Preparation of 2-Iodotryptamine and 2-Iodo-5-methoxytryptamine

Toni Kline

Department of Pharmacology, Mount Sinai School of Medicine of the City University of New York
One Gustave L. Levy Place, New York, New York 10029

Received July 16, 1984

The regiospecific iodination of indole and 5-methoxyindole, and the elaboration of these 2-iodoindoles to the corresponding tryptamines, are described.

J. Heterocyclic Chem., **22**, 505 (1985).

Introduction.

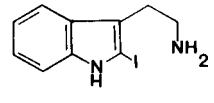
Halogenation at the 2-position of lysergic acid diethylamide alters the pharmacological properties of the resultant compounds. The 2-bromo analogue differs most conspicuously from lysergic acid diethylamide in being nonhallucinogenic [1-7]. 2-Bromolysergic acid diethylamide is an antagonist to certain responses of 5-hydroxytryptamine (5-HT, serotonin) both in brain [8,9] and in peripheral tissues [1,2,6] whereas lysergic acid diethylamide is an agonist (full or partial) [6,9-12] in some of these preparations and an antagonist [1b,6,7] in others. 2-Bromolysergic acid diethylamide has been observed to antagonize some of the behavioral effects of lysergic acid diethylamide [4,5]. In the raphe (serotonergic) neurons, lysergic acid diethylamide but not the 2-bromo analogue inhibits the firing, a 5-hydroxytryptamine-agonist effect [3,13]. 2-Bromolysergic acid diethylamide discriminates between 5-hydroxytryptamine receptors: At the 5-hydroxytryptamine receptor linked to contraction of the rabbit aorta, 2-bromolysergic acid diethylamide has 1000-fold greater antagonist potency than it does at the 5-hydroxytryptamine receptor linked to adenylate cyclase stimulation [8]. Radioautography has revealed differences between tritiated 2-bromolysergic acid diethylamide and tritiated lysergic acid diethylamide at 5-hydroxytryptamine binding sites in rat brain coronal slices [14b,c], differences confirmed in equlibrium binding studies [14,15]. The characteristics in both binding (*e.g.*, receptor and region selectivity) and in activity (pure antagonism *vs.* more complex agonism/antagonism) that distinguish 2-brominated lysergic acid diethylamide from the parent compound are enabling pharmacologists to classify 5-hydroxytryptamine receptors and to elucidate some of the structural requirements for a hallucinogen.

Although first synthesized [16] and found to be a peripheral 5-hydroxytryptamine antagonist [1b] in 1957, 2-iodolysergic acid diethylamide has only recently received much attention, chiefly because the ^{125}I labeled compound has been prepared as a high-specific-activity (2175 Ci/mmole) ligand with nanomolar affinity for only one 5-hydroxytryptamine binding site (5-HT_2) [17-21]. 2-Iodolysergic acid diethylamide also displays some selectivity in binding to a high affinity 5-HT_1 site with a K_i of 32 nM and to a different, low-affinity 5-HT_1 site with a K_i 1000-fold higher [20]; thus, the 2-iodinated analogue, like the 2-brominated analogue, and unlike lysergic acid diethylamide, discriminates among 5-hydroxytryptamine binding sites.

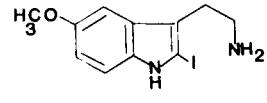
Theoretical treatments of the structural differences between 5-hydroxytryptamine, lysergic acid diethylamide, and other ergoline ligands at 5-hydroxytryptamine receptors, have identified some of the molecular determinants for recognition at high-affinity 5-hydroxytryptamine binding sites in brain [21]. Three critical elements of these molecular determinants are (1) the amino group, attached through an alkyl chain to the indole portion, (2) the negative electrostatic potential surrounding the aromatic system, and in particular the directionality of this potential, *i.e.* the electrostatic orientation vector (EOV) of the indole portion, as well as (3) the position of the aminoalkyl group with respect to the EOV. The rank order of affinity of 5-hydroxytryptamine ligands can be explained by a mechanistic hypothesis based on the geometry defined by the positions of the EOV and aminoalkyl group [21b].

Structure-activity studies on 2-haloindolalkylamines have been limited to the data obtained from very few structures, generally the 2-bromo and 2-iodoergolines discussed above. The 2-halo-5-aminotetrahydrobenzindoles are patented as part of a class of drugs effective in lowering prolactin secretion, in treating Parkinson's disease, and as hypotensive agents [22]. It is not disclosed in the patent how the activities of the 2-halo compounds compare to the non-halogenated analogues. Deprenon, another 2-haloergoline, has been shown to be more effective as a hypotensive agent/prolactin-secretion inhibitor than the corresponsing 2-protio compound [23]. A series of 1-substituted 3-(2′-nitrovinyl)-2-chloroindole compounds are reported as antibacterial agents, without discussion of the contribution of the 2-chloro group [24].

The profound pharamacological consequences of 2-bromination or 2-iodination on the ergoline nucleus are apparent from the pharmacological evaluation of 2-bromo and 2-iodolysergic acid diethylamide, and prompted a study of 2-halogenation of a simpler class of 5-HT ligands, the tryptamines. No 2-halotryptamines were found in the



1



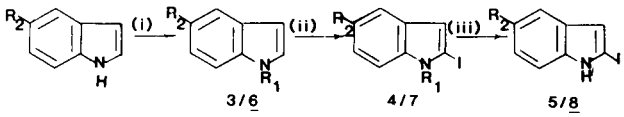
2

literature, so, with some consideration for future ^{125}I labeling studies, we selected as our first synthetic goals 2-iodotryptamine (**1**) and 2-iodo-5-methoxytryptomine (**2**). It was considered that the synthetic efforts directed at **1** and **2** would yield a generalizable protocol for the preparation of a series of substituted 2-iodotryptamines; precisely which substituents would be most useful would be determined by pharmacological screening of **1** and **2**. Accordingly, the preparation of **1** and**2** is reported here, and the results of pharmacological investigations will be presented elsewhere.

Results.

It was clear at the outset that direct iodination of tryptamine, or even indole, could give rise to mixtures of monosubstituted, polysubstituted, cyclized, oxidized, and indole-indole coupled products [25-34]. Activation of the indolic 2-position (at the expense of the inherently more nucleophilic 3-position) appeared the surest strategy (Scheme I) for electrophilic substitution. In the last ten

Scheme I



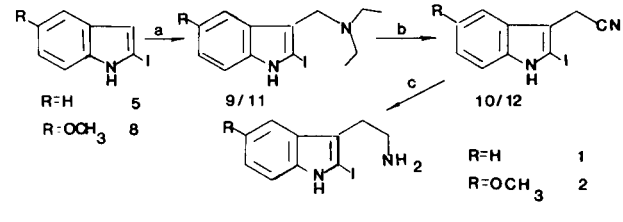
R_2 = H **3**, **4**, **5**, R_2 = OCH_3 **6**, **7**, **8**,
R_1 a, SO_2Ph b, $CH_2OCH_2CH_2Si(CH_3)_3$ c, CO_2t-Bu

See Text for details describing steps (i), (ii), and (iii).

years, methods for 2-metallation of indole have been developed based on easily manipulated N_1 substituents. The requirements for such a group (*i.e.* R_1 in Scheme I) in the present synthesis were that it should (1) protect the N_1 nitrogen, (2) activate the nucleophilicity of the 2-position, and (3) be removed under conditions which did not affect the nascent aryl iodide. Three candidates for R_1 met these criteria and were evaluated experimentally: (a) benzenesulfonyl [25,26], (b) [2-trimethylsilyl) ethoxy]methyl (SEM) [35], and (c) *t*-butoxycarbonyl (BOC) [36,37]. In our hands reactions with **3a**, R_1 = benzenesulfonyl, gave rise to consistently lower yields of **4a** and consequently **5**, necessitating tedious and inefficient separations of starting material, product, and decomposition products. The need to reflux **3a** in order to form the anion seemed responsible for the poor success. Accordingly the SEM group, with some presumed ability to coordinate the Li cation intramolecularly, was introduced: **3b** formed readily but barely lithiated at -78°, partially lithiated with some accompanying decomposition at -60° and decomposed immediately at 0°. The carbamate **3c** proved to form, react, and deprotect in quite acceptable yields for both indole and 5-methoxyindole; the highest and cleanest yields were obtained by addition of the anion of **3c** to a tetrahydrofuran solution of exces iodine, all conducted (*i.e.* formation, transfer, and reaction of the **3c** anion) at -78°. Electrophilic capture of **3c** appeared virtually instantaneous by tlc, although in practice the reaction mixture was usually stirred at least one hour to ensure complete iodination (see Experimental). The extent of iodination could be immediately determined by nmr, particularly clearly for the conversion of **6** to **7**. The H-2 doublet at δ 7.55 (J = 3.6) dissappeared, the H-3 doublet at δ 6.48 (J = 3.6) became a singlet at δ 6.82, and these three well-defined sets of peaks immediately revealed the presence of any uniodinated material. For the conversions of all **3** to**4**, the individual protons were somewhat less well resolved, but upon iodination, the salient H-3 doublet consistently collapsed to a singlet approximately 0.3 parts per million downfield from its initial δ value. Separation of the 2-iodinated products was most efficiently conducted following removal of the BOC function, but all intermediates **3-8** appeared quite stable to chromatography on neutral alumina and could be thus isolated and characterized.

With quantities of **5** (and later **8**) in hand we next considered how best to append the aminoethyl sidechain. The choices were governed by the halogen's deactivation of the indole nucleus and by the need for a reduction method that would affect neither the iodide (both acidand nucleophile-sensitive) nor the indole ring itself. Scheme II seemed most promising, since the Mannich reaction had been performed on a ring-halogenated indole [38], and electrophilic reduction methods exist which can selectively convert a nitrile to an amine without indoline formation [38-40] and which involve a basic workup [38,39]. Nitriles **11** and **12** were formed in quite good yields, without the need for purification of the intermediate oily gramines **9** and **11**. Attempts to reduce the nitrile function using alane [38] or borane-methylsulfide [41] gave only mixtures of deiodinated and decomposition products, but diborane reduction of **10** and **12** at room temperature, followed by treatment with methanolic sodium hydroxide to generate the volatile trimethylborate, gave the corresponding tryptamines **1** and **2**. Since Schemes I/II are applicable to a variety of substituted indoles, these procedures represent

Scheme II



(a) 60% $CH_3CO_2H/(C_2H_5)_2NH/HCHO$. (b) CH_3I, potassium cyanide/-MeOH-DMF-H_2O. (c) (i) BH_3-THF, rt 1 h (ii) 1*M* NaOH/MeOH, reflux 0.5 h.

general access to modified 2-iodotryptamines. Further experiments are now in progress to determine the scope and limitations of this method, as well as the pharmacological properties of **1** and **2**.

EXPERIMENTAL

All reactions were conducted in flame-dried glassware under an argon or nitrogen atmosphere. Tetrahydrofuran was distilled from benzophenone ketyl immediately prior to use in all reactions. All other reaction solvents were dried by distillation over the appropriate agent and stored under nitrogen over molecular sieves; all other solvents and reagents were the highest grade commercially available and were used without additional purification. Thin layer chromatography (tlc) analysis of reactions were run on Polygram Sil G/UV 254 silica gel plates, and visualized using ultraviolet light, Ehrlich's reagent, and/or acidic anisaldehyde solutions [42]. Column chromatography was performed under 'flash' conditions [43] using 230-400 mesh silica gel or Brockmann 1, 150 mesh neutral alumina. Evaporations *in vacuo* were conducted on a Buchi rotavapor at water aspirator pressures. Unless otherwise stated, anhydrous magnesium sulfate was used for the drying of organic phase solutions. Melting points were taken on a Thomas Hoover Capillary Melting Point Apparatus, and are uncorrected. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian FT 80-A instrument, in deuterochloroform solution (unless otherwise indicated) and are reported in parts per million downfield from tetramethylsilane = 0.0; deuterochloroform at 577.3 Hz (δ 7.25) is observed but not reported. High-field nmr spectra for **1** were recorded on a Bruker WM250 MHz Instrument. Infrared spectra were recorded on a Beckman IR 8. Low resolution mass spectra were obtained on a 5980-A HewlittPackard Mass Spectrometer and high resolution mass spectra were obtained on an MS-30 Kratos. Elemental analysis were obtained from Mr. Theodore Bella of the Microanalytical Service at the Rockefeller University.

1-Benzenesulfonyl-2-iodoindole (**4a**).

To a solution of 1-benzenesulfonylindole (**3a**) [25] (6.88 g, 26.7 mmoles) in 75 ml of tetrahydrofuran, cooled in an ice-salt bath, was added, over 25 minutes, a 1.7*M* *t*-butyllithium/pentane solution (20 ml, 34 mmoles). The red anion solution was allowed to come to room temperature, then refluxed 1 hour, during which time the color intensified. After cooling again to room temperature, a solution of molecular iodine (11.5 g, 90 mmoles) in 40 ml of tetrahydrofuran was added. The reaction mixture was stirred overnight, then approximately 100 ml of 5% aqueous thiosulfate solution was added to reduce the excess iodine. An equal volume of methylene chloride was added while the reaction mixture was still under argon, then the organic phase separated and washed with saturated thiosulfate solution, then sodium chloride, dried, and concentrated *in vacuo* to an oily residue. Chromatography on a 2.5 × 30 cm Florisil column (50% ether/-hexane), followed by crystallization from ether/hexane, gave 2.5 g of **4a** (25%) as white needles, mp 92-93°; ^{1}H nmr: δ 8.28 (m, H-4), 7.89 (dd, H-7), 7.18-7.48 (m, phenyl H plus H-5, H-6), 6.99 (s, H-3); ir (chloroform): 1460, 1455, 1390 (N-SO_2Ph), 1235, 1220, 1203, 1195 (N-SO_2Ph), 1170, 1140, 1110 cm^{-1}.

2-Iodo-1-[[2-(trimethylsilyl)ethoxy]methyl]indole (**4b**).

A solution of *N*-[trimethylsilyl)ethoxy]methylindole (**3b**) [34] (638 mg, 2.58 mmoles) in 10 ml of tetrahydrofuran was cooled to -78° and a 2 *M* pentane solution of *t*-butyllithium (3.87 ml, 7.74 mmoles) was added over 30 minutes; a bright yellow color developed almost immediately. The solution was allowed to warm to -60° then transferred to a -78° solution of iodine (1.97 g, 7.75 mmoles) in 10 ml of tetrahydrofuran, and the reaction mixture was allowed to come to room temperature overnight before quenching by addition of 2 ml each of 5% thiosulfate solution and methylene chloride. The organic phase was washed with saturated thiosulfate, then sodium chloride solutions, dried, and concentrated *in vacuo* to an oily residue. Examined by nmr, this residue appeared to be 60:40 mixture of iodinated to uniodinated products. Chromatography on a 2 × 20 cm column of neutral alumina, using 0.25% ethyl acetate/hexane, gave 140 mg **4b** (15%) as a yellow oil; ^{1}H nmr: δ 7.44-7.52 (m, H-4, H-7), 7.08-7.20 (m, H-5, H-6), 6.81 (s, H-3, 5.53, s, NCH_2O), 3.55 (t, J = 7.8, 8.4, OCH_2CH_2), 0.88 (t, J = 7.7, 8.6, CH_2-CH_2Si), -0.05, (s, $SiCH_3$).

1-*t*-Butoxycarbonyl-2-iodoindole (**4c**).

A solution of *N*-*t*-butoxycarbonylindole (**3c**) [35,36] (3.9 g, 18.8 mmoles) in 50 ml of tetrahydrofuran was cooled to -78° and *t*-butyllithium (10.34 ml of a 2*M* pentane solution, 20.68 mmoles) was added over 15 minutes. The bright yellow reaction mixture was allowed to stir at -78° for 1 hour, then added through a chilled needle to a -78° solution of iodine (14.3 g, 56 mmoles) in 50 ml of tetrahydrofuran. After 3 hours at -78°, no more **3c** was detectable by tlc. The reaction was quenched and worked up as for **4a** and **4b** to give crude **4c** as a red oil, whose structure was verified by nmr; the crude material was then deprotected to **5** without further purification of the carbamate **4c**; ^{1}H nmr: δ 8.02-8.14 (m, H-4), 7.12-7.49 (m, H-5, H-6, H-7), 6.97 (s, H-3), 1.71 (s, $C(CH_3)_3$).

2-Iodoindole (**5**). Method a, from **4a**.

A solution of **4a** (1.79 g, 4.7 mmoles), 11 ml of 2*M* potassium carbonate, and 33 ml of 75% aqueous methanol were combined and refluxed for 2.5 hours. The methanol was removed *in vacuo* and the residue partitioned between ether and water. The organic phase was washed with saturated sodium chloride, dried, and concentrated *in vacuo* to give 1.10 g of **5** (89%) as light yellow crystals.

Method b, from **4b**.

A mixture of **4b** (140 mg, 0.38 mmole), *t*-butylammonium fluoride (1.6 ml of a 1 *M* tetrahydrofuran solution), 2.0 ml of dimethylformamide, and 152 μl of ethylenediamine were combined and stirred at 45-70° for 24 hours. The reaction mixture was poured into excess cold water extracted with ether, washed with saturated sodium chloride, dried, and concentrated *in vacuo* to a reddish oily residue. Crystallization (benzene/hexane/Norit) gave 44 mg **5**, (48%) whose spectral and tlc properties were indistinguishable from those of **5** obtained from **4a**.

Method c, from **4c**.

Crude **4c** was dissolved in 94 ml of tetrahydrofuran and methanolic sodium methoxide (6.0 ml of a 6.5 *N* solution, 39.0 mmoles) was added. After 15 minutes of stirring at room temperature the tlc showed the reaction to be complete, and 30 ml each of water and ether were added while the reaction mixture was still under nitrogen. The layers were then separated and the organic phase washed with saturated sodium chloride, dried, and concentrated *in vacuo*. The crude **5** solidified in the refrigerator overnight, and was recrystallized from benzene/hexane/Norit to give, in three crops, 1.29 g (28% overall from **3c**) of **5**, mp. 95°, spectroscopically pure. ^{1}H nmr: δ 8.0 (br s, NH), 7.0-7.7 (m, H-4, H-7), 6.7 (s, H-3); ir (chloroform): 3490 (NH), 2850-3000 (CH), 1455, 1435, 1330, 1170, 780 cm^{-1}; ei-ms: m/z 243 (M+, 100%); hr-ms: 242.9547.

Anal. Calcd. for C_8H_6IN: C, 39.5; H, 2.5; N, 5.8. Found: C, 39.72; H, 2.51; N, 5.63.

1-*t*-Butoxy-5-methoxyindole (**6**).

A slurry of sodium hydroxide (346 mg, 7.2 mmoles of a 50% oil dispersion, washed once in toluene and 3 × in tetrahydrofuran) in 2 ml of tetrahydrofuran was cooled to 0° and a solution of 5-methoxyindole (147 mg, 1 mmole) in 3 ml of tetrahydrofuran was added. The reaction mixture was allowed to come to room temperature over 1 hour, then refluxed 1 hour and cooled again in an ice bath. A solution of BOC-ON (4.18 mg, 1.7 mmoles) in 3 ml of tetrahydrofuran was added and the reaction stirred at room temperature for 3.5 hours. After the mixture was cooled to 0°, excess water (approximately 2 ml) was added and the reaction mixture extracted well with ether, dried, and concentrated *in vacuo* to a residue which was chromatographed on neutral alumina using 1% ethyl acetate/-hexane as elutant to provide 211 mg (85%) of **6** as a colorless oil which solidified on standing. An analytical sample was recrystallized from hexane m.p. 74-76°; ^{1}H nmr: δ 8.05 (d, J = 8.7, H-7), 7.55 (d, J = 3.6, H-2),

6.87-7.02 (m, H-4 and H-6), 6.48 (d, J = 3.6, H-3), 3.83 (s, OCH_3), 1.68 (s, $C(CH_3)_3$); ei-ms: m/z 247.1 (M+, 14%), 191.0 (M^+-C_7H_8, 100%, 147 (M^+-$CO_2C_4H_9$, 60%); hr-ms: 247.1211.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.9; N, 5.7. Found: C, 67.67; H, 6.86; N, 5.57.

1-*t*-Butoxy-2-iodo-5-methoxyindole (**7**).

The general procedure for the formation of **4c** was followed, stirring the reaction mixture for 1 hour at -78° to provide 821 mg (56%) after chromatography on neutral alumina using 0.5% ethyl acetate/hexane as elutant. In an alternative procedure, a solution of iodine in tetrahydrofuran could be added to the -78° solution of the anion of **6**, allowing the loss of the characteristic red iodine color to titrate the anion.

The extraction procedure for **4c** gave a crude red oily residue which was chromatographed on neutral alumina with 0.5% ethyl acetate/hexane to isolate 821 mg (56%) **7** as a yellow oil. More frequently, the crude **7** was subjected to immediate deacetylation to **8**, in which case yields overall from **6** to **8** were essentially the same, approximately 55%; ^1H nmr: δ 8.1 (br d, J = 9, H-7), 6.89 (m, H-4, H-6), 6.82 (s, H-3, 3.82, s, OCH_3), 1.70 (s, $C(CH_3)_3$).

2-Iodo-5-methoxyindole (**8**).

To a mixture of **7** (44.6 mg, 0.12 mmole) in 600 μl of tetrahydrofuran was added 55 μl of a 6.5 *N* methanolic sodium methoxide solution. After 15 minutes all starting material was gone (by tlc) and the reaction was quenched and worked up as described for **5**. Chromatography on neutral alumina using 2.5% ethyl acetate/hexane gave 32 mg (99%) of **8** as white crystals, mp 91-92°; ^1H nmr: δ 8.25 (br s, NH), 7.05 (d, J = 9.2, H-7), 6.99 (d, J_m = 2.1, H-4), 6.72 (dd, J_m = 2.3, J_o = 8.9, H_6), 6.61 (s, H-3), 3.82 (s, OCH_3); ir (chloroform): 3690, 3630, 3500 (NH), 3020, 1620, 1450, 1430, 1150, 900 cm^{-1}; ei-ms: m/z 273 (M^+, 100%), 258 (M^+-CH_3, 57%); hr-ms: 272.9640.

Anal. Calcd. for C_9H_8INO: C, 39.6; H, 2.9; N, 5.1. Found: C, 39.76; H, 2.97; N, 5.06.

3-(2-Iodoindole)acetonitrile (**10**).

A mixture of 60% aqueous acetic acid (1.05 ml, 11.2 mmoles) and diethylamine (543 μl 5.2 mmoles) was cooled to 0° and 37% aqueous formaldehyde (378 μl 5.0 mmoles) added. After stirring at 0° for ten minutes, a cooled ethanolic solution of indole **5** (1.03 g, 4.24 mmoles) was added to the iminium solution and the reaction allowed to come to room temperature over thirty minutes, then refluxed for 25 minutes. After cooling to room temperature, the reaction mixture was poured into excess ice-cold 1*N* sodium hydroxide and extracted well with ether. The organic phase was separated, washed well with saturated sodium chloride, dried, and concentrated *in vacuo* to give 3-(*N,N*-diethylaminomethyl)-2-iodoindole **9** as an amber oil; ^1H nmr: δ 8.4 (br s, NH), 7.8 (m, indole H), 4.6 (s, ind-CH_2-N), 3.6 (q, J = 11, NCH_2), 1.2 (t, J = 11, CH_3).

The oil **9** was dissolved in 71 ml of methanol, and 1.4 ml each of dimethylformamide and water were added, followed by potassium cyanide (2.3 g, 35.3 mmoles) and methyl iodide (1.2 ml, 19.3 mmoles). The reaction mixture was warmed just below reflux for two hours, more methyl iodide being added through a syringe periodically to ensure complete quaternization of the gramine. When tlc revealed all gramine (**9**) had been consumed, the reaction mixture was poured into icewater, extracted with chloroform and the organic phase washed well with saturated sodium chloride, dried and concentrated *in vacuo*. The residue contained appreciable amounts of dimethylformamide, and was therefore dissolved in ether and washed well with water; drying and concentrating gave 986 mg (87%) of **10** as an amber oil, homogenous on tlc (10% ethyl acetate/hexane), which by nmr appeared of sufficient purity to use directly in the reduction; ^1H nmr: δ 8.3 (br s, NH), 7.0-7.7 (m, indolic H), 3.6 (s, CH_2CN); ir (chloroform): 3700, 3600 (NH), 2980, 3020, 2250 (CN) cm^{-1}.

The analytical sample was prepared by alumina chromatography (10% ethyl acetate/hexane); ei-ms: m/z 282 (M+, 40%), 155 (M^+-I, 100%); hr-ms: 281.9658.

Anal. Calcd. for $C_{10}H_7IN_2$: C, 42.6; H, 2.5; N, 9.9. Found: C, 42.83; H, 2.43; N, 9.92.

2-Iodotryptamine (**1**).

To a solution of nitrile **10** (33.6 mg, 0.12 mmole) in 1 ml of tetrahydrofuran was added 600 μl of a 1 *M* borane-tetrahydrofuran complex solution. After 1 hour at room temperature, excess methanol was added (approximately 1 ml) and the reaction mixture concentrated *in vacuo* to a yellow foam. This was dissolved in 1 ml of methanol, 1 ml of a solution of 1 *M* methanolic sodium hydroxide was added, and the reaction mixture refluxed 30 minutes, then cooled to room temperature and concentrated *in vacuo*. More methanol was added and the evaporation repeated to ensure complete removal of trimethylborate. The crude amine was extracted into chloroform, washed well with water, then saturated sodium chloride, dried and concentrated to a dark brown oil. Chromatography on alumina (using 2% methanolic chloroform to which approximately 10 drops/100 ml ammonium hydroxide had been added) gave tryptamine **1** (11.3 mg, 33%) as a colorless oil, which, although homogenous on tlc, failed to crystallize; 400 MHz ^1H nmr: δ 8.15 (br s, NH), 7.53 (d, J = 7.3, H-4), 7.29 (d, J = 7.9, H-7), 7.07-7.12 (m, H-5, H-6), 2.98 (t, J = 6.72, CH_2-NH_2), 2.84 (t, J = 6.72, ind-CH_2), 1.24 (br s, NH_2); ir: 3500, 2950, 1470, 1450, 1265 cm^{-1}; ei-ms: m/z 256 (M^+ -CH_2NH_2, 57%), 159 (M^+-I, 43%). There was negligible molecular ion observed; the fragmentation pattern was identical to that of **2** in which an M+ was observed.

Anal. Calcd. for $C_{10}H_{11}IN_2$: C, 42.0; H, 3.8; N, 9.8. Found: C, 42.09; H, 3.82; N, 9.40.

3-[2-Iodo-5-methoxyindole]acetonitrile (**12**).

Indole **8** (32 mg, 0.117 mmole) was added to a 0° mixture of 60% acetic acid (29 μl) and formalin (11 μl) as described for the conversion of **5** to **9**. Intermediate amine **11** was isolated as a crude oil and converted to nitrile **12** immediately after verification of structure by nmr: 8.10 (br s, NH), 7.12 (d, H-7, overlaps with 7.06, d, J = 9.1, H-4), 6.73 (dd, J_m = 2.3, J_o = 8.8 H-5), 4.62 (s, ind-CH_2-N), 3.81 (s, OCH_3), 3.55 (q, J = 6.9, NCH_2), 1.22 (t, J = 6.9, CH_3; Yield, 35.4 mg, 85%.

Treatment of **11** with potassium cyanide (50 mg, 0.77 mmole) and methyl iodide (26 μl, 0.41 mmole) in a solution of 1.6 ml of methanol/30 μl of dimethylformamide/30 μl of water as described for the conversion of **9** to **10**, gave 29.9 mg (97%) of nitrile **12**. The analytical sample was prepared by chromatography on neutral alumina using 7% ethyl acetate/hexane as the eluent followed by crystallization from ethyl acetate/hexane to give colorless needles, mp 125-128°; ^1H nmr: δ 8.2 (br s, NH), 7.20 (d, J_o = 8.5, H-7), 7.04 (d, J_m = 2.2, H-4), 6.82 (dd, J_o = 8.7, J_m = 2.3, H-6), 3.86 (s, OCH_3), 3.74 (s, CH_2CN); ir (chloroform): 3720, 3650, 3040, 2250 1550, 1490, 1425, 1220 cm^{-1}; ei-ms: m/z 312 (M+, 100%), 297 (M^+-CH_3, 50%), 113 (M+-I, CH_2CN, OCH_3, 46%); hr-ms: 311.9755.

Anal. Calcd. for $C_{11}H_9IN_2O$: C, 42.3; H, 2.9; N, 9.0. Found: C, 42.6; H, 2.96, N, 8.84.

2-Iodo-5-methoxytryptamine (**2**).

Nitrile **12** (377 mg, 1.2 mmoles) was reduced with 5 equivalents of borane-tetrahydrofuran at room temperature, in a manner identical to the reduction of **10** to **1**, to provide, after chromatography, 212 mg (55%) of tryptamine **2**, as a light yellow oil that soldified on standing overnight; ^1H nmr: δ 8.6 (br s, NH), 7.17 (d, J_o = 8.9, H-7), 6.98 (d, J_m = 2.0, H-4), 6.76 (dd, J_m = 2.4, J_o = 8.7, H-6), 3.83 (s, OCH_3), 2.97 (dt, CH_2-CH_2-NH_2), 1.25 (br s, NH_2); in deuteroacetone ind-CH_2 is at δ 3.1, separated from CH_2-NH_2, a br t at δ 3.6; ir: 3500, 3055, 3025, 1460, 1340, 1200 cm^{-1}; ei-ms: m/z 316 (M+, 1%), 189 (M^+ -I, 100%), 286 (M^+ -CH_2NH_2, 45%); hr-ms: 316.0085.

An analytical sample was prepared by further chromatography in the same system (98% chloroform, 2% methanol, plus 5 drops ammonium hydroxide per 50 ml) followed by crystallization from ethyl acetate/hexane to give a yellow solid, mp 108-110°.

Anal. Calcd for $C_{11}H_{13}INO_2$: C, 41.8; H, 4.1; N, 8.9. Found: C, 43.29; H, 4.38; N, 8.48 [44].

Acknowledgements.

I thank Mr. Gerry Zarilli of the Department of Chemistry at Columbia University and Dr. Hermann Wysbrod of the Department of Physiology at Mt. Sinai School of Medicine for the high-field nmr spectra, and Mr. Philip Chen and Dr. Charles Iden of S.U.N.Y Stony Brook for the mass spectral data. I especially thank Dr. Jack Peter Green and Dr. Harel Weinstein of this Department for their comments and criticisms regarding this manuscript. This work was supported by NIH Training Grant DA-07135-03 and NIDA Grant #DA. 01875.

REFERENCES AND NOTES

[1a] A. Cerletti and B. Rothkin, *Nature*, **176**, 785 (1955); [b] A. Cerletti and W. Doepfner, *J. Pharm. Acal. Exp. Ther.*, **122**, 124 (1957).

[2] R. Schneckloth, I. H. Page, F. del Greco and A. C. Corcoran, *Circulation*, **16**, 523 (1957).

[3] M. Trulson and B. Jacobs, *Science*, **205**, 515 (1979).

[4] K. Ginzel and W. Mayer-Gross, *Nature*, **178**, 210 (1956).

[5] J. Bertino, G. Klee and M. Weintraub, *J. Clin. Exp. Psychpathol.*, **20**, 218 (1959).

[6] W. Martin and J. Sloan, *Hanb. Exp. Pharmakol.*, **43**, 327 (1977).

[7] J. H. Gaddum and Z. P. Picarelli, *Brit. J. Pharm.*, **12**, 323 (1957).

[8] A. Shenker, S. Maayani, H. Weinstein and J. P. Green, *Soc. Neurosci. Abstr.*, **9**, 1152 (1983).

[9] K. Von Hungen, S. Roberts and D. Hill, *Brain Res.*, **84**, 257 (1975).

[10] J. Northrup and T. Mansour, *Mol. Pharm.*, **14**, 820 (1978).

[11] M. L. Barbaccia, N. Brunello, D. M. Chuang and E. Costa, *J. Neurochem.*, **40**, 1671 (1982).

[12] A. Enjalbert, M. Hamon, S. Bourgoin and J. Bockaert, *Mol. Pharmacol.*, **14**, 11 (1977).

[13a] G. K. Aghajanian, W. E. Foote and M. H. Sheard, *J. Pharmaco. Exp. Ther.*, **171**, 178 (1970); [b] G. Aghajanian, *Neuropharmacology*, **15**, 521 (1976).

[14a] S. G. Beck, S. Maayani, H. Weinstein and J. P. Green, *Fed. Proc.*, **41**, 1338 (1982); [b] S. G. Beck, R. Meibach, S. Maayani and J. P. Green, *Soc. Neurosci. Abstr.*, **7**, 449 (1981).

[15] S. Peroutka, R. Lebovitz and S. Snyder, *Science*, **212**, 827 (1981).

[16] F. Troxler and A. Hofmann, *Helv. Chim. Acta*, **40**, 2160 (1957).

[17] G. Engel, E. Müller-Schweinitzer and P. Stadler, *Brit. J. Pharm.*, **78**, 83P (1983).

[18] E. Müller-Schweinitzer and G. Engel, *Naunyn-Schmiederberg's Arch. Pharmacol.*, **324**, 287 (1983).

[19] P. R. Hartig, M. J. Kadan, M. J. Evans and A. M. Krohn, *Eur. J. Pharmacol.*, **89**, 321 (1983).

[20] G. Engel, E. Müller-Schweinitzer and J. Palacios, *Naunyn-Schmiederbers's Arch. Pharmacol.*, **325**, 328 (1984).

[21a] A. P. Mazurek, H. Weinstein, R. Osman, S. Topiol and B J. Ebersole, *Int. J. Quantum Chem., Quantum Biol. Symp.*, **11**, in press. [b] H. Weinstein and J. P. Green, *Ann. N. Y. Acad. Sci.*, **367**, 434 (1981).

[22] J. Baldwin, J. Jones and G. Lundell, European Patent, 0,029,581, Appl. 80,107,188.7 (1981); *Chem. Abstr.*, **95**, P150437y (1981).

[23] J. Benes and M. Semonsky, *Collect. Czech. Chem. Commun.*, **47**, 1235 (1982).

[24] R. Gatti, J. Cavriui, P. Rover, F. Bianucci and P. Legnani, *Farmaco. Ed. Sci.*, **36**, 102 (1981).

[25a] R. Sundberg and H. Russel, *J. Org. Chem.*, **38**, 3324 (1973); [b] R. Sundberg and J. Bloom, *ibid.*, **45**, 2282 (1982).

[26a] M. Saulnier and G. Gribble, *J. Org. Chem.*, **47**, 757 (1982); [b] M. Saulnier and G. Gribble, *ibid.*, **47**, 2810 (1982).

[27] R. Sundberg, "The Chemistry of Indoles", Academic Press, New York, London, 1970, p 304.

[28] J. Bergman and N. Elklund, *Tetrahedron*, **36**, 1439 (1980).

[29] V. Bocchi and G. Palla, *Synthesis*, **12**, 1096 (1982).

[30] V. Calo, F. Ciminale, L. Lopez, F. Naso and P. E. Todesco, *J. Chem. Soc., Perkin Trans. I*, 2568 (1972).

[31] T. Hiro and M. Nakagawa, *Heterocycles*, **6**, 1680 (1977).

[32] K. Erickson, M. Brennan and P. Namrum, *Synth. Commun.*, **11**, 253 (1981).

[33] A. D. Settimo, V. Santerini, G. PrimoFiore, G. Biagi and C. Veneziano, *Gazz. Chim. Ital.*, **107**, 367 (1977).

[34] A. Kubo and K. Uchino, *Heterocycles*, **16**, 1441 (1981).

[35] J. Muchowski and D. Solas, *J. Org. Chem.*, **49**, 203 (1984).

[36] I. Hasan, E. R. Marinelli, L. C. Lin, F. W. Fowler and A. B. Levy, *J. Org. Chem.*, **46**, 157 (1981).

[37] A. Cheng, A. Shulgin and N. Castagnoli, *J. Org. Chem.*, **47**, 5258 (1982).

[38] M. Flaugh, T. A. Crowell, J. A. Clemens and B. D. Sawyer, *J. Med. Chem.*, **22**, 63 (1979).

[39] S. A. Monti and R. R. Schmidt, III, *Tetrahedron*, **27**, 3331 (1971).

[40] K. M. Biswis and A. H. Jackson, *Tetrahedron*, **24**, 1145 (1968).

[41] C. F. Lane, *Aldrichimica Acta*, **8**, 20 (1975).

[42] E. Stahl, "Thin Layer Chromatography", Second Ed, Springer-Verlag, New York, Heidelberg, Berlin 1967, pp 857, 868.

[43] W. Still, C. Kahn and M. Milton, *J. Org. Chem.*, **43**, 2923 (1978).

[44] A more satisfactory value for carbon analysis was not possible to obtain. A chromatographically pure product produced multiple spots on tlc upon handling.