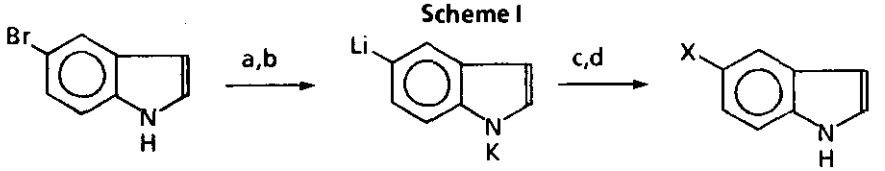
SYNTHESIS OF SOME 5-SUBSTITUTED INDOLES

Youhua Yang†, Arnold R. Martin*†, David L. Nelson#1, and John Regan#
Departments of Pharmaceutical Sciences† and Pharmacology
& Toxicology#, College of Pharmacy
University of Arizona, Tucson, AZ 85721 U.S.A.

Abstract -- A halogen-metal exchange strategy was employed to prepare several 5-substituted indoles from 5-bromoindole. Additional derivatives were elaborated from the formyl, acetyl, thiomethyl, boronic acid and trimethylstannyl analogues thus prepared.

As a part of our ongoing effort to design selective receptor agonists and antagonists of the central nervous system neurotransmitter serotonin (5-hydroxytryptamine, 5-HT),[2] we set out to prepare as starting materials several 5-substituted indoles that had either not previously been described or were not commercially available. Methodology recently described by Moyer *et al.*[3] for the regiospecific metalation of bromoindoles proved to be ideally suited for our purposes (Scheme I). Thus, 5-bromoindole was first converted to the 1-potassio derivative (in order to prevent metalation at C-2 and maintain solubility)[3] and then subjected to halogen-metal exchange using *tert*-butyllithium. The metalated species was then reacted with different eletrophiles (i.e., dimethylformamide,[3] dimethylacetamide, acetone, trimethylsilyl isocyanide,[4] trimethylsilyl chloride, dimethyl disulfide, tri-(*n*-butyl) borate[5] and trimethyltin chloride) to regiospecifically prepare 5-substituted indoles **1**-**8** (Table 1).

Scheme I



Reagents: **a** KH; **b** *tert*-BuLi; **c** Electrophile (see Table I); **d** H_2O

Table 1. Reaction of 5-Lithioindole with Various Electrophiles

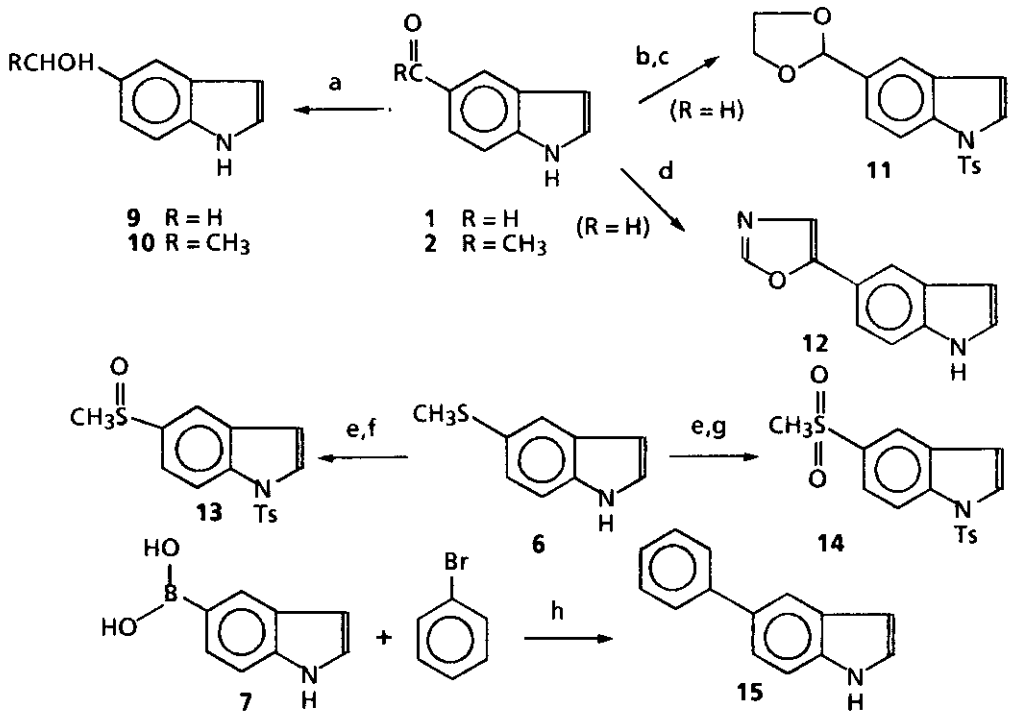
Compd	5-Substituent	Electrophile	mp (°C)	% yield[a]
1	CHO	DMF	99-101[b]	57
2	CH_3CO	DMA	73-75	18
3	$C(OH)(CH_3)_2$	$(CH_3)_2CO$	109-111	35
4	$CONH_2$	$(CH_3)_3SiNC$	165-167[c]	32
5	$Si(CH_3)_3$	$(CH_3)_3SiCl$	oil[d]	21
6	SCH_3	CH_3SSCH_3	oil[e]	94
7	$B(OH)_2$	$(n\text{-}C_4H_9O)_3B$	181-189[f]	44
8	$Sn(CH_3)_3$	$(CH_3)_3SnCl$	g	37

[a]Yields were not optimized.
[b]Lit.,[3] mp 99-101°C.
[c]Lit.,[6] mp 165.5-167.0°C.
[d]Characterized by Belsky *et al.*[7]
[e]bp 130°C at 0.2 mm. Lit.,[8] nmr ($CDCl_3$) δ 2.5 ppm confirmed.
[f]Solidifies above 190° and remelts at 220-223°.
[g]bp128° at 0.7 mm.

Additional analogues (Table 2) were elaborated from **1**, **2**, **6**, and **7** (Scheme II). Thus, 5-hydroxymethylindole (**9**) and 5-(1-hydroxyethyl)indole (**10**) were obtained by sodium borohydride reduction of **1** and **2**, respectively. Successful ketalization of **1** required prior protection of the indole nitrogen as the tosylate, which apparently increases the reactivity of the formyl sufficiently to allow formation of the ketal (**11**). However, unprotected **1** was reactive enough to form 5-(5-isoxazoyl)indole (**12**) when reacted with tosylmethyl isocyanide.[9] Direct oxidation of the sulfur atom of 5-methylthioindole (**6**) to form the corresponding sulfoxide and sulfonyl derivatives was not attempted, because of the anticipation that oxidation of the indolic 2,3-π bond would simultaneously occur.[10] *N*-tosylation of **6** thus sufficiently deactivated the indole ring to allow oxidative formation of the *N*-tosyl-5-sulfinyl and -5-sulfonyl derivatives (**13**) and (**14**), respectively. The boronic acid (**7**) was an important target for our purposes since, in principle, it could serve as a key intermediate for the preparation of 5-aryl- and 5-heteroarylindoles by palladium catalyzed cross-coupling with aryl[11-15] and heteroaryl[16-18] halides. Indeed, an initial attempt to exploit this methodology led to the successful tetrakis(triphenylphosphine)palladium catalyzed couplings of **7** and **8** with bromobenzene to give 5-phenylindole[15].

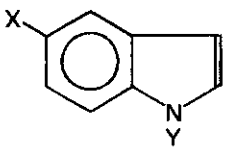
In summary, a wide variety of 5-substituted indoles can be prepared by a metalation strategy applied to 5-bromoindole, followed by reaction of the 5-lithio intermediate with different electrophiles. Indole-5-boronic acid and 5-(Trimethylstannyl)indole prepared in this way provide

Scheme II



Reagents: **a** $NaBH_4$; **b** KH, TsCl; **c** $HOCH_2CH_2OH$, TsOH; **d** $TsCH_2NC$: **e** TsCl, $(n\text{-}C_4H_9)_4NHSO_4$, OH^-; **f** $NaBO_3 \cdot 4H_2O$; **g** $NaIO_4$; **h** $Pd(PPh_3)_4$, Na_2CO_3

Table 2. Additional 5-Substituted Indoles



Compd	X	Y	mp (°C)	% yield[a]
9	CH_2OH	H	oil	48
10	$CH(OH)(CH_3)$	H	oil	49
11	1,3-Dioxolanyl	Ts	97-99	47
12	5-Oxazoyl	H	176.5-179	35
13	CH_3SO	Ts	107-109	60
14	CH_3SO_2	Ts	131-133	14
15	C_6H_5	H	71-73	87

[a]Yields were not optimized.

useful intermediates for the synthesis of 5-aryl- and 5-heteroarylindoles by cross-coupling reactions.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-nmr spectra were recorded on a Jeol FX90Q Spectrometer. The mass spectra were determined on a Hewlett Packard Model 5970 Mass Mass Spectrometer. Infrared spectra were carried out on a Beckman IR-33 Spectrophotometer. Elemental analyses were performed at Desert Analytics, Inc. Tucson, Arizona U.S.A. The nmr, ms and ir spectra were consistent with the structures indicated.

General Procedures for Halogen-Metal Exchange and Reactions of the Resulting 5-Indolyllithium with Electrophiles. To 2.29 g of KH dispersion in mineral oil (35%, 20 mmol) in 40 ml of anhydrous THF at 0°C was added 3.98 g (20 mmol) of 5-bromoindole in 40 ml of anhydrous THF. After 15 min. the solution was cooled to -78°C and *tert*-butyllithium (40 mmol) precooled to -78°C was added *via* a cannula. A white precipitate immediately formed and, after 10 min, 40 mmol of the electrophile dissolved in 10 ml of anhydrous THF was added. The reaction mixture was allowed to slowly warm to room temperature and the suspension was poured into 150 ml of ice cold 1 M H_3PO_4. The organic phase was separated and the aqueous phase was extracted twice with ether. The ether extracts were combined, washed with 5% $NaHCO_3$ solution, dried over anhydrous $MgSO_4$ and the ether was removed *in vacuo*. The residue was chromatographed on silica gel 60, eluting with ethyl acetate/hexanes (1:3) for compounds (**1**), (**2**), (**3**), and (**6**) and chloroform/methanol for compound (**4**). Compound (**5**) was obtained by distillation [bp 89-91°C at 0.1 mm (Lit.,[7] 103-105°C at 1 mm)]. The boronic acid (**7**) was isolated and purified by the following procedure: The combined ether extracts were extracted with IN NaOH solution (3 x 15 ml) and the combined alkaline extracts were acidified with IN HCl solution and then extracted with ether (3 x 20 ml). The combined ether extracts were dried (anhydrous Mg_2SO_4) and evaporated to give **7** as a white crystalline solid which was recrystallized from hot water. The trimethylstannyl derivative was distilled under reduced pressure to give a colorless oil, bp 128° at 0.7 mm.

5-Acetyl-1H-Indole (**2**). Anal. Calcd for $C_{10}H_9NO$: C 75.45; H 5.70; N 8.80. Found: C 75.50; H 5.65; N 8.78.

5-(2-Hydroxy-2-propyl)-1H-Indole (**3**). Anal. Calcd for $C_{11}H_{13}NO$; C 75.40; H 7.48; N 7.99. Found: C 75.59; H 7.62; N 7.68.

5-(1H-Indolyl)boronic Acid (**7**). Anal. Calcd for $C_8H_8BNO_2.3/2\ H_2O$: C 51.45; H 6.00; N 7.43.

Found: C 51.10; H 5.89; N 7.45.

5-(Trimethylstannyl)indole (**8**). Calcd for $C_{11}H_{15}NSn$: 281.0; Found: m/z (low resolution) 281.1.

Sodium Borohydride Reduction of Compounds **1** and **2**. To a solution of 10 mmol of **1** (or **2**) in 20 ml of ethanol was slowly added 1.51g (40 mmol) of $NaBH_4$. The mixture was stirred until no starting material remained (tlc). Then, 50 ml of 5% HCl solution was carefully added (exothermic reaction) and the mixture was cooled and extracted with ethyl acetate (3 x 50 ml). The combined organic phase was dried (anh. $MgSO_4$) and evaporated to yield an oily residue which was chromatographed on a silica gel 60 column using ethyl acetate/hexane (1:2 for compound (**9**), 1:1 for compound (**10**)).

5-(Hydroxymethyl)-1*H*-Indole (**9**). Anal. Calcd for C_9H_9NO: C 73.45; H 6.16; N 9.52. Found C 73.29; H 6.14; N 9.68.

5-(1-Hydroxyethyl)-1H-Indole (**10**). Anal. Calcd for $C_{10}H_{11}NO$: C 74.51; H 6.88; N 8.69. Found: C 74.39; H 6.83; N 8.48.

5-(5-Oxazoyl)-1H-Indole (**12**). To a stirred solution of tosylmethyl isocyanide (0.98 g, 5 mmol) and 0.73 g (5 mmol) of 5-formylindole (**1**) in 40 ml of methanol was added 0.69 g (5 mmol) of anhydrous K_2CO_3. The mixture was refluxed for 4 h, the methanol was removed *in vacuo*. The residue was dissolved in ether and dried over anh. $MgSO_4$. After evaporation of the solvent the residue was chromatographed on silica gel, eluting with ethyl acetate/hexane (35/65) to give a white solid which was recrystallized twice from ethanol/water. Anal. Calcd for $C_{11}H_8N_2O$: C 71.72; H 4.38; N 15.21. Found: C 71.06; H 4.30; N 15.10.

1-(*p*-Toluenesulfonyl)-5-thiomethyl-1H-indole. To a mixture of 1.63 g (10 mmol) of **6**, 2.86 g (15 mmol) of tosyl chloride and 0.5 g of tetrabutyl ammonium hydrogen sulfate in 30 ml of toluene was added 25 ml of 15% aqueous sodium hydroxide in an ice bath. The mixture was stirred for 6 h and the toluene layer was separated and successively washed with 1% HCl, 20% $NaHCO_3$ and water. The toluene phase was then dried (anh. Na_2SO_4) and concentrated *in vacuo* to yield an oily residue that was chromatographed on a silica gel 60 column. Elution with ethyl acetate/hexane (3/1) gave 2.85 g (90%) of a colorless liquid which solidified on standing (mp: 90-92°C). Anal. Calcd for $C_{16}H_{15}NO_2S_2$: C 60.54; H 4.76; N 4.41. Found: C 60.68; H 4.73; N 4.20.

1-(*p*-Toluenesulfinyl)-5-methylsulfinylindole (**13**). A mixture of 1.59 g (2.5 mmol) of 1-tosyl-5-thiomethylindole and 0.78 g (2.5 mmol) of sodium perborate tetrahydrate in 35 ml of methanol was stirred for 4 h at 50°C. The reaction mixture was extracted with two 25 ml portions of ether and the combined ether extracts were dried (anh. Na_2SO_4) and concentrated to give a solid

residue which was chromatographed on silica gel with ethyl acetate to give 0.75 g of **13**. Anal. Calcd for $C_{16}H_{15}NO_3S$: C 57.64; H 4.53; N 4.20. Found: C 57.45; H 4.43; N 4.09.

1-(*p*-Toluenesulfinyl)-5-methylsulfonylindole (**14**). A mixture of 2.80 g (8.8 mmol) of 1-tosyl-5-methylthioindole and 1.96 g (9.2 mmol) of sodium periodate in 35 ml of methanol was stirred for 4 h at 50°C. The reaction mixture was cooled, extracted with two 25 ml portions of ether and the ether extracts were combined and dried over anh. Na_2SO_4. After removal of the ether *in vacuo* the residue was chromatographed on silica gel with ethyl acetate/hexane (1/1) to give 0.44 g (14%) of **14**. Anal. Calcd for $C_{15}H_{18}N_2S$: C 62.04; H 6.25; N 9.65; S 10.04. Found: C 62.04; H 6.16; N 9.31; S 10.54.

5-Phenyl-1H-indole (**15**). Cross-Coupling of Bromobenzene with **7**. To a stirred mixture of 0.80 g (5 mmol) of bromobenzene, 0.18 g (0.15 mmol) of tetrakis(triphenylphosphine)palladium and 20 ml of ethylene glycol dimethyl ether was added 0.89 g (5.5 mmol) of **7**, followed by 1.26 g (15 mmol) of $NaHCO_3$ in 15 ml H_2O. The mixture was then refluxed with vigorous stirring for 4 h. The mixture was concentrated *in vacuo* and the residue was extracted with ether (2 x 50 ml). The ether phase was then dried over anh. K_2CO_3 and the ether was evaporated to give a solid residue that was purified on a silica gel column by elution with hexane/ethyl acetate (1:3) to give 1.09 g of **15**. Anal. Calcd for $C_{14}H_{11}N$: C 87.01; H 5.74; N 7.25. Found: C 86.97; H 5.81; N 7.20.

Cross Coupling of Bromobenzene with **8**. To a stirred mixture of 0.94 g (6 mmol) of bromobenzene, 0.18 g (0.15 mmol) of tetrakis (triphenylphosphine)palladium and 25 ml of DMF was added 1.40 g (5 mmol) of **8**. The mixture was heated to 100-120° under a N_2 atmosphere with stirring for 15 h. The mixture was then concentrated and the residue was partitioned between H_2O and $CHCl_3$. The aqueous phase was separated and extracted again with $CHCl_3$ and the combined organic extracts were dried over anh. Na_2SO_4. After evaporation of the solvent, the residue was chromatographed as above to give 0.84 g (87%) of **15**.

5-(1,3-Dioxolanyl)-1-(p-toluenesulfonyl)indole (**11**). To a stirred solution of 1.45 g (10 mmol) of 1 in 20 ml of DMF was added portionwise 0.41 g (10 mmol) of KH at 0°C. The mixture was stirred for 30 min and then 2.27 g (11 mmol) of p-toluenesulfonylchloride was added. The mixture was allowed to warm to 25°C and then poured into a mixture of 60 ml of H_2O and 20 ml of ether. The precipitate was collected on a filter, washed with water and ether to give 2.51 g. of a white solid (80%). A portion of the solid (1.32 g, 5 mmol) thus obtained was then dissolved in 30 ml of toluene in a round bottomed flask equipped with a water separator and a reflux condensor. Ethylene glycol 0.47 g (7.5 mmol) and a crystal of p-toulenesulfonic acid were added and the

solution was refluxed for 24 h. The reaction mixture was partitioned between ether and saturated sodium bicarbonate solution and the organic phase separated and dried (anh. K_2CO_3). Evaporation of the solvent gave 0.85 g(47%)of **11**. Anal. Calcd for $C_{18}H_{17}NO_4S$: C 62.96; H 4.96; N 4.04; S 9.65. Found: C 63.03; H 4.96; N 4.04; S 9.65.

REFERENCES AND NOTES

1. Present address: Lilly Research Laboratories. Central Nervous System Division, Indianapolis, IN 46285 U.S.A.
2. E. W. Taylor, S. S. Nikam, G. Lambert, A. R. Martin, and D. L. Nelson, *Mol. Pharmacol.*,1988, **34**, 42.
3. M. P. Moyer, J. F. Shiurba, and H. Rapoport, *J. Org. Chem.*, 1986, **51**, 5106.
4. G. Sauer, J. Heindl, and H. Wachtel, *Tetrahedron Lett.*, 1988, **29**, 6425.
5. S. V. Kessar, R. Gopal, and M. Singh, *Tetrahedron*, 1973, **29**, 167.
6. H .I. Abrash and C. Niemann, *Biochemistry* (American Chemical Society), 1965, **4**, 99.
7. I. Belsky, D. Gertner, and A. Zilkha, *J. Org. Chem.*, 1968, **33**, 1348.
8. J. Gullaume, C. Dumont, J. Laurent, and L. Nedelec, *Eur. J. Med. Chem.*, 1987, **22**, 33.
9. A. M. van Leusen, B. E. Hoogenboom, and H. Siderius *Tetrahedron Lett.*, 1972, **23**, 2369.
10. W. A. Remers, 'Heterocyclic Compounds,' Vol. 25, 'Indoles,' Part I, ed. by W. J. Houlihan, John Wiley & Sons, New York, 1972, pp. 153-160.
11. N. Miyaura, T. Yanagi, and A. Suzuki, *Synthetic Commun.*, 1981, **11**, 513.
12. W. Cheng and V. Snieckus, *Tetrahedron Lett.*, 1987, **28**, 5097.
13. U. Schmidt, R. Meyer, V. Lichtenberger, and A. Lieberknecht, *Angew. Chem. Int. Ed. Engl.*, 1989, **28**, 929.
14. R. B. Miller and S. Dugar, *Organometallics*,1984, **3**, 1261.
15. G. W. Gray, M. Hird, D. Lacey, and K. J. Toyne, *J. Chem. Soc., Perkin Trans,II*, 1989, **2041**.
16. W. J. Thompson and J. Guadino, *J. Org. Chem.*, 1984, **49**, 5237.
17. J. Stavenuiter, M. Hamink, R. van der Hulst, G. Zomer, G. Westra, and E. Kriek, *Heterocycles*, 1987 **26**, 2711.
18. S. Gronowitz and D. Peters, *Heterocycles*, 1990, **30**, 645.

Received, 14th February, 1992