A Facile Synthesis of 3-Substituted Indoles

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1-Benzoyl-3-bromomethylindole (**2a**) or 1-benzenesulfonyl-3-bromomethylindole (**2b**) reacts with C, N, O, and P-containing nucleophiles to give potential intermediates for the synthesis of a wide range of indole alkaloids and pharmacologically important substances, in good to excellent yields.

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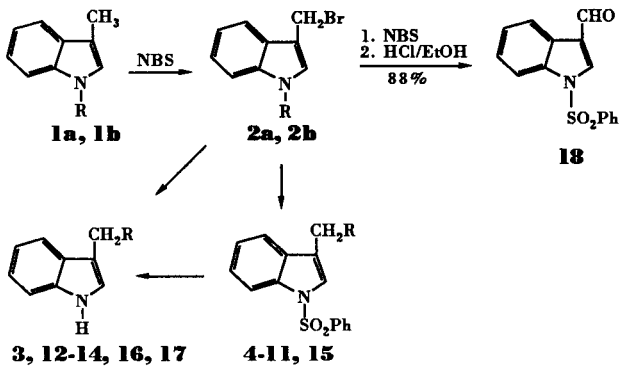
3-Substituted indoles are widespread in nature, and show a variety of biological activities including plant growth regulatory, antiinflammatory, antineoplastic, tumor promoter, antihypertensive, psychomimetic, CNS stimulant, hepatoprotective, 5-HT_3 receptor antagonist and cholecystokinin antagonist properties, *etc.* [1-5]. Development of versatile methods for forming functionally 3-substituted indoles have been the central objective of synthesis of many indole alkaloids and pharmacologically important substances [6-8]. Several methods are reported for the preparation of 3-substituted indoles, among which, the method *via* 3-(dimethylaminomethyl)indole (gramine) has been used extensively [6-9]. 3-Vinylindoles are used as intermediates for the synthesis of many substituted carbazoles, carbolines and DNA intercalating agents. Indole-3-acetonitrile, indole-3-acetic acid, tryptamine, and their derivatives are used as intermediates for several useful substances including ellipticine, aspidospermidine, reserpine, yohimbine, corynantheine and harmaline alkaloids [6-8, 10-14]. Recent computer modeling studies have shown that indole-based molecules have several potential binding sites on sickle hemoglobin [15], and therefore efforts are being made to synthesize several indole derivatives, to evaluate them for their activity against sickle cell anemia.

While the syntheses and utilities of some 2-bromomethylindole derivatives are described [16], the potential use of 3-bromomethylindoles has not yet been explored adequately. The present work describes a simple and high-yielding synthesis of several functionally 3-substituted indoles, required for the synthesis of a wide range of alkaloids and pharmacologically important substances, from 1-benzoyl-3-bromomethylindole (**2a**) and 1-benzenesulfonyl-3-bromomethylindole (**2b**).

Reaction of 3-methylindole with *n*-butyl lithium, followed by treatment with benzoyl chloride gave 1-benzoyl-3-methylindole (**1a**) in almost quantitative yield, which on reaction with *N*-bromosuccinimide provided **2a** in an excellent yield. Compound **2b** was prepared from 3-methylindole in an improved yield of 94% by *N*-benzenesulfonylation [17] followed by bromination using the reported procedures [18]. The bromine in **2a** or **2b** was substituted by nucleophilic attack with nitrogen, oxygen, carbon or phosphorous-containing groups. When **2a** was reacted with 40% aqueous dimethylamine at 50-55°, it gave 3-(*N*,*N*-dimethylaminomethyl)indole (**3**) in 92% yield. The sodio anion generated from diethyl malonate was reacted with **2b** to give the alkylated malonate ester **4** in 97% yield, which on hydrolysis afforded the dicarboxylic acid **12**. Reaction of imidazole with bromomethylindole **2b** in boiling xylene gave **5** (94%), which on hydrolysis with sodium hydroxide provided 3-(1*H*-imidazol-1-ylmethyl)indole (**13**) in 94% yield. Compound **2b** was refluxed with methanol in the presence of anhydrous potassium carbonate to give 1-benzenesulfonyl-3-methoxymethylindole (**6**), which on hydrolysis with sodium hydroxide gave 3-methoxymethylindole (**14**) in 92% and 87% yields, respectively.

Sodium azide reacted with **2b** to give 3-azidomethyl-1-benzenesulfonylindole (**7**) quantitatively, which on hydrogenation in acetic anhydride in the presence of Raney nickel, formed the acetamido compound **15** in 96% yield. Reaction of **2b** with triethyl phosphite at 155-160° gave the phosphonate ester **8** in almost quantitative yield. The sodio anion generated from diethyl acetamidomalonate reacted with **2b** to give the intermediate **9**, which on alkaline hydrolysis followed by acid treatment gave DL-tryptophan (**16**) in 66% yield from **2b**. Reaction of **2b** with potassium cyanide gave the acetonitrile **10**, which on hydrolysis gave indole-3-acetic acid (**17**) in 96% and 82% yields, respectively. Triphenylphosphine reacted with **2b** to give the phosphonium salt **11** in quantitative yield. Compound **2b** on reaction with one more equivalent of *N*-bromosuccinimide followed by treatment with hydrochloric acid in aqueous ethanol gave (1-benzenesulfonylindole)-3-carboxaldehyde (**18**), another potential intermediate for synthetic elaboration of indole, in 88% yield (Scheme 1).

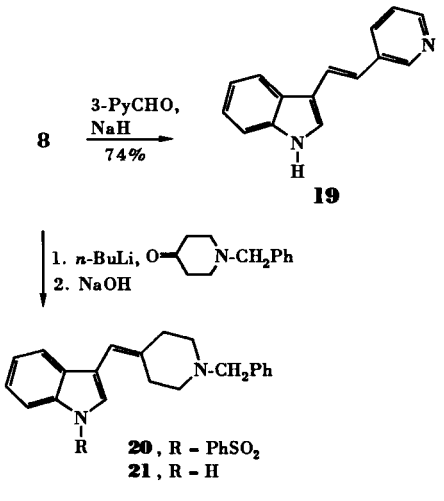
Scheme 1



Compound	R	Compound	R
3	NMe_2	10	CN
4	$CH(CO_2Et)_2$	11	$^{+}PPh_3\ Br^{-}$
5		12	$CH(CO_2H)_2$
6	OMe	13	
7	N_3		
8	$P(O)(OEt)_2$	14	OMe
9	$C(CO_2Et)_2$ | NHAc	15	NHAc
		16	$CH(NH_2)CO_2H$
		17	CO_2H

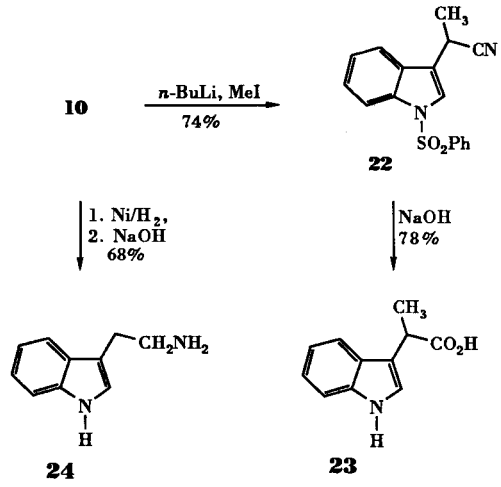
The utility of the phosphonate ester **8** for the synthesis of 3-vinylindoles was demonstrated by the Wittig-Horner reaction with pyridine-3-carboxaldehyde using sodium hydride as the base to give 3-[2-(3-pyridyl)-vinyl]indole (**19**), after work-up, in 74% yield. Reaction of **8** with *n*-butyl lithium at -78° followed by 1-benzyl-4-piperidone gave **20**, with the benzene-sulfonyl group intact, which on hydrolysis provided **21** (Scheme 2).

Scheme 2



Compound **10** on treatment with *n*-butyl lithium followed by methyl iodide gave the methylated product **22**, whose hydrolysis gave the carboxylic acid **23** in 74% and 78% yields, respectively. Raney nickel catalyzed hydrogenation of **10** followed by hydrolysis gave 3-(2-aminoethyl)indole (**24**) in 68% yield (Scheme 3).

Scheme 3



Comparison of the present method to the method *via* gramine shows the present method to give comparable yields of most of the products and, in some instances, to give improved yields. For example, product **13** is obtained in 88% yield here as compared to 53% yield from gramine [5]. Similarly, 3-[2-(3-pyridyl)vinyl]indole (**19**) was reported in 32% yield from gramine [10], and is obtained in 72% yield from **2** in fewer steps. While the phosphonium bromide **11** is prepared here in quantitative yield from **2b**, a similar phosphonium salt was obtained in 56% yield from gramine in three steps [10].

In summary, the present work clearly proves the versatility of the bromomethylindoles **2a** and **2b** for the preparation of a wide range of important indole derivatives in good to excellent yields. It also suggests that compound **2a** or **2b** may be an intermediate of choice for synthetic elaboration of indole into many alkaloids and pharmacologically important substances due to their easy accessibility in high yields.

EXPERIMENTAL

Melting points were determined in capillary tubes on a Mel-Temp apparatus and are uncorrected. Spectra were obtained as follows: ci mass spectra on a Finnegan 4000 spectrometer, fab mass spectra on a Kratos MS-50 spectrometer; pmr spectra on a Chemagnetics A-200 or Nicolet QE-300 or Varian VXR-500S spectrometers with TMS as an internal standard; ir spectra were obtained on a Beckman IR-33 spectrophotometer. All organic solvents were appropriately dried and/or purified prior to use.

1-Benzoyl-3-methylindole (**1a**).

n-Butyl lithium in tetrahydrofuran (1 *M*, 240 ml, 0.24 mole) was added to a well-stirred solution of 3-methylindole (26.2 g, 0.2 mole) in tetrahydrofuran (300 ml) at -78° under

argon in 30 minutes and the mixture was allowed to warm to room temperature. After 2 hours, it was cooled again to -78° and benzoyl chloride (30.91 g, 24 mmoles) was added in 30 minutes. The stirring was continued at -78° for 1 hour, and at room temperature for 6 hours. The mixture was poured into ice-water (600 ml), the organic layer was separated and the aqueous layer was extracted with ether (2 x 200 ml). The combined extracts were washed with 2% sodium bicarbonate (2 x 100 ml), dried (sodium sulfate), and the solvents were evaporated. The residue on trituration with hexane gave 45.6 g (97%) of **1a** as white crystals, mp 80-81° (lit [19] 75-76°); pmr (deuteriochloroform, 300 MHz): δ 2.26 (d, J = 1.5 Hz, 3H), 7.07 (d, J = 1.5 Hz, 1H), 7.33-7.43 (m, 2H), 7.52-7.61 (m, 4H), 7.72-7.75 (m, 2H), 8.42 (d, 1H).

1-Benzenesulfonyl-3-methylindole (**1b**).

Prepared from 3-methylindole (26.2 g, 0.2 mole) by reacting with dimsylsodium and benzenesulfonyl chloride using the procedure reported by Kano *et al.* [17]. The crude product was purified by crystallization from ethanol followed by chromatographic separation of the residue obtained by evaporation of the solvents from the mother liquor using hexane and chloroform (1:1) as eluents to give 53.2 g (98%) of **1b**, mp 121-122° (lit [17] 121-122.5°).

General Procedure for the Preparation of 1-Benzoyl-3-bromomethylindole (**2a**) and 1-Benzenesulfonyl-3-bromomethylindole (**2b**).

Benzoyl peroxide (20 mg) was added to a mixture of benzoylindole **1a** or sulfonylindole **1b** (50 mmoles) and finely powdered *N*-bromosuccinimide (9.0 g, 50 mmoles) in dry carbon tetrachloride (500 ml) and the mixture was refluxed for 6 hours. Succinimide was removed by filtration and washed with carbon tetrachloride (100 ml). The solvent was evaporated from the combined filtrate at reduced pressure, the residue was mixed with hexane (200 ml) and cooled. The pale yellow crystalline product formed was filtered and dried.

Product **2a**: The yield was 15.4 g (98%); mp 72-73°; pmr (deuteriochloroform, 300 MHz): δ 4.60 (d, J = 1.5 Hz, 2H), 7.36-7.72 (m, 9H), 8.39 (d, 1H); ms: ci (isobutane) m/z (%) 314 (MH^+, 7.12), 234 (100).

Anal. Calcd. for $C_{16}H_{12}BrNO$: C, 61.16; H, 3.85. Found: C, 61.23; H, 3.97.

Product **2b**: The yield was 16.8 g (96%); mp 135-137° (lit [18] 135-137°).

3-(*N*,*N*-Dimethylaminomethyl)indole (**3**).

A mixture of aqueous dimethylamine (40%, 30 ml) and 1-benzoyl-3-bromomethylindole (**2a**, 0.63 g, 2 mmoles) was heated at 50-55° for 8 hours and cooled to room temperature. It was extracted with ether (2 x 25 ml) and dried (sodium sulfate). Solvents were evaporated and the residue was purified by passing through a silica gel column using chloroform-methanol (4:1) as eluent. Evaporation of solvents and crystallization of the resultant oil from ethanol afforded 0.32 g (92%) of **3**, mp 132-134° (lit [20] mp 134°).

Preparation of Product **4**.

A solution of diethyl malonate (1.60 g, 10 mmoles) in tetrahydrofuran (50 ml) was added to a well-stirred suspension of sodium hydride (0.24 g, 10 mmoles) in dry tetrahydrofuran (50 ml) at room temperature during 10 minutes, and the stirring was continued for 1 hour. The mixture was cooled to 0° and a solution of **2b** (3.50 g, 10 mmoles) in tetrahydrofuran (50 ml) was added. The mixture was slowly warmed to room temperature and stirred for 6 hours. It was poured into a cold ammonium chloride solution (100 ml) and extracted with ether (4 x 50 ml). The combined ether extracts were washed with water (100 ml) and dried (sodium sulfate). Evaporation of the solvents gave 4.16 g (97%) of product **4** as a viscous oil. The pmr analysis showed that it was almost pure and was used as such in the subsequent reaction; ir (neat): ν 1740-1720, 1460, 1285, 1180, 1120, 1100, 1020, 980 cm^{-1}; pmr (deuteriochloroform, 300 MHz): δ 1.90 (t, 6H), 3.30 (d, 2H), 3.71 (t, 1H), 4.15 (q, 4H), 7.27-8.01 (m, 10H).

Preparation of Acid **12**.

Ester **4** (1.28 g, 3 mmoles) was added to a solution of sodium hydroxide (5 g) in ethanol (25 ml) and water (25 ml) and the mixture was refluxed for 6 hours. Solvents were distilled off, the residue was redissolved in water (25 ml), acidified with 10% hydrochloric acid and kept at 5° for 3 hours. The crystalline solid formed was filtered and recrystallized from water to give 0.586 g (84%) of **12**, mp 176-178° dec (lit [11] mp 178° dec).

1-Benzenesulfonyl-3-(1H-imidazol-1-ylmethyl)indole (**5**).

Imidazole (0.68 g, 10 mmoles) was added to a solution of **2b** (1.40 g, 4 mmoles) in dry xylene (100 ml) and the mixture was heated at 80° for 12 hours. It was cooled to room temperature and washed with saturated sodium bicarbonate solution (2 x 50 ml). The dried (sodium sulfate) solution was concentrated and the residue was chromatographed on a silica gel column (60-200 mesh, 20 g). Elution with 20% ethyl acetate in chloroform gave 1.27 g (94%) of product **5** as an oil; ir (neat): ν 1460, 1380, 1370, 1280, 1190, 1180, 1120, 1080, 980 cm^{-1}; pmr (deuteriochloroform, 300 MHz): δ 5.20 (s, 2H), 6.89 (s, 1H), 7.04-7.63 (m, 9H), 7.86-8.01 (m, 3H); ms: ci (isobutane) m/z (%) 338 (MH^+, 100).

Anal. Calcd. for $C_{18}H_{15}N_3O_2S$: C, 64.07; H, 4.48. Found: C, 64.31 ; H, 4.53.

3-(1H-Imidazol-1-ylmethyl)indole (**13**).

Prepared from **5** (0.337 g, 1 mmole) by treatment with sodium hydroxide using the procedure described for **12**, to give 0.185 g (94%) of **13**, mp 181-182° (lit [5] mp 180-182°).

1-Benzenesulfonyl-3-methoxymethylindole (**6**).

Anhydrous potassium carbonate (0.4 g) was added to a solution of **2b** (0.70 g, 2 mmoles) in methanol (20 ml), and the mixture was refluxed for 8 hours. The solids were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in ether (20 ml) and washed twice with water (10 ml) and dried (sodium sulfate). Evaporation of ether and crystallization of the residue from ethanol gave 0.552 g (92%) of **6**, mp 67-68°; ir (potassium bromide): ν 1460, 1390, 1290, 1190, 1140, 1110, 1080, 990 cm^{-1}; pmr (deuteriochloroform, 300 MHz): δ 3.40 (s, 3H), 4.60 (s, 2H), 7.24-7.62 (m, 7H), 7.86-8.08 (m, 3H); ms: ci (isobutane) m/z (%) 302 (MH^+, 100).

Anal. Calcd. for $C_{16}H_{15}NO_3S$: C, 63.76; H, 5.02. Found: C, 63.82; H, 4.89.

3-Methoxymethylindole (**14**).

Prepared from **6** (0.30 g, 1 mmole) by hydrolysis with sodium hydroxide to give 0.14 g (87%) of **14**, mp 97-99° (lit [9] mp 98-99°).

3-Azidomethyl-1-benzenesulfonylindole (**7**).

A solution of sodium azide (0.26 g, 4 mmoles) in water (10 ml) was added to a well-stirred solution of **2b** (0.70 g, 2 mmoles) in acetone (50 ml) at 0°, and the stirring was continued for 5 hours. Acetone was evaporated under reduced pressure and the residue was extracted with ether (50 ml). The dried (sodium sulfate) ether extract, upon evaporation of the solvent, gave 0.62 g (100%) of **7** as a colorless viscous oil and it was used in the subsequent reaction without any further purification; ir (neat): ν 2100, 1460, 1375, 1280, 1190, 1180, 1130, 1100, 980 cm^{-1}; pmr (deuteriochloroform, 300 MHz): δ 4.45 (s, 2H), 7.26-7.60 (m, 7H), 7.87-8.02 (m, 3H); ms: ci (isobutane) m/z (%) 313 (MH^+, 100).

3-(*N*-Acetamidomethyl)-1-benzenesulfonylindole (**15**).

A solution of **7** (0.312 g, 1 mmole) in acetic anhydride (10 ml) was hydrogenated at 45 psi in the presence of 5% palladium on charcoal (0.05 g) for 24 hours. The catalyst was removed by filtration and washed with 10 ml of acetic acid. Evaporation of solvents from the filtrate and crystallization of the residue from aqueous ethanol gave 0.314 g (96%) of **15**, mp 124-126°; ir (potassium bromide): ν 3310, 1650, 1560, 1460, 1380, 1280, 1175, 1140, 1120, 1090, 980 cm^{-1}; pmr (deuteriochloroform, 300 MHz): δ 1.98 (s, 3H), 4.52 (d, 2H), 5.92 (bs, 1H, N-H), 7.21-7.55 (m, 7H), 7.83-7.98 (m, 3H); ms: ci (isobutane) m/z (%) 329 (MH^+, 100); ms: fab m/z (%) 328 (M^+, 37), 270 (100).

Anal. Calcd. for $C_{17}H_{16}N_2O_3S$: C, 62.17; H 4.91. Found: C, 62.31; H, 4.78.

Diethyl [3-(1-Benzenesulfonylindolyl)methyl]phosphonate (**8**).

A mixture of **2b** (1.4 g, 4 mmoles) and triethyl phosphite (0.83 g, 5 mmoles) was heated at 155-160° under dry nitrogen atmosphere for 3 hours and the excess triethyl phosphite was distilled off at reduced pressure. The oily residue was triturated with hexane to afford 1.60 g (98%) of the phosphonate ester **8** as white needles, mp 88-90°; ir (potassium bromide): ν 2980, 1450, 1370, 1275, 1255, 1180, 1110, 1020, 970 cm^{-1}; pmr (deuteriochloroform, 500 MHz): δ 1.17 (t, 6H), 3.18 (d, J = 21 Hz, 2H), 3.95 (q, 4H), 7.24-8.01 (m, 10H); ms: ci (isobutane) m/z (%) 408 (MH^+, 100).

Anal. Calcd. for $C_{19}H_{22}NO_5PS$: C, 56.01; H, 5.44. Found: C, 56.30; H, 5.57.

Preparation of Phosphonium Bromide **11**.

Triphenylphosphine (2.88 g, 11 mmoles) was added to a solution of **2b** (3.75 g, 10 mmoles) in dry diethyl ether (100 ml), and the mixture was stirred for 24 hours at room temperature. The white crystalline solid formed was filtered and dried at reduced pressure to give 6.10 g (100%) of **11**, mp 175-177°; pmr (DMSO-d_6, 500 MHz): δ 5.38 (d, J = 16 Hz, 2H), 7.00-8.10 (m, 25H).

Anal. Calcd. for $C_{33}H_{27}BrNO_2PS$: C, 64.71; H, 4.44. Found: C, 64.97; H, 4.61.

Preparation of Product **9**.

Diethyl acetamidomalonate (2.17 g, 10 mmoles) was added to a well-stirred suspension of sodium hydride (0.24 g, 10 mmoles) in dry tetrahydrofuran (50 ml) at 0° under nitrogen during 10 minutes, and the mixture was allowed to warm to room temperature in 1 hour. After 2 hours, it was cooled again to 0° and a solution of **2b** (3.50 g, 10 mmoles) in tetrahydrofuran (25 ml) was added in 20 minutes. The mixture was warmed to room temperature in 1 hour, and heated at 55-60° for 5 hours. The solvents were evaporated at reduced pressure and the residue was poured into a mixture of ice (100 g) and hydrochloric acid (10 ml). It was extracted with chloroform (3 x 50 ml) and the combined extracts were washed with water (2 x 25 ml). The solvents were evaporated from the dried (sodium sulfate) extract and the residue was chromatographed on a silica gel column (60-200 mesh, 75 g) using ethyl acetate-chloroform (1:1) as the eluent to give 4.33 g (89%) of **9**, mp 132-133°; ir (potassium bromide): ν 3400, 1740, 1680, 1520, 1450, 1380, 1370, 1320, 1310, 1280, 1220, 1180 cm^{-1}; pmr (deuteriochloroform, 300 MHz): δ 1.26 (t, 6H), 1.95 (s, 3H), 3.78 (s, 2H), 4.24 (q, 4H), 6.59 (bs, 1H, N-H), 7.20-7.54 (m, 7H), 7.81-7.96 (m, 3H); ms: ci (isobutane) m/z (%) 487 (MH^+, 10.28), 347 (9.64), 143 (100).

Anal. Calcd. for $C_{24}H_{26}N_2O_7S$: C, 59.24; H, 5.39. Found: C, 59.47; H, 5.28.

DL-Tryptophan (**16**).

Compound **9** (2.43 g, 5 mmoles) was added to a solution of sodium hydroxide (3 g) in ethanol (10 ml) and water (10 ml) and the mixture was heated under reflux for 4 hours. The mixture was acidified with concentrated hydrochloric acid and the solvents were evaporated under reduced pressure. Sulfuric acid (2 *N*, 15 ml) was added to the residue and the mixture was heated under reflux for 4 hours. It was cooled to room temperature, basified with 10% sodium hydroxide solution and treated with charcoal (2 g). The alkaline solution was acidified with glacial acetic acid and cooled. The product precipitated was filtered and recrystallized from aqueous ethanol to give 0.75 g (74%) of **16**, mp 278-281° dec (lit [21] mp 278-280° dec).

(1-Benzenesulfonylindole)-3-acetonitrile (**10**).

A solution of **2b** (7.0 g, 20 mmoles) in tetrahydrofuran (50 ml) was added to a well-stirred suspension of potassium cyanide (1.95 g, 30 mmoles) in dimethyl sulfoxide (50 ml) and tetrahydrofuran (20 ml) at 0° under nitrogen for 30 minutes. The mixture was warmed to room temperature and the stirring was continued for 12 hours. Ice water (250 ml) was added to the mixture and extracted with chloroform (3 x 60 ml). The combined chloroform extracts were washed with brine (2 x 50 ml) and dried (sodium sulfate). Evaporation of solvents and crystallization of the residue from ethanol afforded 5.68 g (96%) of product **10** as white crystals, mp

148-149°; ir (potassium bromide): ν 2220, 1440, 1360, 1170, 1125, 1115, 1080, 990, 950 cm^{-1}; pmr (deuteriochloroform, 200 MHz): δ 3.74 (s, 2H), 7.29-8.00 (m, 10H); ms: ci (isobutane) m/z (%) 297 (MH^+, 100).

Anal. Calcd. for $C_{16}H_{12}N_2O_2S$: C, 64.84; H, 4.08. Found: C, 64.92; H, 4.22.

Indole-3-acetic Acid (**17**).

Compound **10** (1.48 g, 5 mmoles) was added to a solution of sodium hydroxide (4 g) in ethanol (10 ml) and water (10 ml) and the mixture was refluxed for 6 hours. Solvents were distilled off and the residue was dissolved in water (50 ml) and treated with charcoal. The aqueous solution was cooled, acidified with 10% hydrochloric acid and kept at 5° for 2 hours. The solid formed was filtered and recrystallized from aqueous ethanol to give 0.72 g (82%) of **17**, mp 163-165° (lit [23] mp 164-166°).

(1-Benzenesulfonylindole)-3-carboxaldehyde (**18**).

Powdered *N*-bromosuccinimide (1.78 g, 10 mmoles) and benzoyl peroxide (20 mg) were added to a solution of **2b** (3.50 g, 10 mmoles) in carbon tetrachloride (150 ml) and the mixture was stirred and refluxed for 14 hours. The succinimide formed was filtered off and the solvents were evaporated from the filtrate. The residue was mixed with hydrochloric acid (0.5 *N*, 20 ml) and ethanol (80 ml) and stirred at 60-65° for 10 hours. Solvents were evaporated to dryness and the residue was dissolved in ethyl acetate and chromatographed on a silica gel column (60-200 mesh, 80 g). Elution with chloroform gave 2.51 g, (88%) of **18**, mp 157-158° (lit [22] 157.5-158.5°).

3-[2-(3-Pyridyl)vinyl]indole (**19**).

Sodium hydride (0.096 g, 4 mmoles) was added to a well-stirred solution of **8** (0.814 g, 2 mmoles) and pyridine-3-carboxaldehyde (0.214 g, 2 mmoles) in dry dimethyl sulfoxide (50 ml) at 0° under nitrogen atmosphere in 10 minutes. The reaction mixture was allowed to warm to room temperature in 1 hour and the stirring was continued for 24 hours. Water (10 ml) was added cautiously and after 1 hour, the mixture was extracted with ethyl acetate (4 x 25 ml). The combined extracts were washed water (2 x 50 ml), dried (sodium sulfate) and the solvents were evaporated. The residue was chromatographed on a silica gel column (60-200 mesh, 25 g). Elution with 10% ethyl acetate in chloroform gave 0.343 g (74%) of **19**, mp 196-197° (lit [10] mp 195-196°); pmr (deuteriochloroform, 500 MHz): δ 7.08-7.11 (d, J = 17 Hz, 1H), 7.25-7.29 (m, 3H), 7.37-7.40 (d, J =17 Hz, 1H), 7.42-7.44 (m, 2H), 7.82-7.86 (m, 1H), 7.99-8.01 (dd, 1H), 8.42 (bs, 1H, N-H), 8.43-8.45 (dd, 1H), 8.73 (d, 1H); ms: ci (isobutane) m/z (%) 221 (MH^+, 100).

Preparation of Compound **20**.

n-Butyl lithium in tetrahydrofuran (1 *M*, 5.5 ml, 5.5 mmoles) was added to a well-stirred solution of **8** (2.04 g, 5 mmoles) in tetrahydrofuran (40 ml) at -78° under argon and to the resultant orange colored reaction, a solution of 1-benzyl-4-piperidone (0.96 g, 5.5 mmoles) in tetrahydrofuran (5 ml) was added in 10 minutes and the mixture was allowed to warm to room temperature. After 24 hours, the reaction was quenched by pouring into a mixture of ice (500 g) and acetic acid (5 ml) and extracted with ether (3 x 50 ml). The solvents were evaporated from the combined, dried (sodium sulfate) ether extracts and the residue was chromatographed on a silica gel column. Elution with chloroform gave 1.62 g (73%) of **20** as a colorless viscous oil; pmr (deuteriochloroform, 300 MHz): δ 2.47-2.52 (m, 4H), 2.53-2.59 (m, 4H), 3.57 (s, 2H), 6.16 (s, 1H), 7.10-7.55 (m, 12H), 7.86-7.91 (dd, 2H), 8.06 (d, 1H); ms: ci (isobutane) m/z (%) 443 (MH^+, 100), 301 (23).

Anal. Calcd. for $C_{27}H_{26}N_2O_2S$: C, 73.27; H, 5.92. Found: C, 73.41; H, 5.99.

Preparation of Compound **21**.

Prepared from **20** (0.88 g, 2 mmoles) by hydrolysis with sodium hydroxide to give 0.58 g (96%) of **21** as an oil. An analytical sample was obtained by preparative tlc using 20% ethyl acetate in chloroform; pmr (deuteriochloroform, 300 MHz): δ 2.44-2.49 (m, 4H), 2.55-2.59 (m, 4H), 3.55 (s, 2H), 6.36 (s, 1H), 7.04-7.34 (m, 8H), 7.64 (d, 1H), 8.40 (bs, 1H, N-H); ms: ci (isobutane) m/z (%) 303 (MH^+, 100).

Anal. Calcd. for $C_{21}H_{22}N_2$: C, 83.40; H, 7.33. Found: C, 83.56; H, 7.51.

Preparation of Compound **22**.

A solution of *n*-butyl lithium in hexane (1 *M*, 4 ml, 4 mmoles) was added to a well-stirred solution of **10** (1.18 g, 4 mmoles) in tetrahydrofuran (50 ml) at -78° under argon, and stirred for 40 minutes. To this, a solution of methyl iodide (0.640 g, 4.5 mmoles) in tetrahydrofuran (5 ml) was added rapidly and the mixture was allowed to warm to room temperature. After 4 hours, it was poured into a mixture of ice (100 g) and acetic acid (2 ml). It was extracted with chloroform (2 x 25 ml) and the combined extracts were washed with brine (50 ml). Solvents were evaporated from the dried (sodium sulfate) solution and the residue was chromatographed on a silica gel column (230-400 mesh, 30 g). Elution with hexane-chloroform (19:1) first gave **10** (0.06 g, 5%) and further elution with hexane-chloroform (5:1) gave 0.92 g (74%) of product **22** as an oil, which on trituration with hexane became a white crystalline solid, mp 112-113°; ir (potassium bromide): ν 2200, 1430, 1350, 1160, 1115, 1105, 1070, 940 cm^{-1}; pmr (deuteriochloroform, 200 MHz): δ 1.72 (d, 3H), 4.06 (q, 1H), 7.24-8.03 (m, 10H); ms: ci (isobutane) m/z (%) 311 (MH^+, 21).

Anal. Calcd. for $C_{17}H_{14}N_2O_2S$: C, 65.78; H, 4.55. Found: C, 65.91: H, 4.57.

Preparation of Compound **23**.

Prepared from **22** (0.62 g, 2 mmoles) by hydrolysis with sodium hydroxide, as described for **17**, to give 0.29 g (78%) of **23**, mp 108-111° (lit [21, 22] 111-112°, 105-110°).

Preparation of 3-(2-Aminoethyl)indole (**24**).

Raney nickel (0.5 g, W-4) was added to a solution of **10** (1.18 g, 4 mmoles) in ethanol (100 ml), and hydrogenated at 35 psi for 2 hours. The catalyst was removed by filtration and the filtrate was mixed with sodium hydroxide solution (40%, 10 ml) and heated under reflux for 2 hours. Solvents were evaporated and the residue was treated with saturated ammonium chloride solution (20 ml). The mixture was extracted with ether (2 x 20 ml) and dried (potassium

carbonate). Evaporation of solvent and crystallization of the residue from hexane gave 0.436 g (68%) of **24**, mp 116-117° (lit [24,25] mp 114-116°).

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