Synthesis of Novel 5-Hydroxy-3-alkoxy- and 5-Hydroxy-3-alkylthio-indole-2-carboxamides

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The preparation of several novel 5-hydroxyindole-2-carboxamides is described. A 5-benzyloxyindole ester was elaborated to the 3-bromo, 3-hydroxy, and 3-alkoxy ester intermediates followed by conversion to the amide and debenzylation. A related 5-acetyloxy indole ester was converted to 3-sulfinyl and 3-alkylthio intermediates before simultaneous amidation and removal of the 5-hydroxy protecting group.

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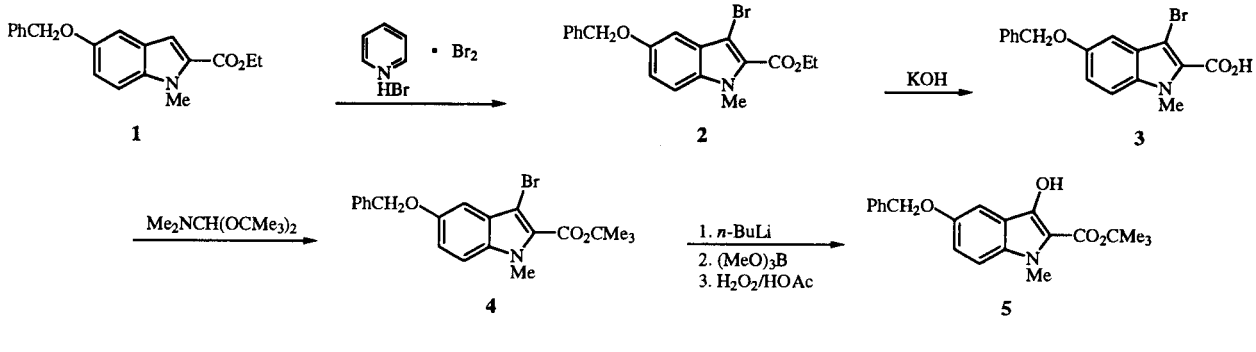
A variety of pharmacological activities have been demonstrated by 3,5-substituted indole-2-carboxamides [1-3]. In an accompanying paper [4] we described the preparation of several novel 5-methoxy-3-methylthio-indole-2-carboxamides prepared as part of an anti-inflammatory drug discovery program. In this paper we describe the preparation of related 5-hydroxy-3-alkoxy-and 5-hydroxy-3-alkylthioindole-2-carboxamides.

The 3-alkoxy function of an initial indole target compound was introduced by lithiation and the Hawthorne boronic acid procedure [5,6] on an indole substrate. The known [7] indole ester **1** (Scheme I) was prepared from the commercially available NH ester by alkylation with iodomethane and sodium hydride. Ester **1** was brominated with pyridinium bromide perbromide in order to ensure predominant bromination at the indole 3-position [8]. An attempt at displacement of the bromine of **2** with sodium isopropoxide gave only the carboxylic acid **3**, apparently due to nucleophilic attack at the ethyl moiety of the ester.

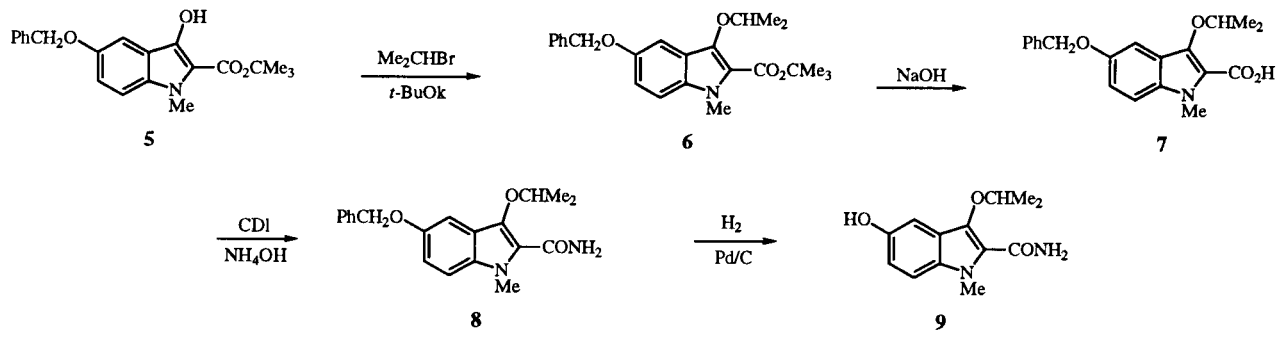
The ester **2** was saponified with potassium hydroxide, and the acid **3** was converted to the *tert*-butyl ester **4** [9]. Lithium-halogen exchange on **4**, followed by introduction and oxidation of the boronic ester gave the enolic ester **5**. Alkylation of **5** in dimethyl sulfoxide yielded the desired alkoxy ester **6** (Scheme II), and saponification of **6** gave the alkoxy acid **7**. Conversion of **7** to the amide **8** and catalytic hydrogenolysis to remove the benzyl protecting group yielded the final target 5-hydroxyindole **9**.

The 5-hydroxy protecting group of **1** was changed to an acetate ester to permit preparation of a 5-hydroxy-3-

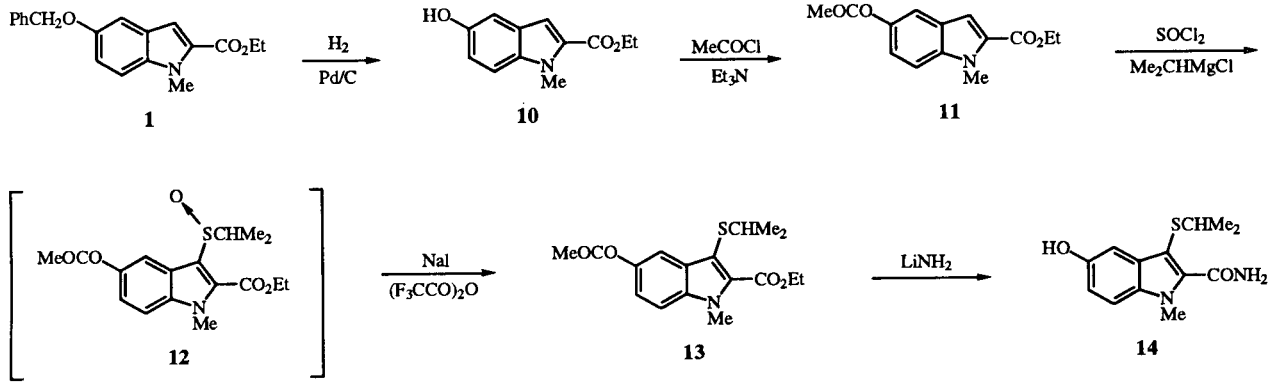
Scheme I



Scheme II



Scheme III



alkylthioindole target (Scheme III). The starting ester **1** was debenzylated, and the resulting 5-hydroxyindole **10** was acylated with acetyl chloride to give the acetate ester **11**. Treatment of **11** with thionyl chloride and the isopropyl Grignard reagent [10] gave the 3-alkylsulfinyl intermediate **12**. Reduction of **12** gave the alkylthio derivative **13**, and treatment of **13** with lithium amide resulted in amidation and removal of the acetyl protecting group to yield the target 5-hydroxyindole **14**.

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 ^{1}H nmr spectra were recorded on a Varian Unity 400 spectrometer (compounds **6**, **8**, **9**, **13**, **14**) or on a Bruker AM 250 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.

Ethyl 3-Bromo-1-methyl-5-(phenylmethoxy)-1*H*-indole-2-carboxylate (**2**).

A solution of **1** [7] (60.9 g, 197 mmoles) in 550 ml of pyridine was cooled in ice and treated dropwise with a solution of pyridinium bromide perbromide (67.0 g, 209 mmoles) in 200 ml of pyridine. The ice bath was removed, and the mixture was stirred for 16 hours, then added to 4.0 liters of cold water. The precipitated solid was filtered, washed with water, and recrystallized from ethyl acetate-hexane to give 58.4 g (76%) of **2**, mp 125-127°; ir: 1701, 1507, 1253, 1107 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.46 (t, J = 7.2 Hz, 3H), 4.00 (s, 3H), 4.44 (q, J = 7.2 Hz, 2H), 5.12 (s, 2H), 7.10-7.51 (m, 8H); ms: m/z 388 (M$^+$).

Anal. Calcd. for $C_{19}H_{18}BrNO_3$: C, 58.77; H, 4.67; N, 3.61. Found: C, 58.64; H, 4.66; N, 3.52.

3-Bromo-1-methyl-5-(phenylmethoxy)-1*H*-indole-2-carboxylic Acid (**3**).

A solution of potassium hydroxide (17.0 g, 303 mmoles) in 3.0 liters of 50% aqueous methanol was treated with **2** (55.4 g, 143 mmoles). The mixture was stirred at reflux for 5 hours, then decanted while hot from any insoluble material into 600 ml of hot water. The warm solution was rapidly acidified with 100 ml of 4.0 *N* hydrochloric acid. An additional 1.0 liter of cold water was added, and the mixture was stirred for 1 hour. The precipitated solid was filtered, stirred in 1.0 liter of 25% methanol in water, and refiltered to give 49.6 g (96%) of **3**. A sample recrystallized from aqueous acetonitrile had mp 210° dec; ir: 1670, 1511, 1272, 1192 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.97 (s, 3H), 5. 17 (s, 2H), 7.03 (d, J = 2.3 Hz, 1H), 7.13 (dd, J = 2.3, 9.0 Hz, 1H), 7.30-7.51 (m, 5H), 7.58 (d, J = 9.1 Hz, 1H); ms: m/z 361 (M+1)$^+$.

Anal. Calcd. for $C_{17}H_{14}BrNO_3$: C, 56.68; H, 3.92; N, 3.89. Found: C, 56.55; H, 3.78; N, 3.71.

1,1-Dimethylethyl 3-Bromo-1-methyl-5-(phenylmethoxy)-1*H*-indole-2-carboxylate (**4**).

A suspension of **3** (43.0 g, 110 mmoles) in 500 ml of toluene was heated in an oil bath at 85-90° while *N,N*-dimethylformamide di-*tert*-butyl acetal (115 ml, 98.0 g, 480 mmoles) was added dropwise. Heating was continued for 2 hours, and the reaction mixture was cooled, filtered, and diluted with additional toluene. The solution was washed with brine, 5% aqueous sodium bicarbonate solution, brine again, then dried (anhydrous sodium sulfate) and evaporated. Recrystallization of the residue from hexane yielded 36.6 g (74%) of **4**, mp 97-99°; ir: 1692, 1505, 1388, 1161 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.66 (s, 9H), 3.98 (s, 3H), 5.12 (s, 2H), 7.09-7.51 (m, 8H); ms: m/z 417 (M+1)$^+$.

Anal. Calcd. for $C_{21}H_{22}BrNO_3$: C, 60.58; H, 5.33; N, 3.37. Found: C, 60.84; H, 5.53; N, 3.00.

1,1-Dimethylethyl 3-Hydroxy-1-methyl-5-(phenylmethoxy)-1*H*-indole-2-carboxylate (**5**).

A solution of **4** (18.6 g, 45 mmoles) in 200 ml of tetrahydrofuran was cooled to -78° and treated dropwise with a solution of 1.6 *M n*-butyllithium in hexane (29.0 ml, 46 mmoles). After 15 minutes a solution of trimethyl borate (5.2 ml, 4.8 g, 46 mmoles) in 25 ml of tetrahydrofuran was added dropwise. The mixture was stirred for 1 hour, and 4.0 ml of acetic acid was slowly added. The mixture was stirred for an additional 10 minutes, and a solution of 30% hydrogen peroxide in water (5.4 ml, 1.8 g, 53

mmoles) was added slowly. After 30 minutes, an additional 4.5 ml (1.5 g, 44 mmoles) of peroxide solution was added, and the mixture was stirred at room temperature for 20 hours. The mixture was added to 1.0 liter of water and extracted with ethyl acetate. The combined organic layers were washed with brine, 5% aqueous sodium bicarbonate solution, brine again, then dried (anhydrous sodium sulfate) and evaporated to an oil. Purification of the oil residue by flash chromatography (50% dichloromethane in hexane elusion) gave 8.2 g (52%) of **5**. A sample recrystallized from hexane had mp 101-103°, ir: 1656, 1545, 1452, 1159 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.66 (s, 9H), 3.82 (s, 3H), 5.08 (s, 2H), 7.09-7.48 (m, 8H), 8.68 (br s, 1H); ms: m/z 353 (M^+).

Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.22; H, 6.61; N, 4.12.

1-1-Dimethylethyl 1-Methyl-3-(1-methylethoxy)-5-(phenylmethoxy)-1*H*-indole-2-carboxylate (**6**).

A solution of potassium *tert*-butoxide (4.0 g, 36 mmoles) in 20 ml of dimethyl sulfoxide was treated dropwise with a solution of **5** (8.2 g, 23 mmoles) in 200 ml of dimethyl sulfoxide. After 45 minutes, 2-bromopropane (4.0 ml, 5.2 g, 43 mmoles) was added, the mixture was stirred for 18 hours, and 2-bromopropane (3.5 ml, 4.6 g, 37 mmoles) was again added. After stirring for an additional 24 hours, the mixture was added to a solution of 6.0 ml of acetic acid and 250 ml of methanol in 1.0 liter of water. The crude solid product was filtered and washed with 25% methanol in water. Purification of the product by flash chromatography (33% hexane in dichloromethane elusion) gave 5.6 g (61%) of **6**. A sample recrystallized from aqueous 2-propanol had mp 113- 115°; ir: 1690, 1524, 1379, 1167 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.31 (d, J = 6.4 Hz, 6H), 1.63 (s, 9H), 3.91 (s, 3H), 4.48 (heptet, J = 6.0 Hz, 1H), 5.09 (s, 2H), 7.05-7.48 (m, 8H); ms: m/z 395 (M^+).

Anal. Calcd. for $C_{24}H_{29}NO_4$: C, 72.88; H, 7.39; N, 3.54. Found: C, 72.61; H, 7.36; N, 3.15.

1-Methyl-3-(1-methylethoxy)-5-(phenylmethoxy)-1*H*-indole-2-carboxylic Acid (**7**).

A suspension of **6** (5.6 g, 14 mmoles) in 80 ml of 2-methoxyethanol was treated with a solution of 50% aqueous sodium hydroxide (5.0 g, 63 mmoles), followed by 15 ml of water. The mixture was stirred at reflux for 3 hours, then cooled and added to 700 ml of water. The aqueous mixture was heated on a hot plate until nearly one phase and filtered hot. The warm filtrate was immediately treated with 50 ml of 4.0 *N* hydrochloric acid in order to prevent precipitation of the sodium salt of the acid product. After cooling to room temperature followed by 1 hour in an ice bath, the precipitated solid was filtered and washed with 25% methanol in water to give 4.2 g (88%) of **7**. A sample recrystallized from ethyl acetate-hexane had mp 136° dec; ir: 1653, 1516, 1454, 1200 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.23 (d, J = 6.0 Hz, 6H), 3.88 (s, 3H), 4.37 (heptet, J = 6.1 Hz, 1H), 5.14 (s, 2H), 7.04-7.49 (m, 8H), ms: m/z 395 (M^+).

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.92, H, 6.22; N, 4.11.

1-Methyl-3-(1-methylethoxy)-5-(phenylmethoxy)-1*H*-indole-2-carboxamide (**8**).

A mixture of **7** (4.2 g, 12.4 mmoles) and 1,1'-carbonyldiimidazole (2.1 g, 13 mmoles) in 70 ml of acetonitrile was stirred at reflux for 2 hours. The mixture was cooled slightly and 40 ml of concentrated ammonium hydroxide was added. The mixture was again heated at reflux for 30 minutes, cooled, and added to 500 g of ice and water. The precipitated solid was filtered, washed with 25% methanol in water, and recrystallized from ethylacetate-hexane to yield 2.2 g (52%) of **8**, mp 164-166°; ir: 3427, 1670, 1489, 1217 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.29 (d, J = 6.0 Hz, 6H), 3.92 (s, 3H), 4.57 (heptet, J = 6.0 Hz, 1H), 7.19 (dd, J = 2.4, 8.8 Hz, 1H), 7.11 (d, J = 2.0 Hz, 1H), 7.33 (br s, 1H), 7.34-7.51 (m, 8H), 7.53 (br s, 1H); ms: m/z 338 (M^+).

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 70.74; H, 6.56; N, 8.35.

5-Hydroxy-1-methyl-3-(1-methylethoxy)-1*H*-indole-2-carboxamide (**9**).

A suspension of **8** (2.1 g, 6.2 mmoles) in 100 ml of methanol was hydrogenated over 0.5 g of 20% palladium on carbon catalyst. The catalyst was filtered and the filtrate evaporated. Recrystallization of the residue from aqueous acetonitrile gave 0.87 g (58%) of **9**, mp 234-237°; ir: 3447, 3339, 1638, 1383, 1256 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.31 (d, J = 6.4 Hz, 1H), 3.89 (s, 3H), 4.54 (heptet, J = 6.2 Hz, 1H), 6.83 (dd, J = 2.2, 9.0 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 7.28 (br s, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.48 (brs, 1H), 9.00 (s, 1H); ms: m/z 248 (M^+).

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.29. Found: C, 62.94; H, 6.60; N, 11.27.

Ethyl 5-Hydroxy-1-methyl-1*H*-indole-2-carboxylate (**10**).

Prepared from **1** [7] (5.7 g, 18.4 mmoles) by catalytic hydrogenolysis in ethanol as described in the preparation of **9**. Recrystallization from ether gave 3.2 g (80%) of **10**, mp 140-142°; ir: 3387, 1667, 1537, 1276 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.33 (t, J = 7.1 Hz, 3H), 3.96 (s, 3H), 4.30 (q, J = 7.1 Hz, 2H), 6.89 (d, J = 8.9 Hz, 1H), 6.95 (s, 1H), 7.07 (s, 1H), 7.39 (d, J = 8.9 Hz, 1H), 9.03 (s, 1H); ms: m/z 219 (M^+).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.67; H, 6.14; N, 6.39.

Ethyl 5-(Acetyloxy)-1-methyl-1*H*-indole-2-carboxylate (**11**).

A solution of **10** (2.2 g, 10.0 mmoles) in 50 ml of tetrahydrofuran was treated dropwise with acetyl chloride (0.80 ml, 0.88 g, 11.3 mmoles), followed by triethylamine (1.6 ml, 1.2 g, 11.5 mmoles). The mixture was stirred at room temperature for 16 hours, then 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 ether-pentane gave 2.0 g (77%) of **11**, mp 87-89°; ir: 1760, 1694, 1531, 1300 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.34 (t, J = 7.0 Hz, 3H), 2.28 (s, 3H), 4.03 (s, 3H), 4.32 (q, J = 7.0 Hz, 2H), 7.11 (dd, J = 2.1, 9.0 Hz, 1H), 7.26 (s, 1H), 7.41 (d, J = 1.9 Hz, 1H), 7.61 (d, J = 9.1 Hz, 1H); ms: m/z 261 (M^+).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.79; N, 5.36. Found: C, 64.19; H, 5.86; N, 5.33.

Ethyl 5-(Acetyloxy)-1-methyl-3-[(1-methylethyl)thio]-1*H*-indole-2-carboxylate (**13**).

A solution of **11** (0.90 g, 3.4 mmoles) in 10 ml of dichloromethane was treated dropwise with thionyl chloride (1.1 ml, 1.8 g, 15 mmoles). The mixture was stirred for 15 minutes, then diluted with 40 ml of hexane. After stirring for an additional 30 minutes, the precipitated crude sulfinyl chloride intermediate (1.0 g, 2.9 mmoles) was filtered, dissolved in

30 ml of tetrahydrofuran, and the solution was cooled to -78°. A solution of 2.0 *M* isopropylmagnesium chloride (1.5 ml, 3.0 mmoles) was added dropwise, and the resulting mixture was stirred at -78° for 2 hours. The reaction was quenched by the dropwise addition of 6.0 ml of 2.0 *N* hydrochloric acid. The mixture was warmed to room temperature, diluted with water, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (anydrous magnesium sulfate), and evaporated. The residue was purified by flash chromatography (20% ethyl acetate in hexane elusion) to yield 0.38 g (38%) of intermediate ethyl 5-(acetyloxy)-1-methyl-3-[(1-methylethyl) sulfinyl]-1*H*-indole-2-carboxylate (**12**) as a waxy solid, mp 36-38°; ir: 1757, 1692, 1511, 1144 cm^{-1}; ^1H nmr (DMSO-d_6 and trifluoroacetic acid): δ 1.20 (d, J = 6.8 Hz, 3H), 1.27 (d, J = 6.9 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 2.30 (s, 3H), 3.27 (heptet, J = 6.8 Hz, 1H), 4.06 (s, 3H), 4.39 (q, J = 7.0 Hz, 2H), 7.21 (d, J = 9.1 Hz, 1H), 7.33 (d, J = 9.1 Hz, 1H), 8.06 (s, 1H); ms: m/z 352 $(M+1)^+$.

A solution of **12** (0.82 g, 2.3 mmoles) and sodium iodide (1.2 g, 8.0 mmoles) in 20 ml of acetone was cooled in ice and treated dropwise with trifluoroacetic anydride (1.1 ml, 1.6 g, 7.8 mmoles). The mixture was stirred for 15 minutes, then added to 100 ml of cold 5% aqueous sodium bicarbonate solution. After extracting with ether, the combined organic layers were washed with 5% aqueous sodium thiosulfate solution and brine. The organic layer was dried and evaporated. Purification of the residue by flash chromatography (10% ethyl acetate in hexane elusion) gave 0.40 g (51%) of **13**, mp 60-62°; ir: 1761, 1707, 1497, 1165 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.11 (d, J = 6.4 Hz, 6H), 1.36 (t, J = 7.0 Hz, 3H), 2.27 (s, 3H), 3.25 (heptet, J = 6.8 Hz, 1H), 3.93 (s, 3H), 4.37 (q, J = 6.8 Hz, 2H), 7.12 (dd, J = 2.2, 9.0 Hz, 1H), 7.42 (d, J = 1.6 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H); ms: m/z 336 $(M+1)^+$.

Anal. Calcd. for $C_{17}H_{21}NO_4S$: C, 60.87; H, 6.31; N, 4.18. Found: C, 60.84; H, 6.48; N, 4.29.

5-Hydroxy-1-methyl-3-[(1-methylethyl)thio]-1*H*-indole-2-carboxamide (**14**).

Lithium amide in liquid ammonia was generated as previously described [11] from lithium metal ribbon (0.070 g, 10 mmoles). A solution of **13** (0.37 g, 1.1 mmoles) in 3.0 ml of tetrahydrofuran was added dropwise, the mixture was stirred for 1 hour, and excess ammonia was allowed to evaporate. The residue was diluted with 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 (anydrous magnesium sulfate), and evaporated. Purification of the residue by flash chromatography (20% ethyl acetate in hexane elusion) followed by recrystallization from ethyl acetate-hexane gave 0.22 g (76%) of **14**, mp 213-215°; ir: 3408, 1634, 1452, 1327 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.13 (d, J = 6.8 Hz, 6H), 3.08 (heptet, J = 6.7 Hz, 1H), 3.84 (s, 3H), 6.81 (dd, J = 2.3, 8.8 Hz, 1H), 6.99 (d, J = 1.9 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 7.86 (br s, 1H), 7.92 (br s, 1H), 9.05 (s, 1H); ms: m/z 264 (M^+).

Anal. Calcd. for $C_{13}H_{16}N_2O_2S$: C, 59.06; H, 6.10; N, 10.60. Found: C, 58.70; H, 6.14; N, 10.26.

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