis Pharmaceutical Research,
Division of Warner-Lambert Company, 2800 Plymouth Road,
Ann Arbor, MI 48105

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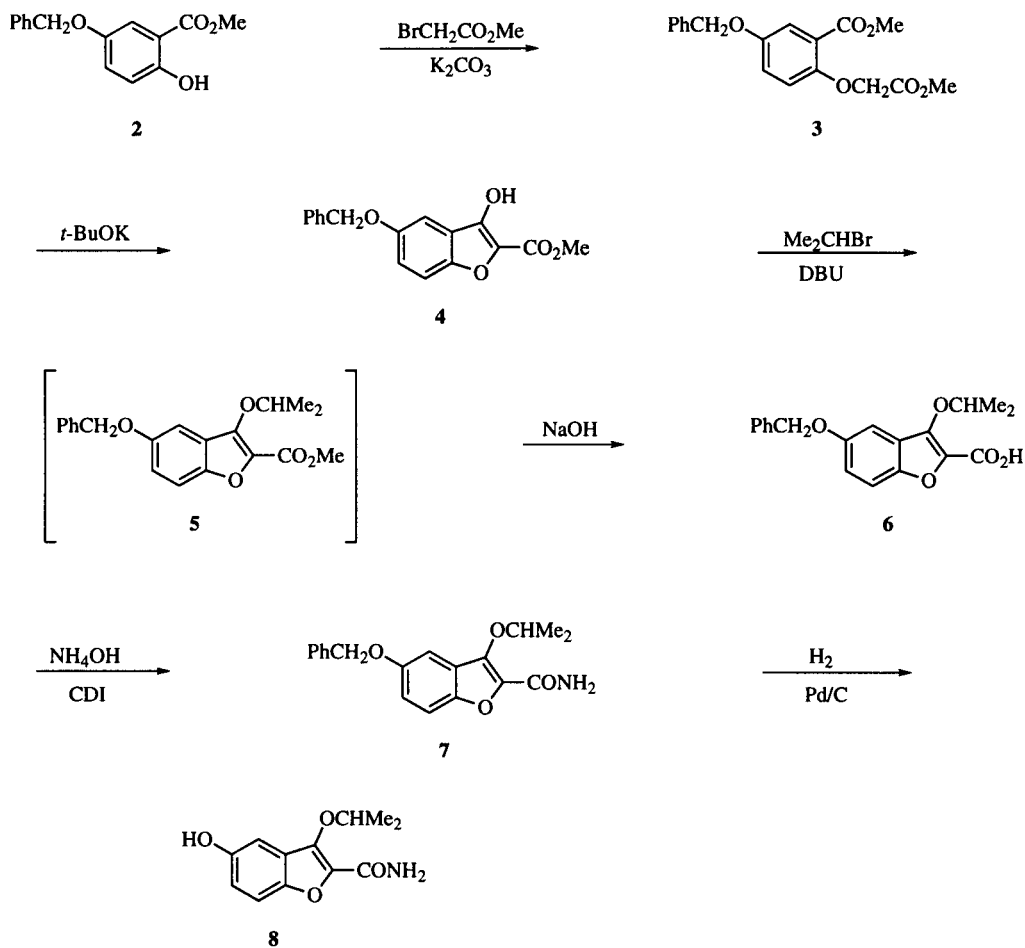
The preparation of a series of 3,5-substituted indole- and benzofuran-2-carboxamides is described. A 3-alkoxy-5-hydroxybenzofuran was prepared by elaboration of a benzyloxy salicylate ester. A related 3-alkylthiobenzofuran was obtained by the addition of thionyl chloride and isopropylmagnesium chloride to a benzofuran ester. A series of 3-(methylthio)indoles was prepared from an indole sulfonium salt intermediate.

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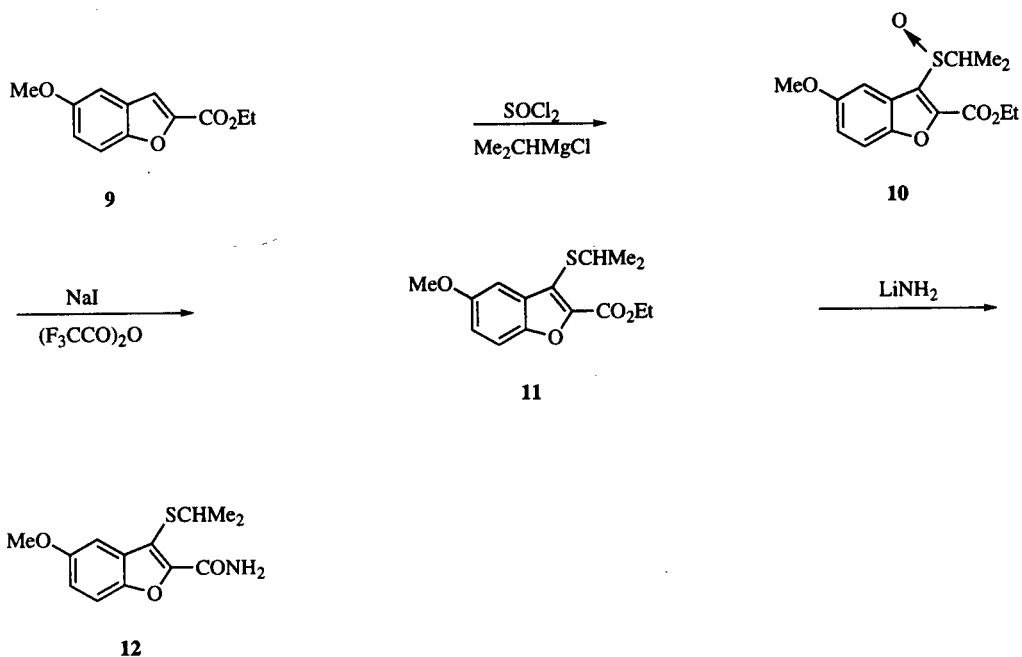
We have maintained a continuing interest in the chemistry and potential pharmacological activity of 3-alkoxybenzofuran and -indole-2-carboxamides, 3-alkylthioindole-2-carboxamides, and their synthetic precursors [1-3]. Recently [4], certain 3-alkoxybenzofuran and -indole-2-carboxamides **1** were found to inhibit the expression of spe-



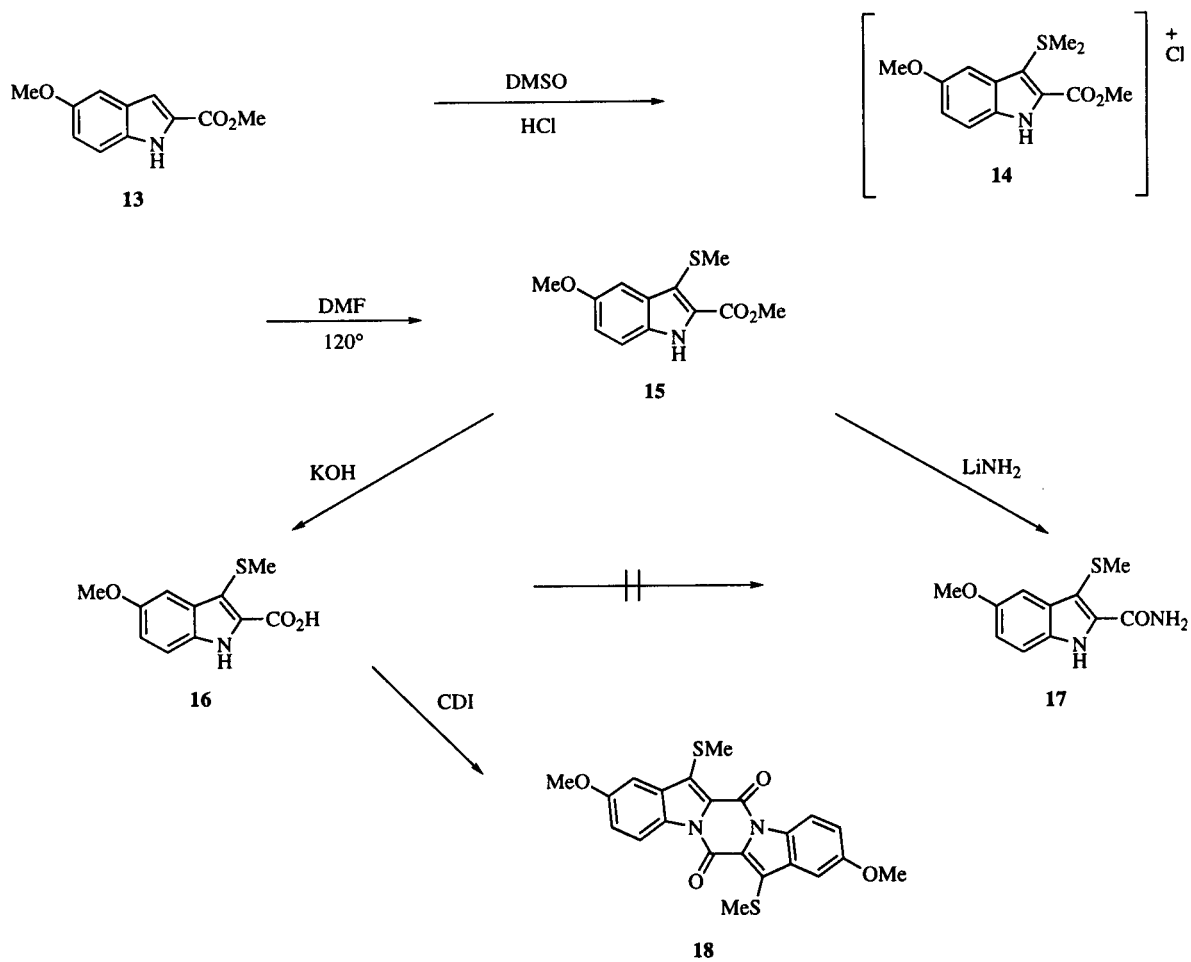
Scheme I



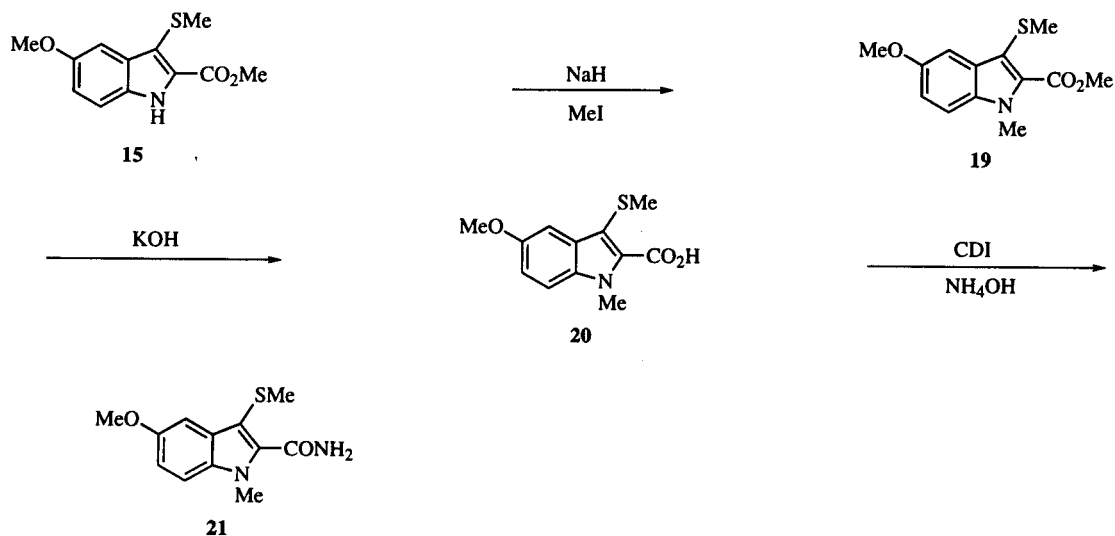
Scheme II



Scheme III



Scheme IV



cific cell surface proteins, classes of cell adhesion molecules [5] that are essential in the pathogenesis of acute inflammation. In addition, certain 3-(phenylthio)indole-2-carboxamides have been shown to be inhibitors of the enzyme HIV reverse transcriptase [6]. In this paper, we describe the synthesis of a variety of novel 3,5-substituted benzofuran and indole-2-carboxamides prepared as part of an antiinflammatory drug discovery program.

Preparation of a 5-hydroxybenzofuran target began with the known [7] benzyloxy salicylate ester **2** (Scheme I). Alkylation of **2** with methyl bromoacetate gave the diester **3**, and a Dieckmann cyclization of **3** yielded the benzyl protected 5-hydroxybenzofuran **4**. Alkylation of **4** gave the 3-alkoxy ester **5** as an oil, and saponification of **5** produced the carboxylic acid **6**. The acid was converted to the amide **7** with 1,1'-carbonyldiimidazole and ammonia, and catalytic hydrogenolysis of **7** yielded the target 5-hydroxy amide **8**.

A 3-alkylthiobenzofuran target was prepared by the use of the thionyl chloride addition method used successfully previously in the indole series [3]. The benzofuran ester **9** was converted in low yield to the sulfinyl intermediate **10** (Scheme II). Sulfinyl group reduction produced the alkylthio ester **11**, and treatment of **11** with lithium amide [8] gave the target benzofurancarboxamide **12**.

Several indole targets were prepared from the known [9] ester **13** (Scheme III). This ester was prepared from the corresponding indole carboxylic acid by esterification with methanol and sulfuric acid. Reaction of **13** with dimethyl sulfoxide and hydrogen chloride gas [10] gave the sulfonium salt **14**. Thermal decomposition of the crude salt produced the 3-(methylthio) ester **15**, which was saponified to yield the carboxylic acid **16**. An attempt at converting **16** to the amide **17** by means of an imidazole

intermediate gave instead a highly insoluble dimer **18** [11]. The target amide was ultimately prepared by the reaction of ester **15** with lithium amide.

The ester intermediate **15** was also methylated with iodomethane (Scheme IV). The resulting *N*-methyl ester **19** was saponified, and the carboxylic acid **20** was readily converted to the target amide **21** by means of the imidazole.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover or Electrothermal capillary apparatus and are uncorrected. Elemental analyses were performed by the Analytical Chemistry staff of Parke-Davis (Ann Arbor, MI). The IR spectra were recorded as potassium bromide disks on a Mattson Cygnus 100 FTIR spectrometer. The ^1H NMR spectra were recorded on a Bruker AM 250 spectrometer (compounds **14-16**, **19**) or on a Varian Unity 400 spectrometer (remaining compounds) with chemical shifts reported in ppm relative to internal tetramethylsilane. Mass spectra were recorded on a VG Masslab Trio-2A mass spectrometer. Reactions were usually run under a nitrogen atmosphere, and organic solutions were concentrated at aspirator pressure on a rotary evaporator. Flash chromatography was performed with E. Merck silica gel 60, 230-400 mesh ASTM.

Methyl 2-(2-Methoxy-2-oxoethoxy)-5-(phenylmethoxy)benzoate (**3**).

A mixture of **2** [7] (11.8 g, 46 mmoles), methyl bromoacetate (5.7 ml, 9.2 g, 60 mmoles), and potassium carbonate (8.5 g, 62 mmoles) in 300 ml of *N,N*-dimethylformamide was stirred at room temperature for 48 hours, then cooled in ice and filtered. The insoluble material was washed with water and recrystallized from ethyl acetate-hexane to yield 12.4 g (82%) of **3**, mp 67-69°; IR: 1753, 1730, 1499, 1084 cm^{-1} ; ^1H NMR (DMSO- d_6): δ 3.68 (s, 3H), 3.79 (s, 3H), 4.79 (s, 2H), 5.09 (s, 2H), 7.01 (d, $J = 9.2$ Hz, 1H), 7.16 (dd, $J = 3.3, 9.2$ Hz, 1H), 7.27 (d, $J = 3.1$

Hz, 1H), 7.31-7.45 (m, 5H); ms: m/z 330 (M^+).

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found: C, 65.60; H, 5.56.

Methyl 3-Hydroxy-5-(phenylmethoxy)-2-benzofurancarboxylate (4).

A solution of **3** (9.0 g, 27 mmoles) in 200 ml of dry toluene was treated with potassium *tert*-butoxide (3.7 g, 33 mmoles), and the resulting mixture was stirred at reflux for 16 hours. The reaction mixture was cooled and the precipitated product filtered and recrystallized from ethyl acetate-hexane to yield 5.2 g (77%) of **4**, mp 141-143°; ir: 3364, 1670, 1586, 1451, 1200 cm^{-1} ; 1H nmr (DMSO- d_6): δ 3.82 (s, 3H), 5.14 (s, 2H), 7.19 (dd, $J = 2.7, 8.9$ Hz, 1H), 7.32-7.50 (m, 7H), 10.67 (s, 1H); ms: m/z 299 ($M+1$) $^+$.

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.48; H, 4.66.

3-(1-Methylethoxy)-5-(phenylmethoxy)-2-benzofurancarboxylic Acid (6).

A solution of **4** (5.0 g, 17 mmoles) in 200 ml of tetrahydrofuran was treated with 1,8-diazabicyclo[5.4.0]undecene-7-ene (3.8 ml, 3.9 g, 25 mmoles) and 2-bromopropane (2.4 ml, 6.2 g, 51 mmoles). The resulting mixture was stirred at reflux for 16 hours, then cooled and evaporated. The residue was dissolved in ethyl acetate, and the solution was washed with saturated ammonium chloride solution and brine. The organic layer was dried (anhydrous magnesium sulfate) and evaporated. Purification of the residue by flash chromatography (20% ethyl acetate in hexane elution) gave 3.7 g (65%) of intermediate methyl 3-(1-methylethoxy)-5-(phenylmethoxy)-2-benzofurancarboxylate (**5**) as an oil; ir: 1721, 1478, 1225, 1165 cm^{-1} ; 1H nmr (DMSO- d_6): δ 1.30 (d, $J = 6.0$ Hz, 6H), 3.86 (s, 3H), 4.77 (m, 1H), 5.17 (s, 2H), 7.16-7.62 (m, 8H); ms: m/z 341 ($M+1$) $^+$.

A mixture of **5** (0.61 g, 1.8 mmoles) and 20 ml of 2.0 *N* aqueous sodium hydroxide solution in 20 ml of methanol was stirred at 60° for 2 hours. The cooled reaction mixture was added to 100 g of ice and water and acidified with 2.0 *N* hydrochloric acid. The mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried (anhydrous magnesium sulfate), and evaporated. Recrystallization of the residue from ethyl acetate-hexane gave 0.48 g (83%) of **6**, mp 178-179°; ir: 1674, 1566, 1481, 1184 cm^{-1} ; 1H nmr (DMSO- d_6): δ 1.30 (d, $J = 6.0$ Hz, 6H), 4.78 (m, 1H), 5.18 (s, 2H), 7.19 (dd, $J = 2.6, 9.0$ Hz, 1H), 7.23 (d, $J = 2.4$ Hz, 1H), 7.32-7.55 (m, 6H), 13.18 (br s, 1H); ms: m/z 327 ($M+1$) $^+$.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.56; H, 5.63.

3-(1-Methylethoxy)-5-(phenylmethoxy)-2-benzofurancarboxamide (7).

A mixture of **6** (0.53 g, 1.6 mmoles) and 1,1'-carbonyldiimidazole (0.29 g, 1.8 mmoles) in 20 ml of tetrahydrofuran was stirred at reflux for 2 hours. The cooled reaction mixture was treated with 3.0 ml of ammonium hydroxide solution and stirred at room temperature for an additional 2 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (anhydrous magnesium sulfate) and evaporated. Purification of the residue by flash chromatography (50% ethyl acetate in hexane elution) yielded 0.27 g (53%) of **7**, mp 158-160°; ir: 3423, 1669, 1466, 1225 cm^{-1} ; 1H nmr (DMSO- d_6): δ 1.31 (d, $J = 6.1$ Hz,

1H), 4.94 (m, 1H), 5.18 (s, 2H), 7.15 (dd, $J = 2.5, 9.1$ Hz, 1H), 7.27-7.53 (m, 8H), 7.63 (br s, 1H); ms: m/z 326 ($M+1$) $^+$.

Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.17; H, 5.95; N, 4.26.

5-Hydroxy-3-(1-methylethoxy)-2-benzofurancarboxamide (8).

A solution of **7** (0.50 g, 1.5 mmoles) in 75 ml of methanol was treated with 20% palladium on carbon catalyst (0.25 g) and hydrogenated for 2 hours at 50 psi hydrogen pressure. The reaction mixture was filtered and the filtrate evaporated. Recrystallization of the residue from aqueous methanol yielded 0.28 g (78%) of **8**, mp 183-185°; ir: 3435, 1659, 1609, 1227 cm^{-1} ; 1H nmr (DMSO- d_6): δ 1.32 (d, $J = 6.3$ Hz, 6H), 4.86 (m, 1H), 6.93 (dd, $J = 2.7, 8.9$ Hz, 1H), 6.98 (d, $J = 2.4$ Hz, 1H), 7.25 (br s, 1H), 7.38 (d, $J = 8.9$ Hz, 1H), 7.56 (br s, 1H), 9.46 (s, 1H); ms: m/z 236 ($M+1$) $^+$.

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.16; H, 5.58; N, 5.91.

Ethyl 5-Methoxy-3-[(1-methylethyl)sulfinyl]-2-benzofurancarboxylate (10).

A solution of **9** (30.0 g, 136 mmoles) in thionyl chloride (50 ml, 81.6 g, 685 mmoles) was heated at reflux for 16 hours. An additional 20 ml (32.6 g, 274 mmoles) of thionyl chloride was added, and heating was continued for an additional 8 hours. The mixture was cooled and diluted with 100 ml of cold hexane and let stand for 16 hours. The precipitated solid was filtered to yield 10.5 g (25%) of the crude sulfinyl chloride intermediate.

The solid was dissolved in 200 ml of tetrahydrofuran. The solution was cooled in ice and a solution of 2.0 *M* isopropyl magnesium chloride (18.0 ml, 36 mmoles) was added dropwise. The mixture was stirred in the cold for 2 hours, then at room temperature for 16 hours. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution, and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried (anhydrous magnesium sulfate) and evaporated. Purification of the residue by flash chromatography (30% ethyl acetate in hexane elution) gave 4.3 g (41% from the sulfinyl chloride intermediate) of **10**, mp 103-104°; ir: 1732, 1317, 1188, 1049 cm^{-1} ; 1H nmr (DMSO- d_6): δ 1.06 (d, $J = 6.8$ Hz, 3H), 1.26 (d, $J = 7.0$ Hz, 3H), 1.34 (t, $J = 7.1$ Hz, 3H), 3.22 (m, 1H), 3.91 (s, 3H), 4.37 (q, $J = 7.0$ Hz, 2H), 7.40 (d, $J = 9.2$ Hz, 1H), 7.91 (dd, $J = 0.72, 9.2$ Hz, 1H), 8.15 (d, $J = 0.96$ Hz, 1H); ms: m/z 311 ($M+1$) $^+$.

Anal. Calcd. for $C_{15}H_{18}O_5S$: C, 58.05; H, 5.85. Found: C, 57.92; H, 5.86.

Ethyl 5-Methoxy-3-[(1-methylethyl)thio]-2-benzofurancarboxylate (11).

A solution of **10** (2.0 g, 6.4 mmoles) in 60 ml of tetrahydrofuran was treated with anhydrous sodium iodide (3.9 g, 26 mmoles). The resulting mixture was stirred for 30 minutes, then cooled in ice while trifluoroacetic anhydride (3.6 ml, 5.4 g, 25 mmoles) was added dropwise. The mixture was stirred for an additional 15 minutes, then added to a mixture of ice and saturated sodium bicarbonate solution. The mixture was extracted with ethyl acetate. The combined organic layers were washed with 5% aqueous sodium thiosulfate solution and brine. The organic layer was dried (anhydrous magnesium sulfate) and evaporated. Purification of the residue by flash chromatography (20% ethyl acetate in hexane elution) gave 1.8 g (95%) of **11**, mp 69-71°; ir: 1728, 1557, 1316, 1181 cm^{-1} ; 1H nmr

(DMSO- d_6): δ 1.14 (d, $J = 6.8$ Hz, 6H), 1.35 (t, $J = 7.1$ Hz, 3H), 3.53 (m, 1H), 3.89 (s, 3H), 4.36 (q, $J = 7.1$ Hz, 2H), 7.32 (d, $J = 9.2$ Hz, 1H), 7.59 (d, $J = 0.97$ Hz, 1H), 7.73 (dd, $J = 0.72, 9.2$ Hz, 1H); ms: m/z 295 ($M+1$)⁺.

Anal. Calcd. for $C_{15}H_{18}O_4S$: C, 61.20; H, 6.16. Found: C, 61.02; H, 6.26.

5-Methoxy-3-[(1-methylethyl)thio]-2-benzofurancarboxamide (12).

Lithium amide in liquid ammonia was generated as previously described [8] from lithium metal ribbon (0.15 g, 22 mmoles). A solution of **11** (0.60 g, 2.0 mmoles) in 7.0 ml of tetrahydrofuran was added dropwise. The mixture was stirred for 2 hours, then quenched by the dropwise addition of saturated ammonium chloride solution. Excess ammonia was allowed to evaporate, and the residue was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (anhydrous magnesium sulfate), and evaporated. Recrystallization of the residue from ethyl acetate-hexane gave 0.45 g (83%) of **12**, mp 148-150°; ir: 3480, 1682, 1393, 1242 cm^{-1} ; 1H nmr (DMSO- d_6): δ 1.14 (d, $J = 6.8$ Hz, 6H), 3.52 (m, 1H), 3.88 (s, 3H), 7.23 (d, $J = 9.2$ Hz, 1H), 7.57 (d, $J = 0.72$ Hz, 1H), 7.62 (dd, $J = 0.72, 9.1$ Hz, 1H), 7.68 (br s, 1H), 8.14 (br s, 1H); ms: m/z 265 (M^+).

Anal. Calcd. for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.90; H, 5.86; N, 5.39.

Methyl 5-Methoxy-3-(methylthio)-1*H*-indole-2-carboxylate (15).

A mixture of **13** [9] (8.3 g, 40 mmoles) and dimethyl sulfoxide (4.0 ml, 4.4 g, 56 mmoles) in 75 ml of methanol was cooled in ice and treated with excess hydrogen chloride gas. The temperature of the reaction mixture increased to 45°. Additional hydrogen chloride gas was added intermittently, and the cooling bath was adjusted so that the temperature of the reaction mixture was kept at 40-50° for 3 hours. The mixture was cooled and the precipitated solid was filtered and washed with ether to yield 6.3 g (52%) of [5-methoxy-2-(methoxycarbonyl)-1*H*-indol-3-yl] dimethylsulfonium chloride intermediate **14**, mp 130° dec; 1H nmr (deuterium oxide): δ 3.44 (s, 6H), 3.92 (s, 3H), 4.10 (s, 3H), 7.05 (dd, $J = 2.2, 9.1$ Hz, 1H), 7.26 (d, $J = 2.2$ Hz, 1H), 7.43 (d, $J = 9.1$ Hz, 1H).

A suspension of **14** (8.3 g, 8.0 mmoles) in 50 ml of *N,N*-dimethylformamide was immersed in an oil bath preheated to 120°. The mixture was occasionally stirred as the solid gradually dissolved over 10 minutes. The cooled reaction mixture was added to 500 g of ice and water, and the precipitated solid was filtered and washed with 25% methanol in water to yield 6.1 g (88%) of **15**. A sample recrystallized from aqueous acetonitrile had mp 128-130°; ir: 3314, 1684, 1507, 1206 cm^{-1} ; 1H nmr (DMSO- d_6): δ 2.40 (s, 3H), 3.82 (s, 3H), 3.91 (s, 3H), 6.98 (dd, $J = 2.2, 8.9$ Hz, 1H), 7.12 (d, $J = 2.1$ Hz, 1H), 7.38 (d, $J = 8.8$ Hz, 1H), 12.03 (s, 1H); ms: m/z 252 ($M+1$)⁺.

Anal. Calcd. for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.58. Found: C, 57.40; H, 5.26; N, 5.52.

5-Methoxy-3-(methylthio)-1*H*-indole-2-carboxylic Acid (16).

A suspension of **15** (1.8 g, 7.2 mmoles) in 50 ml of methanol was treated with a solution of potassium hydroxide (1.3 g, 23 mmoles) in 15 ml of water. The mixture was stirred at reflux for 3 hours, then cooled and added to 300 g of ice and water. The mixture was acidified with 4.0 *N* hydrochloric acid. The precipitated solid was filtered and washed with 25% methanol in water

to yield 1.5 g (88%) of **16**. A sample recrystallized from aqueous acetonitrile had mp 182° dec; ir: 3357, 1668, 1516, 1154 cm^{-1} ; 1H nmr (DMSO- d_6): δ 2.40 (s, 3H), 3.82 (s, 3H), 6.95 (dd, $J = 2.4, 9.0$ Hz, 1H), 7.12 (d, $J = 2.2$ Hz, 1H), 7.37 (d, $J = 8.8$ Hz, 1H), 11.85 (s, 1H), 13.17 (br s, 1H); ms: m/z 237 (M^+).

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90. Found: C, 55.51; H, 4.98; N, 5.84.

5-Methoxy-3-(methylthio)-1*H*-indole-2-carboxamide (17).

Lithium amide in liquid ammonia was generated as previously described [8] from lithium metal ribbon (0.41 g, 58 mmoles). A solution of **15** (1.8 g, 7.2 mmoles) in 20 ml of tetrahydrofuran was added dropwise, and the mixture was stirred for 16 hours while excess ammonia evaporated. The residue was treated with 300 g of ice and water, and the insoluble material was filtered and washed with 25% methanol in water. Recrystallization from aqueous acetonitrile gave 1.1 g (65%) of **17**, mp 217-219°; ir: 3420, 1661, 1505, 1209 cm^{-1} ; 1H nmr (DMSO- d_6): δ 2.35 (s, 3H), 3.82 (s, 3H), 6.91 (dd, $J = 2.4, 9.2$ Hz, 1H), 7.09 (d, $J = 2.0$ Hz, 1H), 7.37 (d, $J = 8.4$ Hz, 1H), 7.93 (br s, 1H), 8.05 (br s, 1H), 11.86 (s, 1H); ms: m/z 237 ($M+1$)⁺.

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.86. Found: C, 55.71; H, 5.06; N, 11.99.

2,9-Dimethoxy-7,14-bis(methylthio)pyrazino[1,2-*a*:4,5-*a'*]indole-6,13-dione (18).

A mixture of **16** (1.3 g, 5.5 mmoles) and 1,1'-carbonyldiimidazole (0.90 g, 5.6 mmoles) in 20 ml of acetonitrile was stirred at reflux for 2 hours. To the warm reaction mixture was added 40 ml of concentrated ammonium hydroxide. The mixture was stirred for a few minutes, then added to 250 g of ice and water. The precipitated solid was filtered and washed with 25% methanol in water. The solid was digested briefly on the steam bath in 100 ml of acetonitrile. Filtration gave 0.85 g (36%) of **18**, mp >300°; ir: 1684, 1516, 1379, 1208 cm^{-1} ; ms: m/z 438 (M^+). (The compound was not sufficiently soluble to determine an nmr spectrum).

Anal. Calcd. for $C_{22}H_{18}N_2O_4S_2$: C, 60.25; H, 4.14; N, 6.39. Found: C, 60.24; H, 4.10; N, 6.21.

Methyl 5-Methoxy-1-methyl-3-(methylthio)-1*H*-indole-2-carboxylate (19).

A suspension of 60% sodium hydride in mineral oil (0.30 g, 7.5 mmoles) in 3.0 ml of *N,N*-dimethylformamide was cooled in ice while a solution of **15** (1.3 g, 5.2 mmoles) in 10 ml of *N,N*-dimethylformamide was added dropwise. The mixture was stirred for 45 minutes, and iodomethane (0.50 ml, 1.1 g, 8.0 mmoles) was added. After stirring at room temperature for 16 hours, the mixture was added to 100 g of ice and water. The solid was filtered and washed with 10% methanol in water to yield 1.2 g (88%) of **19**. A sample purified by flash chromatography (25% hexane in dichloromethane elution) and recrystallized from hexane had mp 89-91°; ir: 1698, 1501, 1207, 1120 cm^{-1} ; 1H nmr (deuteriochloroform): δ 2.41 (s, 3H), 3.90 (s, 3H), 3.98 (s, 3H), 4.01 (s, 3H), 7.05 (dd, $J = 2.5, 8.9$ Hz, 1H), 7.26-7.30 (m, 2H); ms: m/z 265 (M^+).

Anal. Calcd. for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.93; H, 5.75; N, 5.08.

5-Methoxy-1-methyl-3-(methylthio)-1*H*-indole-2-carboxylic Acid (20).

A suspension of **19** (3.2 g, 12 mmoles) in 65 ml of methanol

was treated with a solution of potassium hydroxide (2.5 g, 45 mmoles) in 25 ml of water. The mixture was stirred at reflux for 2 hours, then cooled and added to 400 g of ice and water. The mixture was extracted with dichloromethane, and the aqueous layer was stirred with Celite filter-aid and filtered. The filtrate was acidified with 4.0 *N* hydrochloric acid. The precipitated solid was filtered and washed with 10% methanol in water to yield 2.6 g (87%) of **20**. A sample recrystallized from hexane-ethyl acetate had mp 165° dec; ir: 1670, 1503, 1209, 1036 cm⁻¹; ¹H nmr (DMSO-d₆): δ 2.36 (s, 3H), 3.83 (s, 3H), 3.93 (s, 3H), 7.01 (dd, J = 2.6, 9.0 Hz, 1H), 7.15 (d, J = 2.0 Hz, 1H), 7.52 (d, J = 9.2 Hz, 1H), 13.37 (br s, 1H); ms: m/z 251 (M⁺).

Anal. Calcd. for C₁₂H₁₃NO₃S: C, 57.35; H, 5.21; N, 5.58. Found: C, 57.15; H, 5.18; N, 5.35.

5-Methoxy-1-methyl-3-(methylthio)-1*H*-indole-2-carboxamide (**21**).

A mixture of **20** (1.3 g, 5.2 mmoles) and 1,1'-carbonyldiimidazole (0.90 g, 5.6 mmoles) in 25 ml of acetonitrile was stirred at reflux for 2 hours. To the cooled reaction mixture was added 20 ml of concentrated ammonium hydroxide, and heating at reflux was continued for an additional 30 minutes. The cooled mixture was added to 200 g of ice and water. The precipitated solid was filtered, washed with 20% methanol in water, and recrystallized from aqueous acetonitrile to yield 0.75 g (58%) of **21**, mp 204-206°; ir: 3374, 1638, 1499, 1211 cm⁻¹; ¹H nmr (DMSO-d₆/trifluoroacetic acid): δ 2.32 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 6.97 (dd, J = 2.6, 9.0 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.48 (d, J = 9.2 Hz, 1H); ms: m/z 250 (M⁺).

Anal. Calcd. for C₁₂H₁₄N₂O₂S: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.49; H, 5.69; N, 11.21.

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