Synthesis of Novel 1-Phenyl-1*H*-indole-2-carboxylic Acids. II. Preparation of 3-Dialkylamino, 3-Alkylthio, 3-Alkylsulfinyl, and 3-Alkylsulfonyl Derivatives

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The synthesis of novel indole-2-carboxylic acids with amino- and sulfur-containing substituents in the indole 3-position is described. An Ullmann reaction with bromobenzene converted 1*H*-indoles with 3-(acetylamino)- and 3-(diethylamino)-substituents into 1-phenyl-1*H*-indoles. Reaction of 3-unsubstituted indoles with thionyl chloride provided indole 3-sulfinyl chlorides, which reacted with alkyl and aryl Grignard reagents to form the corresponding sulfoxides. The indole sulfoxides thus obtained were reduced to sulfides or oxidized to sulfones.

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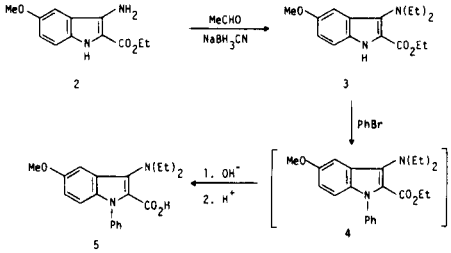
In the accompanying paper [1], we described the preparation of various 1-phenyl-1*H*-indole-2-carboxylic acids containing 3-hydroxy, 3-alkoxy, and 3-alkyl substituents. Our continuing interest in indole-2-carboxylic acids containing electron-releasing groups in the 3-position has now led to the preparation of the corresponding sulfur- and nitrogen- substituted compounds. The synthesis of these compounds **1** is the basis for this paper.

1

Indoles containing 3-amino substituents in addition to a 2-carbonyl function have previously been prepared by Thorpe cyclization of a suitable nitrile [2-4], amine displacement of a 3-haloindole [5], and addition of various arylsulfonyl azides [6,7] and aryldiazonium salts [8,9] to 3-unsubstituted indoles.

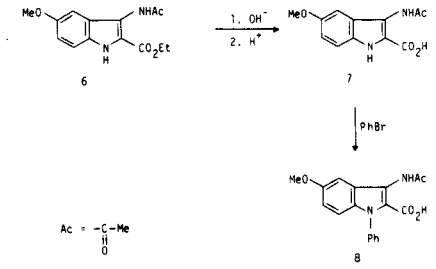
Aminoindole ester **2**, obtained by the diazonium salt procedure [9], was alkylated with acetaldehyde and sodium cyanoborohydride [10] to yield the 3-(diethylamino)-1*H*-indole **3** (Scheme I). An Ullmann-type reaction [1] on **3** provided the 1-phenyl-1*H*-indole **4** as a crude oil, and saponification of **4** yielded the target amino indole carboxylic acid **5**. Similarly, the acetylated aminoindole **6** [11] was saponified to the carboxylic acid **7** [12], and an Ullmann reaction on **7** yielded the desired acetylated indole carboxylic acid **8** (Scheme II).

Scheme I



2 3 4 5

Scheme II



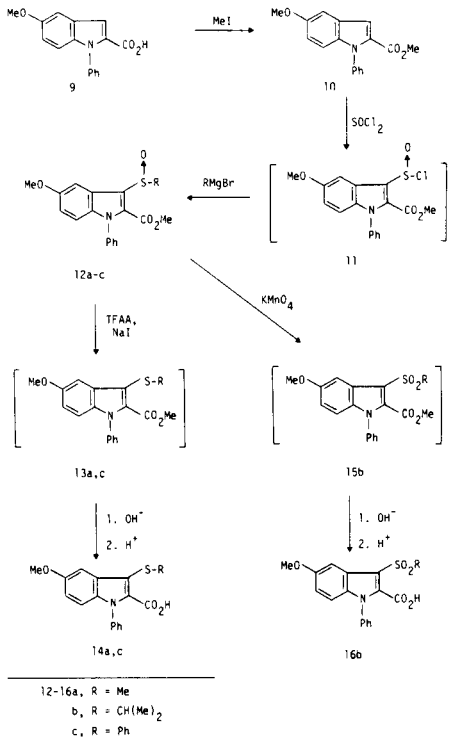
6 7 8

A limited number of procedures have been described for the preparation of indoles containing an ester or carboxylic acid function in the 2-position and a direct bond to a sulfur function in the 3-position. These include a low yield Fischer indole cyclization utilizing a thiopropynoate [13], thiocyanation of indoles with thiocyanogen or iodine thiocyanate [14], oxidative coupling of indoles and ethylenethiourea with iodine and potassium iodide [15], and the reaction of indole derivatives with thionyl chloride and sulfuryl chloride [16-19]. The latter procedures result in the direct introduction of the chlorosulfinyl and chlorosulfonyl functions onto the indole 3-position; a recent paper [20] described the related reaction with aromatic ethers as the substrate. We have combined the thionyl chloride procedure with Grignard reagent addition to the intermediate sulfinyl chlorides to prepare 3-alkylsulfinyl and 3-arylsulfinyl indole carboxylic acids.

Indole carboxylic acid **9** [1] was esterified with iodomethane (Scheme III). Reaction of ester **10** with neat thionyl chloride provide the reactive intermediate indolesulfinyl chloride **11**, which cleanly underwent reaction with a series of Grignard reagents to yield the indolesulfoxide esters **12a-c**. Reduction of sulfoxides **12a,c** with sodium iodide and trifluoroacetic anhydride [21] yielded the intermediate 3-methylthio and 3-phenylthioindole esters **13a,c**. Permanganate oxidation of sulfoxide **12b** pro-

vided the corresponding sulfone ester **15b**, and saponification of the intermediate esters yielded the target indolecarboxylic acids **14a,c** and **16c**.

Scheme III



In this and the preceding paper, we have described synthetic procedures for the preparation of 1-phenyl-1*H*-indole-2-carboxylic acids with hydroxy, alkoxy, alkyl, amino, and sulfur-containing substituents in the indole 3-position. These compounds are intermediates in the preparation of potential antiallergy agents [22].

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, except for compounds **5**, which was recorded in chloroform solution. 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.

3-(Diethylamino)-5-methoxy-1*H*-indole-2-carboxylic Acid, Ethyl Ester (**3**).

A stirred solution of 12.0 g (0.051 mole) of **2** [9] and 11.5 g (0.26 mole) of acetaldehyde in 250 ml of acetonitrile (under a nitrogen atmosphere) was cautiously treated with 14.0 g (0.22 mole) of sodium cyanoborohydride. After stirring for 15 minutes, 4.0 ml (4.2 g, 0.07 mole) of acetic acid was added in portions over two hours. The reaction mixture was poured over a mixture of ice and 400 ml of 1.0 *N* sodium hydroxide solution, and the resulting mixture was extracted with ether. The combined ether layers were washed several times with brine, dried (anhydrous magnesium sulfate), and evaporated to an orange oil. Flash chromatographic purification (silica gel, dichloromethane/ethyl acetate/hexane (1:6:3) elution) of a residual oil yielded 11.5 g (76% yield) of the analytically pure ester **3**, mp 85-89°; ir: ν 3345, 1686, 1532, 1208 cm^{-1}; nmr (deuteriochloroform): δ 1.00 (t, 6H, J = 8.3 Hz, NCH_2CH_3), 1.43 (t, 3H, J = 8.3 Hz, OCH_2CH_3), 3.32 (q, 4H, J = 8.3 Hz, NCH_2CH_3), 3.90 (s, 3H, OCH_3), 4.40 (q, 2H, J = 8.3 Hz, OCH_2CH_3), 6.88-7.37 (m, 3H, Ar*H*), 8.43 (broad s, 1H, N*H*).

Anal. Calcd. for $C_{15}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.07; H, 7.55; N, 9.90.

3-(Diethylamino)-5-methoxy-1-phenyl-1*H*-indole-2-carboxylic Acid (**5**).

A mixture of 3.0 g (0.010 mole) of amino ester **3**, 5.0 g (0.036 mole) of potassium carbonate, 0.50 g (0.009 mole) of potassium hydroxide, 0.30 g (0.001 mole) of copper(I) bromide, and 30.0 ml (44.7 g, 0.28 mole) of bromobenzene under an argon atmosphere was stirred and heated at reflux for three hours. The reaction mixture was filtered while hot through a bed of Celite filter-aid. The filter cake was washed twice with warm toluene, and the combined filtrates were evaporated. The residue was dissolved in a small amount of dichloromethane and purified by flash chromatography (silica gel, 15% ethyl acetate in hexane elution) to yield 2.4 g (66% yield) of the intermediate **4** as an oil. The oil and 1.6 g (0.040 mole) of sodium hydroxide in 50 ml of ethanol plus 15 ml of water was stirred at 65° for four hours. The reaction mixture was cooled, added to 250 g ice/brine, and acidified to *p*H 2 with dilute hydrochloric acid. The product was extracted with ether, and the combined organic layers were washed twice with brine and dried (anhydrous magnesium sulfate). Evaporation of the ether solution left a solid residue, which was triturated with ether/hexane to yield 1.55 g (70% yield) of the crude acid product. Recrystallization of a sample from ether/hexane yielded carboxylic acid **5**, mp 141-143°, ir: ν 1719, 1503, 1214, 1034 cm^{-1}; nmr (DMSO-d_6): δ 1.25 (t, 6H, J = 8.3 Hz, CH_2CH_3), 3.45 (q, 4H, J = 8.3 Hz, CH_2CH_3), 3.70 (s, 3H, OCH_3), 6.78-7.70 (m, 8H, Ar*H*), 15.90 (s, 1H, COO*H*).

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 71.12; H, 6.48; N, 8.39.

3-(Acetylamino)-5-methoxy-1*H*-indole-2-carboxylic Acid (**7**).

A suspension of 4.2 g (0.015 mole) of ester **6** [11] in 60 ml of 95% ethanol was treated with 15 ml of 2.0 *N* aqueous sodium hydroxide solution. The mixture was stirred at 35° for one hour, cooled, and added to 300 g of ice/water. Acidification to *p*H 2 precipitated the product, which was filtered and washed with water to yield 3.5 g (94% yield) of acid **7**, mp 224°-dec, lit [11] mp 232-234°; ir: ν 3295, 1664, 1565, 1218 cm^{-1}; nmr (deuteriochloroform): δ 2.08 (s, 3H, CCH_3), 3.71 (s, 3H, OCH_3), 6.86-7.29 (m, 3H, Ar*H*), 9.46 (s, 1H, N*H*), 11.42 (s, 1H, N*H*), 12.99 (broad s, 1H, COO*H*).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 57.91; H, 5.01; N, 11.15.

3-(Acetylamino)-5-methoxy-1-phenyl-1*H*-indole-2-carboxylic Acid (**8**).

A mixture of 8.1 g (0.033 mole) of carboxylic acid **7**, 3.8 ml (5.7 g, 0.036 mole) of bromobenzene, 3.6 g (0.064 mole) of potassium hydroxide, and 2.0 g (0.025 mole) of copper(II) oxide in 200 ml of *N,N*-dimethylformamide was stirred and heated at reflux under a nitrogen atmosphere for six hours. The cooled reaction mixture was added to 400 ml of ice/water and filtered through a bed of Celite filter-aid. Acidification of the filtrate with dilute hydrochloric acid precipitated the product. The solid was filtered and washed with water to yield 3.4 g (32% yield) of acid **8** after trituration with ether/pentane, mp 162-164°; ir: ν 1653, 1501, 1390, 1243 cm^{-1}; nmr (deuteriochloroform): δ 2.23 (s, 3H, CCH_3), 3.85 (s, 3H, OCH_3), 6.83-7.51 (m, 8H, Ar*H*), 7.90 (broad s, 1H, N*H*).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.45; H, 5.20; N, 8.75.

5-Methoxy-1-phenyl-1*H*-indole-2-carboxylic Acid, Methyl Ester (**10**).

A solution of 30.0 g (0.11 mole) of indolecarboxylic acid **9** [1] in 300 ml of *N,N*-dimethylformamide was treated with 9.6 g (0.12 mole) of 50% aqueous sodium hydroxide solution. The resulting mixture was stirred for 15 minutes, 8.0 ml (18.4 g, 0.13 mole) of iodomethane was added, and

stirring was continued at room temperature for four hours. The reaction mixture was added to 1.0 l of cold water and extracted with dichloromethane. The combined organic layers were washed twice with water, dried (anhydrous magnesium sulfate) and evaporated. Recrystallization of the residue from petroleum ether yielded 25 g (82% yield) of the analytically pure ester **10**, mp 67-68°, ir: ν 1726, 1502, 1267, 1109 cm^{-1}; nmr (deuteriochloroform): δ 3.79 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.98-7.55 (m, 4H, Ar*H* + indole #3-H).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.40; H, 5.34; N, 5.03.

5-Methoxy-3-(methylsulfinyl)-1-phenyl-1*H*-indole-2-carboxylic Acid, Methyl Ester (**12a**).

A mixture of 4.0 g (0.014 mole) of ester **10** in 7.0 ml (11.4 g, 0.096 mole) of thionyl chloride (under a nitrogen atmosphere) was stirred at ambient temperature for ten minutes. After the addition of 50 ml of 20% hexane in ether solution, the new mixture was cooled in ice for 30 minutes to precipitate the crude intermediate sulfinyl chloride. The solid was filtered and washed with hexane to yield 3.0 g (63% yield) of sulfinyl chloride **11**.

The total crude intermediate described above (3.0 g, 0.0087 mole) was dissolved (under a nitrogen atmosphere) in 100 ml of tetrahydrofuran and cooled to −70°. After dropwise addition of 15.0 ml (0.015 mole) of methyl magnesium bromide (1.0 *M* in ether), the new mixture was stirred at −70° for 15 minutes, then quenched by the careful addition of 10.0 ml of 10% aqueous hydrochloric acid. The product was extracted with ether, and the combined organic layers were washed several times with brine and dried (anhydrous magnesium sulfate). Evaporation of the ether solution yielded an oil which was subjected to flash chromatography (silica gel, 50% ethyl acetate/chloroform elution) to yield 2.7 g (57% yield) of the analytically pure indole sulfoxide **12a**, mp 140-144°; ir: ν 1726, 1501, 1217, 1054 cm^{-1}; nmr (deuteriochloroform): δ 3.10 (s, 3H, SCH_3), 3.70 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.87-8.07 (m, 8H, Ar*H*).

Anal. Calcd. for $C_{18}H_{17}NO_4S$: C, 62.97; H, 4.99; N, 4.08. Found: C, 63.00; H, 4.98; N, 4.08.

5-Methoxy-3-[(1-methylethyl)sulfinyl]-1-phenyl-1*H*-indole-2-carboxylic Acid, Methyl Ester (**12b**).

Prepared in 41% yield from **11** and isopropylmagnesium bromide by the procedure described in the preparation of **12a**. Sulfoxide **12b** had mp 103-104°; ir: ν 1726, 1500, 1215, 1027 cm^{-1}; nmr (deuteriochloroform): δ 1.38 (d, 3H, J = 6.2 Hz, $CH(CH_3)_2$), 1.42 (d, 3H, J = 6.2 Hz, $CH(CH_3)_2$), 3.44 (heptet, 1H, J = 6.2 Hz, $CH(CH_3)_2$), 3.68 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.95-7.93 (m, 8H, Ar*H*).

Anal. Calcd. for $C_{20}H_{21}NO_4S$: C, 64.67; H, 5.70; N, 3.77. Found: C, 64.57; H, 5.73; N, 3.75.

5-Methoxy-1-phenyl-3-(phenylsulfinyl)-1*H*-indole-2-carboxylic Acid, Methyl Ester (**12c**).

Prepared in 65% yield from **11** and phenylmagnesium bromide by the procedure described in the preparation of **12a**. Sulfoxide **12c** had mp 146-148°; ir: ν 1707, 1496, 1219, 1030 cm^{-1}; nmr (deuteriochloroform): δ 3.76 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.85-8.07 (m, 13H, Ar*H*).

Anal. Cacld. for $C_{23}H_{19}NO_4S$: C, 68.13; H, 4.72; N, 3.45. Found: C, 68.31; H, 4.58; N, 3.44.

5-Methoxy-3-(methylthio)-1-phenyl-1*H*-indole-2-carboxylic Acid (**14a**).

A mixture of 8.0 g (0.023 mole) of sulfoxide **12a** and 10.0 g (0.067 mole) of sodium iodide in 200 ml of acetone (under a nitrogen atmosphere) was maintained at 0-5° and treated dropwise with 10.0 ml (14.9 g, 0.071 mole) of trifluoroacetic anhydride. The reaction mixture was stirred for ten minutes, then poured into 300 ml of ice/5% sodium bicarbonate solution. The product was extraced with ether, and the combined extracts were washed with 5% aqueous sodium thiosulfate solution, followed by brine. The organic layer was dried (anhydrous magnesium sulfate) and evaporated to yield 7.5 g (100% yield) of the crude methylthio ester **13a**.

The total crude intermediate ester described above (7.5 g, 0.023 mole) was dissolved in 200 ml of methanol and treated with 55.0 ml (0.11 mole) of 2.0 *N* aqueous sodium hydroxide solution. The mixture was stirred at 60° for 2.5 hours, cooled, and added to 500 g ice/water. Acidification with 10% hydrochloric acid followed by filtration and washing with water, yielded 5.0 g, (67% yield) of the analytically pure carboxylic acid **14a**, mp 161° dec; ir: ν 1671, 1502, 1214, 700 cm^{-1}; nmr (deuteriochloroform): δ 2.50 (s, 3H, SCH_3), 3.91 (s, 3H, OCH_3), 6.98-7.54 (m, 8H, Ar*H*).

Anal. Calcd. for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47. Found: C, 64.90; H, 4.92; N, 4.41.

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

Prepared in 58% yield from **12c** by the procedure described in the preparation of **14a**. The crude product was triturated with ether/hexane (1/4) to yield carboxylic acid **14c**, mp 153°-dec; ir: ν 1685, 1503, 1217, 736 cm^{-1}; nmr (deuteriochloroform): δ 3.75 (s, 3H, OCH_3), 6.95-7.56 (m, 13H, Ar*H*).

Anal. Calcd. for $C_{22}H_{17}NO_3S$: C, 70.38; H, 4.56; N, 3.73. Found: C, 70.33; H, 4.64; N, 3.68.

5-Methoxy-3-[(1-methylethyl)sulfonyl)-1-phenyl-1*H*-indole-2-carboxylic Acid (**16b**).

A solution of 3.0 g (0.0081 mole) of sulfoxide ester **12b** in 250 ml of acetone was treated with a slurry of 2.6 g (0.016 mole) of potassium permanganate in 50 ml of water. After stirring at ambient temperature for four hours, the excess oxidant was destroyed by the addition of solid potassium iodide. The reaction mixture was filtered through a bed of Celite filter-aid, and a volume of water equivalent to that of the filtrate was added. The precipitated solid was filtered and washed with water to yield 1.2 g (40% yield) of crude intermediate sulfone **15b**, mp 164-166°.

A 1.0 g (0.0026 mole) sample of sulfone ester **15b** was saponified with sodium hydroxide as described in the preparation of **14a** to yield 0.75 g (77% yield) of sulfone carboxylic acid **16b**, mp 171-173°; ir: ν 1735, 1499, 1287, 1130 cm^{-1}; nmr (deuteriochloroform): δ 1.42 (d, 6H, J = 6.2 Hz, $CH(CH_3)_2$), 3.58 (heptet, 1H, J = 6.2 Hz, $CH(CH_3)_2$), 3.88 (s, 3H, OCH_3), 7.01-7.58 (m, 8H, Ar*H*).

Anal. Calcd. for $C_{19}H_{19}NO_5S$: C, 61.11; H, 5.13; N, 3.75. Found: C, 61.32; H, 5.08; N, 3.66.

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