Synthesis of Novel 1-Phenyl-1*H*-indole-2-carboxylic Acids. I. Utilization of Ullmann and Dieckmann Reactions for the Preparation of 3-Hydroxy, 3-Alkoxy, and 3-Alkyl Derivatives

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Methods for the synthesis of novel 3-hydroxy, 3-alkoxy, and 3-alkyl indole-2-carboxylic acids and esters are described. Dieckmann cyclization of various 2-[(carboxymethyl)amino]benzoic acid diesters yielded 1-unsubstituted-, 1-methyl-, and 1-phenyl-3-hydroxy-1*H*-indole-2-carboxylic acid esters. An Ullmann reaction with bromobenzene converted 1*H*-indoles to 1-phenylindoles.

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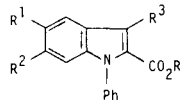
We previously described [1-3] the use of indole-2-carboxylic acids and esters as synthetic intermediates for the preparation of compounds of potential medicinal interest. In a continuation of this work, we have now prepared additional novel indoles **1** containing a 1-phenyl substituent. This paper describes the use of Ullmann and Dieckmann reactions to prepare indole-2-carboxylic acids with hydroxy, alkoxy, or alkyl substituents in the indole 3-position. An accompanying paper discusses the preparation of analogs with amino and thioalkyl substituents in the 3-position.



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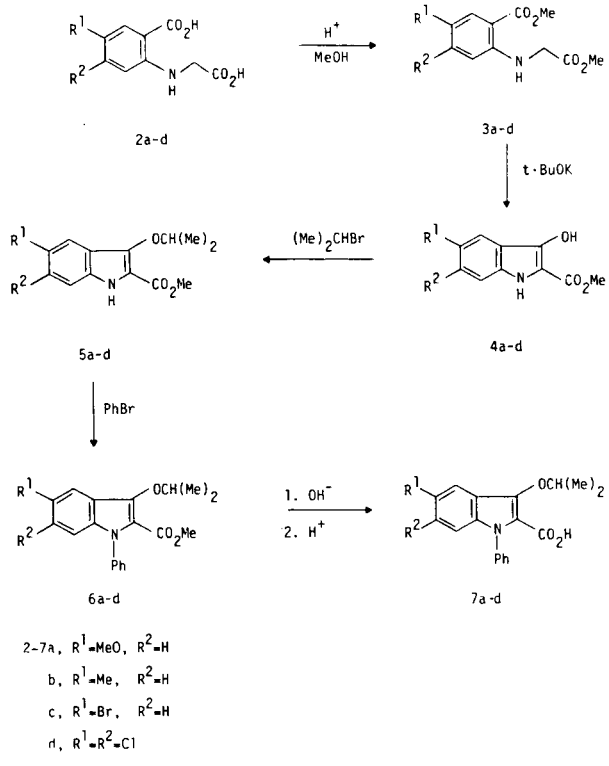
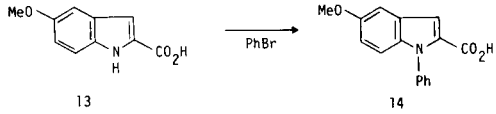
Condensation of aromatic halides and 1-unsubstituted indoles under basic conditions (an Ullmann-type reaction) has received little attention as a means of introducing 1-aryl substituents onto the indole nucleus [4-6]. We have utilized this methodology in the preparation of several indole acid and ester targets.

Diesters **3a-d** were obtained by esterification of the known [7] diacids **2a-d** (Scheme I). A Dieckmann condensation on **3a-d** yielded indole esters **4a-d**, unsubstituted on the indole nitrogen. Indoles **4a-c** were previously prepared [8,9] by a more complex synthetic scheme involving isatogen intermediates. Alkylation of **4a-d** with 2-bromopropane provided the alkoxy esters **5a-d**. A copper catalysed Ullmann reaction in bromobenzene as solvent and reagent convertd **5a-d** to the 1-phenyl alkoxy esters **6a-d**. Carboxylic acids **7a-d** were obtained by saponification of the corresponding esters.

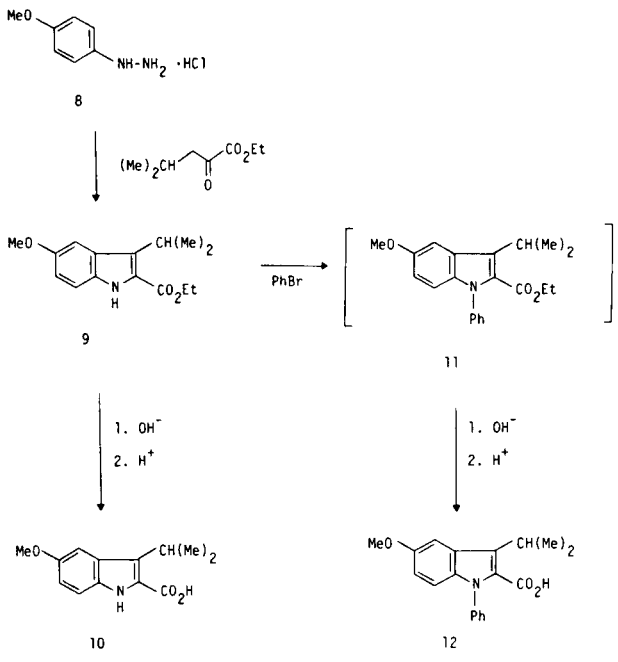
The Ullmann reaction was also employed to prepare 1-phenyl indoles unsubstituted, or with an alkyl substituent in the indole 3-position. An indole ester **9** containing an isopropyl group in the 3-position was prepared by Fischer indole reaction of the hydrazine salt **8** and 4-methyl-2-oxopentanoic acid, ethyl ester (Scheme II). Ester **9** was saponified to carboxylic acid **10** or reacted with bromobenzene under Ullmann conditions. The intermediate 1-phenyl ester **11** (obtained as an oil) was saponified to carboxylic acid **12**. Indole acid **14** was similarly prepared from commercially-available carboxylic acid **13**.

Scheme I



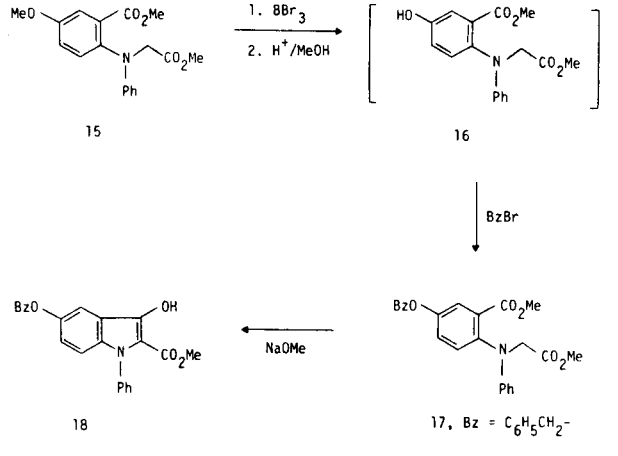


Scheme II



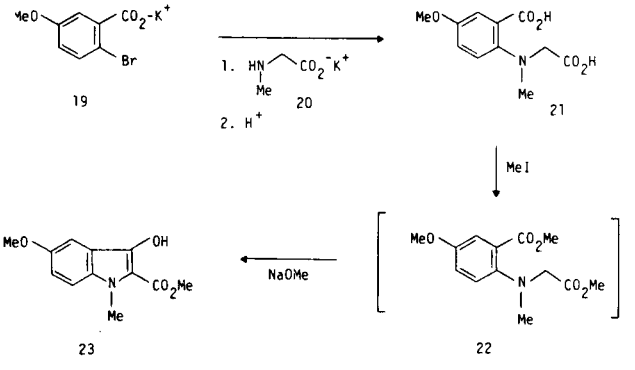
An alternative to the Ullmann method for the synthesis of methyl 1-substituted-3-hydroxy-1*H*-indole-2-carboxylates is illustrated in Schemes III and IV. This method also utilizes Dieckmann condensation of an appropriately substituted glycine ester [3,10] and was employed in the preparation of a 1-phenylindole containing a protected hydroxy group in the indole benzene ring. Diester **15** [3] was treated with boron tribromide to effect concomitant demethylation of the 5-methoxy and diester functional groups (Scheme III). The total reaction product was re-esterified to yield the crude intermediate 5-hydroxy diester **16**. Alkylation of **16** with (bromomethyl)benzene under phase-transfer conditions provided the protected diester **17**, and Dieckmann condensation yielded the 1-phenylindole **18**.

Scheme III



A final application of the Dieckmann condensation was the preparation of 1-methylindole ester **23** (Scheme IV). Diacid **21**, obtained by copper catalysed condensation [6,11] of the potassium salts of *N*-methylglycine (sarcosine) **20** and 2-bromo-5-methoxybenzoic acid **19**, was esterified with iodomethane to yield diester **22** as an oil. Cyclization of **22** yielded the desired 1-methylindole ester **23**.

Scheme IV



EXPERIMENTAL

Melting points were determined in a Mel-Temp or Electrothermal capillary apparatus and are uncorrected. The infrared spectra were recorded as potassium bromide disks on a Digilab FTS-14 or a Nicolet FT-IRMS-1 spectrophotometer. All nmr spectra were recorded with tetramethylsilane internal standard at 100 MHz on an IBM-WP100SY spectrometer or at 200 MHz on a Varian XL-200 spectrometer. Microanalyses and spectra were provided by the Analytical Chemistry staff of Warner-Lambert/Parke-Davis under the direction of Dr. F. A. MacKellar.

5-Methoxy-2[(2-methoxy-2-oxoethyl)amino]benzoic Acid, Methyl Ester (**3a**).

A solution of 16.8 g (0.0075 mole) of the diacid **2a** [7] in 170 ml of methanol was stirred under a nitrogen atmosphere and treated dropwise with 21.9 ml (40.3 g, 0.39 mole) of concentrated sulfuric acid over 20 minutes. The resulting mixture was stirred at reflux for 24 hours, cooled, and added to 2.0 Kg of ice/water. The crude product was filtered, washed with saturated sodium bicarbonate solution and water. Recrystallization from aqueous methanol yielded 14.7 g (77% yield) of the analytically pure diester **3a**, mp 118-120°; ir: ν 3372, 1750, 1442, 1073 cm^{-1}; nmr (deuteriochloroform): δ 3.76 (s, 6H, OCH_3), 3.87 (s, 3H, OCH_3), 3.96 (d, 2H, J = 6.7 Hz, CH_2), 6.45 (d, 1H, J = 8.5 Hz, # 3 Ar*H*), 7.03 (dd, 1H, J = 8.5, 2.0 Hz, # 4 Ar*H*), 7.43 (d, 1H, J = 2.0 Hz, # 6 Ar*H*), 7.80 (broad t, 1H, N*H*).

Anal. Calcd. for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.81; H, 5.85; N, 5.46.

2-[(2-Methoxy-2-oxoethyl)amino]-5-methylbenzoic Acid, Methyl Ester (**3b**).

Prepared from **2b** [7] by the procedure employed in the preparation of **3a**. Recrystallization from absolute ethanol yielded diester **3b**, mp 64-66°; ir: ν 3365, 1746, 1682, 1440 cm^{-1}; nmr (deuteriochloroform): δ 2.3 (s, 3H, CCH_3), 3.78 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.00 (s, 2H, CH_2), 6.46 (d, 1H, J = 8.5 Hz, # 3 Ar*H*), 7.19 (dd, 1H, J = 8.5, 2.0 Hz, # 4 Ar*H*), 7.75 (d, 1H, J = 2.0 Hz, # 6 Ar*H*), 8.00 (broad s, 1H, N*H*).

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.88; H, 6.39; N, 5.98.

5-Bromo-2-[(2-methoxy-2-oxoethyl)amino]benzoic Acid, Methyl Ester (**3c**).

Prepared from **2c** [7] by the procedure employed in the preparation of

3a. Recrystallization from aqueous methanol yielded diester **3c**, mp 89-91°; ir: ν 3329, 1740, 1512, 1079 cm^{-1}; nmr (deuteriochloroform): δ 3.80 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.99 (s, 2H, CH_2), 6.42 (d, 1H, J = 8.5 Hz, # 3 Ar*H*), 7.43 (dd, 1H, J = 8.5, 2.0 Hz, # 4 Ar*H*), 8.05 (d, 1H, J = 2.0 Hz, # 6 Ar*H*).

Anal. Calcd. for $C_{11}H_{12}BrNO_4$: C, 43.73; H, 4.00; N, 4.64; Br, 26.45. Found: C, 43.89; H, 4.20; N, 4.71; Br, 26.55.

4,5-Dichloro-2-[(2-methoxy-2-oxoethyl)amino]benzoic Acid, Methyl Ester (**3d**).

Prepared from **2d** [7] by the procedure employed in the preparation of **3a**, except that the product precipitated from the cooled reaction mixture. Recrystallization from methanol yielded diester **3d**, mp 127-128°; ir: ν 3342, 1748, 1438, 1092 cm^{-1}; nmr (deuteriochloroform): δ 3.82 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.98 (d, 2H, J = 6.7 Hz, CH_2), 6.62 (s, 1H, Ar*H*), 7.99 (s, 1H, Ar*H*), 8.24 (broad t, 1H, N*H*).

Anal. Calcd. for $C_{11}H_{11}Cl_2NO_4$: C, 45.22; H, 3.80; N, 4.80; Cl, 24.28. Found: C, 45.40; H, 3.80; N, 5.03; Cl, 24.05.

3-Hydroxy-5-methoxy-1*H*-indole-2-carboxylic Acid, Methyl Ester (**4a**).

A suspension of 11.8 (0.11 mole) of potassium *t*-butoxide in 200 ml of tetrahydrofuran under a nitrogen atmosphere was stirred and cooled in a cold water bath. A solution of 20.4 g (0.081 mole) of diester **3a** in 100 ml of tetrahydrofuran was added over 20 minutes, and the new mixture was stirred at reflux for 2 hours. The cooled reaction mixture was added to 2.0 Kg of ice/water and acidified with glacial acetic acid. The precipitated solid was filtered and washed several times with water to yield 13.0 g (73% yield) of analytically pure indole ester **4a**, mp 138-140°, lit [8,9] mp 136-140°, 140-141°; ir: ν 3358, 1669, 1443, 1221 cm^{-1}; nmr (deuteriochloroform): δ 3.83 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.97-7.25 (m, 3H, Ar*H*), 7.73 (broad s, 1H, O*H* or N*H*).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.36; H, 4.80; N, 6.25.

3-Hydroxy-5-methyl-1*H*-indole-2-carboxylic Acid, Methyl Ester (**4b**).

Prepared from **3b** by the procedure employed in the preparation of **4a**. Recrystallization from 2-propanol yielded indole ester **4b**, mp 162-165°; lit [9] mp 178-180° [12]; ir: ν 3354, 1653, 1281, 1104 cm^{-1}; nmr (deuteriochloroform): δ 2.42 (s, 3H, CCH_3), 3.93 (s, 3H, OCH_3), 7.14-7.49 (m, 3H, Ar*H*), 7.73 (broad s, 1H, O*H* or N*H*).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.09; H, 5.32; N, 6.84.

5-Bromo-3-hydroxy-1*H*-indole-2-carboxylic Acid, Methyl Ester (**4c**).

Prepared from **3c** by the procedure employed in the preparation of **4a**. Trituration of the crude product with hexane yielded analytically pure indole ester **4c**, mp 196° dec; lit [9] mp 193-194° [12]; ir: ν 3375, 1650, 1550, 1145 cm^{-1}; nmr (deuteriochloroform): δ 3.97 (s, 3H, OCH_3), 7.13 (d, 1H, J = 8.5 Hz, # 7 Ar*H*), 7.38 (dd, 1H, J = 8.5, 2.0 Hz, # 6 Ar*H*), 7.67 (broad s, 1H, O*H* or N*H*), 7.87 (d, 1H, J = 2.0 Hz, # 4 Ar*H*).

Anal. Calcd. for $C_{10}H_8BrNO_3$: C, 44.47; H, 2.99; N, 5.19; Br, 29.59. Found: C, 44.44; H, 3.19; N, 5.31; Br, 29.33.

5,6-Dichloro-3-hydroxy-1*H*-indole-2-carboxylic Acid, Methyl Ester (**4d**).

Prepared from **3d** by the procedure employed in the preparation of **4a**. Recrystallization from aqueous ethanol yielded indole ester **4d**, mp 215° dec; ir: ν 3328, 1698, 1495, 1133 cm^{-1}; nmr (DMSO-d_6): δ 3.87 (s, 3H, OCH_3), 7.50 (s, 1H, Ar*H*), 8.10 (s, 1H, Ar*H*), 9.80 (broad s, 1H, O*H* or N*H*), 11.27 (broad s, 1H, O*H* or N*H*).

Anal. Calcd. for $C_{10}H_7Cl_2NO_3$: C, 46.18; H, 2.71; N, 5.39; Cl, 27.27. Found: C, 46.44; H, 2.90; N, 5.44; Cl, 27.07.

5-Methoxy-3-(1-methylethoxy)-1*H*-indole-2-carboxylic Acid, Methyl Ester (**5a**).

A solution of 12.9 g (0.11 mole) of potassium *t*-butoxide in 100 ml of dimethyl sulfoxide under a nitrogen atmosphere was cooled in a cold water bath and treated dropwise with a solution of 17.0 g (0.077 mole) of enol ester **4a** in 170 ml of dimethyl sulfoxide over 20 minutes. The mixture was stirred for one hour, then 10.8 ml (14.1 g, 0.12 mole) of 2-bromopropane was added in one portion. The new mixture was stired at room temperature for 30 hours, then added to 800 g of ice/water. The precipitated solid was filtered, washed several times with water, then with hexane to yield 10.2 g (50% yield) of analytically pure ester **5a**, mp 127-129°; ir: ν 3312, 1695, 1539, 1220 cm^{-1}; nmr (deuteriochloroform): δ 1.40 (d, 6H, J = 6.2 Hz, CH(CH_3)$_2$), 3.85 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.57 (heptet, 1H, J = 6.2 Hz, CH(CH$_3$)$_2$), 6.88-7.30 (m, 3H, Ar*H*), 8.37 (broad s, 1H, N*H*).

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.84; H, 6.57; N, 5.21.

5-Methyl-3-(1-methylethoxy)-1*H*-indole-2-carboxylic Acid, Methyl Ester (**5b**).

Prepared from **4b** by the procedure employed in the preparation of **5a**. Trituration of the crude product with hexane yielded analyticaly pure ester **5b**, mp 123-124°; ir: ν 3320, 1685, 1481, 1259 cm^{-1}; nmr (deuteriochloroform): δ 1.38 (d, 6H, J = 6.2 Hz, CH(CH_3)$_2$), 2.42 (s, 3H, CCH_3), 3.94 (s, 3H, OCH_3), 4.57 (heptet, 1H, J = 6.2 Hz, CH(CH$_3$)$_2$), 7.09-7.45 (m, 3H, Ar*H*), 8.43 (broad s, 1H, N*H*).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.69; H, 7.06; N, 5.66.

5-Bromo-3-(1-methylethoxy)-1*H*-indole-2-carboxylic Acid, Methyl Ester (**5c**).

Prepared from **4c** by the procedure employed in the preparation of **5a**. Trituration of the crude product with ether and hexane yielded analytically pure ester **5c**, mp 161-163°; ir: ν 3328, 1686, 1472, 1265 cm^{-1}; nmr (deuteriochloroform): δ 1.36 (d, 6H, J = 6.2 Hz, CH(CH_3)$_2$), 3.94 (s, 3H, OCH_3), 4.55 (heptet, 1H, J = 6.2 Hz, CH(CH$_3$)$_2$), 7.17-7.81 (m, 3H, Ar*H*), 8.53 (broad s, 1H, N*H*).

Anal. Calcd. for $C_{13}H_{14}BrNO_3$: C, 50.02; H, 4.52; N, 4.49; Br, 25.60. Found: C, 49.77; H, 4.62; N, 4.66; Br, 25.90.

5,6-Dichloro-3-(1-methylethoxy)-1*H*-indole-2-carboxylic Acid, Methyl Ester (**5d**).

Prepared from **4d** by the procedure employed in the preparation of **5a**. Recrystallization from aqueous ethanol yielded ester **5d**, mp 221-223°; ir: ν 3325, 1685, 1485, 1288 cm^{-1}; nmr (deuteriochloroform + DMSO-d_6): δ 1.36 (d, 6H, J = 6.2 Hz, CH(CH_3)$_2$), 3.59 (s, 3H, OCH_3), 4.52 (heptet, 1H, J = 6.2 Hz, CH(CH$_3$)$_2$), 7.55 (s, 1H, Ar*H*), 7.72 (s, 1H, Ar*H*), 10.48 (broad s, 1H, N*H*).

Anal. Calcd. for $C_{13}H_{13}Cl_2NO_3$: C, 51.67; H, 4.34; N, 4.64; Cl, 23.47. Found: C, 51.47; H, 4.51; N, 4.56; Cl, 23.49.

5,6-Dichloro-3-(1-methylethoxy)-1-phenyl-1*H*-indole-2-carboxylic Acid, Methyl Ester (**6d**).

A mixture of 7.9 g (0.026 mole) of ester **5d**, 13.9 g (0.10 mole) of anhydrous potassium carbonate, 0.80 g (0.0028 mole) of cuprous bromide, and 100 ml (149 g, 0.95 mole) of bromobenzene under a nitrogen atmospere was stirred vigorously and heated to 100° with an oil bath. The mixture was cooled slightly and treated with 0.70 g (0.012 mole) of potassium hydroxide [13] and a spatula tip of anhydrous cupric acetate, then stirred and heated at 140-150° for 21 hours. The reaction mixture was cooled slightly and filtered warm through a bed of Celite filter aid. The filter cake was washed with warm toluene, and the combined filtrates were evaporated under vacuum. The residue was subjected to flash chromatography over 360 g of silica gel (E. Merck Catalog # 9385) with 2:1 dichloromethane/hexane elution to obtain 8.3 g (84% yield) of purified indole product. Recrystallization of a sample from aqueous ethanol yielded indole **6d**, mp 110-112°; ir: ν 1711, 1452, 1268, 1164 cm^{-1}; nmr (deuteriochloroform): δ 1.40 (d, 6H, J = 6.2 Hz, CH(CH_3)$_2$), 3.77 (s, 3H, OCH_3), 4.53 (heptet, 1H, J = 6.2 Hz, CH(CH$_3$)$_2$), 7.10-7.87 (m, 7H, Ar*H*).

Anal. Calcd. for $C_{19}H_{17}Cl_2NO_3$: C, 60.33; H, 4.53; N, 3.70; Cl, 18.75. Found: C, 60.48; H, 4.67; N, 3.65; Cl, 18.77.

Variation of the above procedure in which the heating time was reduc-

ed to 2 hours at 135-140° also permitted the preparation of 5-methoxy-3-(1-methylethoxy)-1-phenyl-1*H*-indole-2-carboxylic acid, methyl ester (**6a**) from **5a**, 5-methyl-3-(1-methylethoxy)-1-phenyl-1*H*-indole-2-carboxylic acid, methyl ester (**6b**) from **5b**, and 5-bromo-3-(1-methylethoxy)-1-phenyl-1*H*-indole-2-carboxylic acid, methyl ester (**6c**) from **5c**.

These compounds were obtained as oils after chromatography, and were converted to the corresponding carboxylic acids without further purification.

5-Methoxy-3-(1-methylethoxy)-1-phenyl-1*H*-indole-2-carboxylic Acid (**7a**).

A solution of 50.9 g (0.15 mole) of ester **6a** in 300 ml of methanol was treated with a solution of 22.5 g (0.40 mole) of potassium hydroxide in 300 ml of water. The mixture was stirred at reflux for 3 hours, cooled, filtered and condensed on a rotary evaporator (bath temperature 40-45°) until a precipitate began to form. The evaporation was halted, and the residue was allowed to stand at room temperature until precipitation of the potassium salt of the product was complete. The salt was filtered, washed several times with cold acetone, and then redissolved in 850 ml of water plus 140 ml of acetone. The solution was cooled in ice and slowly acidified with 10 ml of glacial acetic acid. The precipitated product was filtered, washed with water, and then with hexane to yield 36.0 g (74% crude yield) of the carboxylic acid product. A sample recrystallized from aqueous methanol yielded acid **7a**, mp 110° dec; ir: ν 1742, 1675, 1502, 1214 cm^{-1}; nmr (deuteriochloroform): δ 1.53 (d, 6H, J = 6.2 Hz, $CH(CH_3)_2$), 3.89 (s, 3H, OCH_3), 4.99 (heptet, 1H, J = 6.2 Hz, $CH(CH_3)_2$), 6.96-7.52 (m, 8H, ArH).

Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.13; H, 6.07; N, 4.38.

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

A solution of 6.91 g (0.021 mole) of ester **6b** in 50 ml of methanol was treated with a solution of 3.12 g (0.056 mole) of potassium hydroxide in 50 ml of water. The mixture was stirred at reflux for 2 hours, cooled, and added to 300 g of ice/water. Acidification with glacial acetic acid yielded a gum, which was extracted with dichloromethane (3 × 150 ml). The combined organic layers were washed with water (2 × 150 ml), dried (anhydrous sodium sulfate) and evaporated to leave an oil which slowly crystallized. Trituration of the residue with hexane yielded 4.2 g (65% yield) of analytically pure acid **7b**, mp 100-102°; ir: ν 1745, 1670, 1501, 1184 cm^{-1}; nmr (deuteriochloroform): δ 1.45 (d, 6H, J = 6.2 Hz, $CH(CH_3)_2$), 2.39 (s, 3H, CH_3), 5.00 (heptet, 1H, J = 6.2 Hz, $CH(CH_3)_2$), 6.94-7.45 (m, 8H, ArH).

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.46; H, 6.21; N, 4.48.

5-Bromo-3-(1-methylethoxy)-1-phenyl-1*H*-indole-2-carboxylic Acid (**7c**).

Prepared from **6c** by the procedure employed in the preparation of **7b**. Trituration of the crude product with ether and hexane yielded analytically pure acid **7c**, mp 122-124°; ir: ν 1748, 1677, 1469, 1105 cm^{-1}; nmr (DMSO-d_6): δ 1.25 (d, 6H, J = 6.2 Hz, $CH(CH_3)_2$), 4.43 (heptet, 1H, J = 6.2 Hz, $CH(CH_3)_2$), 6.93-8.00 (m, 8H, ArH).

Anal. Calcd. for $C_{18}H_{16}BrNO_3$: C, 57.77; H, 4.31; N, 3.74; Br, 21.35. Found: C, 57.48; H, 4.39; N, 3.91; Br, 21.49.

5,6-Dichloro-3-(1-methylethoxy)-1-phenyl-1*H*-indole-2-carboxylic Acid (**7d**).

A suspension of 7.0 g (0.019 mole) of ester **6d** in 90 ml of methanol was treated with a solution of 2.7 g (0.048 mole) of potassium hydroxide in 90 ml of water. The mixture was stirred at reflux for 3 hours, then filtered warm. The cooled filtrate was added to 350 g of ice/water, and the new mixture was extracted with ether (3 × 150 ml). The aqueous layer was cooled in ice and acidified with 6.0 *N* hydrochloric acid. The precipitated product was filtered, washed with water and dried to yield 5.3 g (79% crude yield) of the acid product. A sample recrystallized from ethyl acetate/hexane yielded acid **7d**, mp 176° dec; ir: ν 1679, 1499, 1186, 1105 cm^{-1}; nmr (DMSO-d_6): δ 1.27 (d, 6H, J = 6.2 Hz, $CH(CH_3)_2$), 4.47 (heptet, 1H, J = 6.2 Hz, $CH(CH_3)_2$), 7.10-8.02 (m, 7H, ArH), 13.00 (broad s, 1H, COOH).

Anal. Calcd. for $C_{18}H_{15}Cl_2NO_3$: C, 59.35; H, 4.15; N, 3.85; Cl, 19.47. Found: C, 59.51; H, 4.18; N, 3.87; Cl, 19.67.

5-Methoxy-3-(1-methylethyl)-1*H*-indole-2-carboxylic Acid, Ethyl Ester (**9**).

A suspension of 25.0 g (0.14 mole) of (4-methoxyphenyl)hydrazine hydrochloride **8** in 200 ml of absolute ethanol was treated at 50-60° over 10 minutes with 23.0 ml (22.3 g, 0.14 mole) of 4-methyl-2-oxovalerate, ethyl ester. The resulting solution was stirred at reflux for 18 hours, cooled, and added to 500 g of ice/water. The mixture was extraced with ether (3 × 200 ml), and the combined organic layers were washed with brine (2 × 200 ml) and dried (anhydrous magneisum sulfate). Evaporation (vacuum) and trituration of the resulting residue with hexane yielded 13.6 g (36% yield) of analytically pure indole **9**, mp 96-97°; ir: ν 3328, 1671, 1436, 1218 cm^{-1}; nmr (deuteriochloroform): δ 1.43 (t, 3H, J = 8.3 Hz, CH_2CH_3), 1.50 (d, 6H, J = 6.2 Hz, $CH(CH_3)_2$), 3.88 (s, 3H, OCH_3), 4.08 (heptet, 1H, J = 6.2 Hz, $CH(CH_3)_2$), 4.43 (q, 2H, J = 8.3 Hz, CH_2CH_3), 6.90-7.36 (m, 3H, ArH), 8.60 (broad s, 1H, NH).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.76; H, 7.53; N, 5.29.

5-Methoxy-3-(1-methylethyl)-1*H*-indole-2-carboxylic Acid (**10**).

Prepared from **9** by the saponification procedure described in the preparation of **12**. Recrystallization from ether/hexane yielded acid **10**, mp 167° dec; ir: ν 3410, 1667, 1546, 1217 cm^{-1}; nmr (deuteriochloroform): δ 1.53 (d, 6H, J = 6.2 Hz, $CH(CH_3)_2$), 3.90 (s, 3H, OCH_3), 4.15 (heptet, 1H, J = 6.2 Hz, $CH(CH_3)_2$), 6.93-7.40 (m, 3H, ArH), 8.70 (s, 1H, NH), 9.13 (broad s, 1H, COOH).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.01. Found: C, 66.80; H, 6.38; N, 6.01.

5-Methoxy-3-(1-methylethyl)-1-phenyl-1*H*-indole-2-carboxylic Acid (**12**).

A solution of 5.0 g (0.019 mole) of ester **9** in 110 ml (164 g, 1.05 mole) of bromobenzene was treated with 8.0 g (0.058 mole) of potassium carbonate, 2.0 g (0.036 mole) of potassium hydroxide, 1.2 g (0.0042 mole) of cuprous bromide, and 0.10 g (0.006 mole) of anhydrous cupric acetate. The mixture was stirred at reflux under a nitrogen atmosphere for 6 hours. The procedure described in the preparation of **6d** was then employed to isolate intermediate ester **11** as an oil.

Crude oil **11** described above was dissolved in 100 ml of 95% ethanol, and the solution was treated with a solution of 12.0 g (0.21 mole) of potassium hydroxide in 15 ml of water. The new mixture was stirred at room temperature for 18 hours, then added to 500 g of ice/water. After acidification to *p*H 2 with 4.0 *N* hydrochloric acid, the acid product was extracted with ether (3 × 200 ml). The combined organic layers were washed with brine (2 × 200 ml) and dried (anhydrous magnesium sulfate). Evaporation (vacuum) and recrystallization of the residue yielded 4.3 g (73% yield from **9**) of acid **12**, mp 163° dec; ir: ν 1674, 1532, 1218, 1034 cm^{-1}; nmr (deuteriochloroform): δ 1.51 (d, 6H, J = 6.2 Hz, $CH(CH_3)_2$), 3.87 (s, 3H, OCH_3), 4.10 (heptet, 1H, J = 6.2 Hz, $CH(CH_3)_2$), 6.87-7.57 (m, 8H, ArH).

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.75; H, 6.43; N, 4.61.

5-Methoxy-1-phenyl-1*H*-indole-2-carboxylic Acid (**14**).

A solution of 60.0 g (0.31 mole) of indole acid **13** in 750 ml of *N,N*-dimethylformamide was treated with 35.0 ml (52.2 g, 0.33 mole) of bromobenzene, 10.0 g (0.13 mole) of cupric oxide, and 36.0 g (0.64 mole) of potassium hydroxide. The mixture was stirred at reflux under a nitrogen atmosphere for 6 hours, cooled, and added to 1500 g of ice/water. The solution was filtered through a bed of Celite filter aid, and the filtrate was acidified with 4.0 *N* hydrochloric acid. The precipitated product was filtered and washed with water to yield 78.7 g (95% crude yield) of the acid product. A sample recrystallized from ether/hexane yielded acid **14**, mp 200° dec; ir: ν 1682, 1526, 1228, 1028 cm^{-1}; nmr (deuteriochloroform + deuterium oxide): δ 3.84 (s, 3H, OCH_3), 6.90-7.63 (m, 9H, ArH + indole # 3H).

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.82; H, 4.96; N, 5.55.

2-[(2-Methoxy-2-oxoethyl)phenylamino]-5-(phenylmethoxy)benzoic Acid, Methyl Ester (**17**).

A solution of 25.0 g (0.076 mole) of the methoxy diester **15** [3] in 200 ml of dichloromethane under a nitrogen atmosphere was stirred and cooled to −78°. A solution (220 ml of 1.0 *M*, or 0.22 mole) of boron tribromide in dichloromethane was added dropwise over 45 minutes. The mixture was stirred for 18 hours as it slowly warmed to room temperature, then cooled again in ice and treated with 250 ml of cold water. After stirring for an additional 2 hours, the insoluble material was filtered, washed with water, and dried.

The above solid (18.9 g) was suspended in 500 ml of methanol and treated with 5.0 ml of concentrated sulfuric acid. The mixture was stirred at reflux for 20 hours with the use of a Soxhlet extractor charged with 3Å° molecular sieve. The cooled reaction mixture was condensed (vacuum) to one-third of its original volume and distributed between 1.0 l of water and 300 ml of dichloromethane. The aqueous layer was extracted with fresh dichloromethane (3 × 250 ml), and the combined organic layers were washed with water (1 × 500 ml), 5% aqueous sodium bicarbonate (4 × 500 ml), and water again. The dried (anhydrous sodium sulfate) organic layer was evaporated (vacuum) to yield a crude residue (17.1 g) of hydroxy diester **16**.

The total crude residue described above (17.1 g, 0.055 mole) was dissolved in 200 ml of dichloromethane. The solution was treated with 170 ml of water, 29.0 ml (0.058 mole) of 2.0 *N* aqueous sodium hydroxide solution, 17.1 g (0.055 mole) of *N,N,N*-tributylbenzenemethanaminium chloride, and 12.0 ml (17.3 g, 0.10 mole) of (bromomethyl)benzene. The two-phase mixture was stirred vigorously for 24 hours, and the layers were separated. The aqueous layer was extracted with fresh dichloromethane (3 × 100 ml), and the combined organic layers were washed with water (1 × 250 ml), 1.0 *N* aqueous sodium carbonate solution (3 × 250 ml), and water again. The dried (anhydrous sodium sulfate) organic layer was evaporated (vacuum), and the residue was stirred in 80 ml of ether. The crude product was filtered to yield 21.0 g (68% crude yield from **15**) of phenylmethyl ether **17**. A sample recrystallized several times from aqueous 2-propanol yielded ether **17**, mp 118-120°; ir: ν 1755, 1721, 1502, 1224 cm^{-1}; nmr (deuteriochloroform): δ 3.72 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.40 (s, 2H, NCH_3), 5.15 (s, 2H, OCH_2), 6.33-7.65 (m, 13H, Ar*H*).

Anal. Calcd. for $C_{24}H_{23}NO_5$: C, 71.09; H, 5.72; N, 3.46. Found: C, 70.98; H, 5.40; N, 3.34.

3-Hydroxy-1-phenyl-5-(phenylmethoxy)-1*H*-indole-2-carboxylic Acid, Methyl Ester (**18**).

A mixture of 22.1 g (0.055 mole) of diester **17** and 4.1 g (0.076 mole) of sodium methoxide in 130 ml of methanol under a nitrogen atmosphere was stirred at reflux for 2 hours. The warm reaction mixture was filtered, cooled in ice, and treated with 5.0 ml of glacial acetic acid. The precipitated solid was filtered and washed several times with cold methanol to yield 10.6 g (52% yield) of the analytically pure indole **18**, mp 128-130°; ir: ν 3328, 1663, 1447, 1222 cm^{-1}; nmr (deuteriochloroform): δ 3.73 (s, 3H, OCH_3), 5.13 (s, 2H, CH_2), 6.92-7.63 (m, 13H, Ar*H*), 8.73 (s, 1H, O*H*).

Anal. Calcd. for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75. Found: C, 73.62; H, 5.06; N, 3.69.

2-[(Carboxymethylmethylamino]-5-methoxybenzoic Acid (**21**).

A solution of 338.4 g (1.46 moles) of 2-bromo-5-methoxybenzoic acid in 700 ml of warm 2-propanol was treated with a solution of 96.5 g (1.72 moles) of potassium hydroxide in 150 ml of methanol. The new solution was cooled in ice, and the precipitated solid was filtered to yield 244 g (62% yield) of potassium salt **19**, mp 191-193° (a sample recrystallized from hexane had mp 195-197°).

A solution of 176.2 g (1.98 moles) of *N*-methylglycine (sarcosine) in 1000 ml of methanol and 50 ml of water was prepared by warming on the steam bath. The warm solution was treated with a solution of 277.7 g (4.95 moles) of potassium hydroxide in 600 ml of methanol. The new solution was condensed (vacuum) 25% and cooled in ice. The precipitated solid was filtered to yield 196 g (78% yield) of potassium of salt **20**, mp 289-291°.

A mixture of 244 g (0.91 mole) of salt **19**, 196 g (1.54 moles) of salt **20**, 113.3 g (0.82 mole) of potassium carbonate, and 0.66 g (0.01 mole) of copper powder in 220 ml of water was stirred at reflux for six hours. The cooled mixture was added to 4.0 kg of ice/water and acidified with 6.0 *N* hydrochloric acid. The precipitated product was filtered and washed with water to yield 186 g (86% crude yield) of the diacid product. A sample recrystallized from 2-methoxyethanol yielded diacid **21**, mp 203-205°; ir: ν 1734, 1508, 1259, 1035 cm^{-1}; nmr (deuteriochloroform + DMSO-d_6): δ 2.80 (s, 3H, NCH_3), 3.77 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 7.10 (dd, 1H, J = 8.5, 2.0 Hz, # 4 Ar*H*), 7.43 (d, 1H, J = 8.5 Hz, # 3 Ar*H*), 7.62 (d, 1H, J = 2.0 Hz, # 6 Ar*H*).

Anal. Calcd. for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.85. Found: C, 54.87; H, 5.59; N, 5.84.

3-Hydroxy-5-methoxy-1-methyl-1*H*-indole-2-carboxylic Acid, Methyl Ester (**23**).

A solution of 186 g (0.78 mole) of diacid **21** in 1500 ml of *N,N*-dimethylformamide was treated with a solution of 62.2 g (1.56 moles) of sodium hydroxide in 185 ml of water. After stirring for 30 minutes at room temperature, 138 ml (315 g, 2.22 moles) of iodomethane was added, and stirring was continued for 5 hours. The mixture was added to 4.0 kg of ice/water, and the product was extracted with dichloromethane (4 × 500 ml). The combined organic layers were washed with water (1 × 1.0 l), saturated aqueous sodium bicarbonate (3 × 1.0 l), and water again. The dried (anhydrous magnesium sulfate) solution was evaporated (vacuum) to yield the crude diester **22** as an oil containing some residual *N,N*-dimethylformamide.

The total crude residue described above was dissolved in 1.0 l of methanol. The solution (under a nitrogen atmosphere) was treated with 54.0 g (1.0 mole) of sodium methoxide, and the new mixture was stirred at reflux for 5 hours. The cooled reaction mixture was added to 4.0 kg of ice/water and acidified with glacial acetic acid. The precipitated product was filtered and washed with water to yield 71.7 g (39% crude yield) of the indole product. A sample recrystallized from ethanol yielded indole **23**, mp 103-105°; ir: ν 1711, 1663, 1547, 1213 cm^{-1}; nmr (deuteriochloroform): δ 3.83 (s, 6H, OCH_3 + NCH_3), 3.97 (s, 3H, OCH_3), 7.02-7.25 (m, 3H, Ar*H*), 8.49 (s, 1H, O*H*).

Anal. Calcd. for $C_{12}H_{13}NO_4 \cdot 0.25\ H_2O$: C, 60.12; H, 5.57; N, 5.84. Found: C, 59.80; H, 5.56; N, 5.69.

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[12] Reference [9], above, is the only previously reported preparation of compounds **4b** and **4c**. No spectroscopic characterization is provided for these compounds in this reference.

[13] The Ullmann reaction is very sluggish without the addition of potassium hydroxide.