Synthesis of 6,7,8,9-Tetrahydro-*N,N*-di-*n*-propyl-1*H*-benz[*g*]indol-7-amine, a Potential Dopamine Receptor Agonist [1]

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In this work, the synthesis of 6,7,8,9-tetrahydro-*N,N*-di-*n*-propyl-1*H*-benz[*g*]indol-7-amine (**1**) is described. This compound was designed as an indole bioisostere to the known dopamine receptor agonist 5-OH-aminotetraline **2**. The key step of the synthesis was a Mukaiyama type aldol condensation between the dimethyl acetal of 1-(*p*-toluenesulfonyl)pyrrole-3-acetaldehyde (**4**) and 4-di-*n*-propylamino-1-trimethylsilyloxycyclohexene (**8**) followed by cycloaromatization to afford 1-*p*-toluenesulfonyl-6,7,8,9-tetrahydro-*N,N*-di-*n*-propyl-1*H*-benz[*g*]indol-7-amine (**10**). Scission of the sulfonamide bond in **10** gave the target compound **1**. A byproduct which was isolated was assigned to the structure of 1-(*p*-toluenesulfonyl)-6-[3-[1-(*p*-toluenesulfonyl)]pyrrolyl]indole (**11**). This compound was also synthesized in good yield by an acid catalyzed dimerization of the dimethyl acetal of 1-(*p*-toluenesulfonyl)pyrrole-3-acetaldehyde (**4**). Preliminary screening of **1** indicated that it possesses central dopamine receptor agonist properties.

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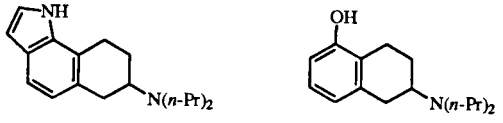
Phenolic dopamine receptor agonists suffer from poor bioavailability due to rapid metabolic inactivation *via* conjugation. Thus, an approach which has been pursued to overcome this problem is to develop non phenolic heterocyclic analogues. In this respect, evidence indicates that an indole NH moiety can be a bioisostere of the hydrogen-bonding H donor properties of the phenolic OH group in dopamine agonists [2-5]. Based on the above, in the present study we synthesized the 6,7,8,9-tetrahydro-*N,N*-di-*n*-propyl-1*H*-benz[*g*]indol-7-amine (**1**) in which the indole NH moiety is in a similar spatial position with the phenolic hydroxyl of the potent dopamine receptor agonist 5-OH-aminotetraline **2** (Scheme I).

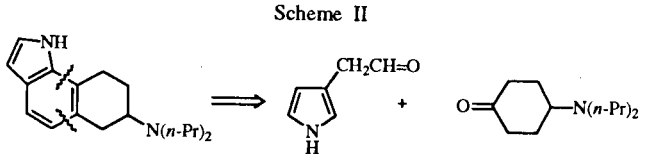
Scheme I



1 **2**

Our strategy for the synthesis of **1** was based on the disconnection illustrated in Scheme II. This approach leads to two synthons: a) the heterocycle which contains the structure of pyrrole-3-acetaldehyde, and b) the carbocycle which contains the structure of 4-(di-*n*-propylamino)cyclohexanone. An analogous strategy has been previously applied for the synthesis, however, of unsubstituted tetrahydrobenz[*e*]indoles [6].

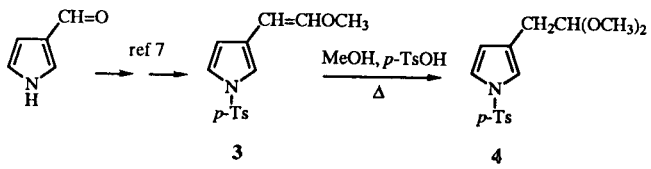
Scheme II



1

As a chemical equivalent to the heterocyclic synthon we used the acetal **4**, which was prepared from the known [7] vinyl ether **3** by the action of methanol and an acid catalyst (Scheme III).

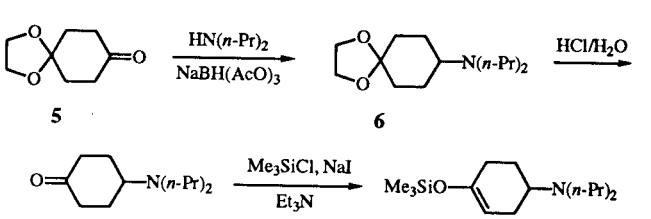
Scheme III



3 **4**

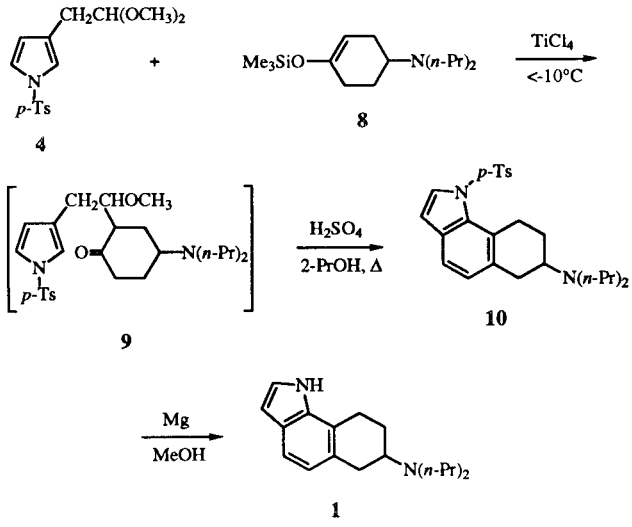
As a chemical equivalent to the carbocyclic synthon we used the silyl enol ether **8**, the synthesis of which is outlined in Scheme IV. The literature procedure [8] for the preparation of **7** from 1,4-cyclohexanonedione *mono*-ethylene ketal **5** involved reaction with dipropylamine in the presence of titanium(IV) isopropoxide, reduction of the enamine formed with sodium cyanoborohydride and acidic hydrolysis of the ketal group. However, the reported yield for the two step amination procedure was relatively low (46%). Thus, we investigated alternative

Scheme IV



5 **6** **7** **8**

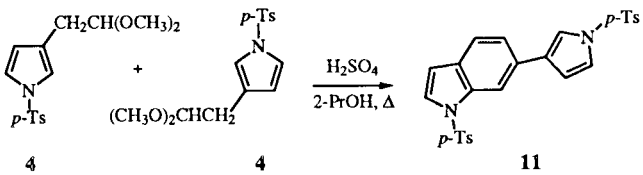
Scheme V



methodologies of direct reductive amination with sodium cyanoborohydride [9] or sodium triacetoxyborohydride [10]. We found that the best results are obtained with sodium triacetoxyborohydride. In this way, the overall yield for the formation of **7** from **5** was 68%, while it was unnecessary to purify the intermediate ketal **6**. Finally, the silyl enol ether **8** was formed by the action of the chlorotrimethylsilane-sodium iodide reagent in the presence of triethylamine, according to the general procedure described in reference [11].

The formation of the indole ring in **10** involved two steps (Scheme V). The first step was a Mukaiyama type aldol condensation between the acetal **4** and the enol ether **8**. For this reaction, we studied various catalysts: tin tetrachloride [6], titanium tetrachloride [12], fluoride ion [13] and bismuth trichloride combined with sodium iodide or zinc iodide [14]. We found that the best results are obtained with the titanium tetrachloride catalyst. The product of this reaction, **9**, was not isolated but it was directly cycloaromatized to **10** by the action of sulfuric acid in 2-propanol, according to the general procedure described in reference [6]. A minor byproduct was isolated from this synthesis, which we assigned to the structure of 1-(*p*-toluenesulfonyl)-6-[3-[1-(*p*-toluenesulfonyl)]-pyrrolyl]indole (**11**). A possible mechanism for the formation of this compound is an acid catalyzed dimerization of

Scheme VI



acetal **4**, or similarly functionalized structures, which could be present during the reaction with sulfuric acid in 2-propanol. Support for this hypothesis is the fact that when we heated acetal **4** in 2-propanol in the presence of concentrated sulfuric acid, **11** was obtained in good yield (Scheme VI).

The final step of the synthesis of indolamine **1** involved scission of the sulfonamide bond in **10**. For this purpose, we studied three different methodologies: alkaline hydrolysis with sodium hydroxide in a mixture of methanol-water, reaction with lithium aluminum hydride in refluxing tetrahydrofuran [15] and reaction with magnesium in methanol [16]; the best results were obtained with the third method.

In a preliminary biological screening, it was found that **1** at low dosage range (20 and 40 μmoles/kg, ip) induces hypokinesia in rats, while at higher doses (80 and 160 μmoles/kg, ip) it reverses the hypokinesia induced in rats by a previous treatment with reserpine. These results might indicate that **1** is a centrally acting dopamine receptor agonist with a degree of selectivity for presynaptic sites [17]. Further work is under way to determine the pharmacological profile of indolamine **1**.

EXPERIMENTAL

Melting points are uncorrected and were determined in open glass capillaries using a Mel-Temp II apparatus. Infrared spectra were recorded with a Perkin-Elmer 597 spectrophotometer, nuclear magnetic resonance spectra with a Bruker AW-80 spectrometer with internal tetramethylsilane reference, and mass spectra with a Finnigan MAT90 spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 CHN analyzer. Flash chromatography was carried out using Merck 9385 silica gel. Petroleum ether refers to the fraction of bp 40-60°.

Dimethyl Acetal of 1-(*p*-Toluenesulfonyl)pyrrole-3-acetaldehyde (**4**).

A mixture of **3** [7] (2 g, 7.3 mmoles) and *p*-toluenesulfonic acid (0.1 g) in methanol (100 ml) was refluxed for 6 hours under a nitrogen atmosphere. It was cooled to room temperature, basified with triethylamine and the volatiles were evaporated under reduced pressure. The residue was dissolved in ether (300 ml), washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent evaporated under reduced pressure. The residue was flash chromatographed on silica gel with ethyl acetate-petroleum ether (1:4) as the eluent to afford 1.890 g (85%) of product which crystallized slowly on refrigerating. An analytical sample was recrystallized from ether-petroleum ether, mp 61-62°; ^{1}H nmr (deuteriochloroform): δ 7.70 (d, 2H, $HArSO_2$, J = 7.8 Hz), 7.24 (d, 2H, $HArSO_2$, J = 7.8 Hz), 6.92-7.11 (m, 2H, C-2-H and C-5-H), 6.11-6.25 (m, 1H, C-4-H), 4.40 (t, 1H, CH, J = 5.7), 3.27 (s, 6H, OCH_3), 2.65 (d, 2H, CH_2, J = 5.7 Hz), 2.36 (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{19}NO_4S$: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.40; H, 6.21; N, 4.75.

4-Di-*n*-propylaminocyclohexanone Fumarate (**7**).

A mixture of sodium borohydride (0.908 g, 24 mmoles) and acetic acid (4 ml, 72 mmoles) in 1,2-dichloroethane (80 ml) was stirred under cooling (bath temperature <20°) for 7 hours under a nitrogen atmosphere. Di-*n*-propylamine (10 ml, 72 mmoles), acetic acid (0.9 ml, 16 mmoles) and **5** (2.5 g, 16 mmoles) were then added and stirring was continued for 24 hours at room temperature. A solution of 10% sodium hydroxide (100 ml) was then added, the two phases were separated and the aqueous extracted with dichloromethane (3 x 100 ml). The combined organic extracts were washed with saturated sodium chloride solution, dried (potassium carbonate) and concentrated under reduced pressure, until constant weight, to afford crude **6** (3.934 g) as an oil which was homogeneous by tlc and used in the next step without purification; ^{1}H nmr (deuteriochloroform): δ 3.89 (s, 4H, CH_2O), 2.22-2.67 (m, 5H, CHN and CH_2N), 1.20-1.90 (m, 12H, CH_2), 0.67-0.97 (m, 6H, CH_3).

Crude **6** (3.934 g) was dissolved, with cooling, in a mixture of water (10 ml) and concentrated hydrochloric acid solution (3 ml) and then was left at room temperature for 48 hours. After this period, it was diluted with water (70 ml), washed with ether (2 x 30 ml), basified with solid sodium hydroxide with cooling and extracted with ether (4 x 50 ml). The combined organic extracts were washed with saturated sodium chloride solution, dried (potassium carbonate) and the solvent evaporated under reduced pressure. The residue (2.634 g) was dissolved in acetone (50 ml), added to a mixture of fumaric acid (1.7 g) in acetone (150 ml) and stirred for 15 minutes. The solvent was evaporated under reduced pressure and the residue was recrystallized from 2-propanol-ether to afford 3.398 g (68%) of **7**, mp 137-139°; ir (neat): (free base) 1710 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): (free base) δ 2.79-3.08 (m, 1H, CHN), 2.25-2.53 (m, 8H, CH_2N and CH_2C=O), 1.70-2.14 (m, 4H, CH_2), 1.23-1.66 (m, 4H, CH_2), 0.70-0.98 (m, 6H, CH_3).

Anal. Calcd. for $C_{12}H_{23}NO{\bullet}C_4H_4O_4$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.26; H, 8.61; N, 4.40.

4-Di-*n*-propylamino-1-trimethylsilyloxycyclohexene (**8**).

A mixture of **7** (0.565 g, 2.87 mmoles), sodium iodide (1.291 g, 8.61 mmoles), chlorotrimethylsilane (1.09 ml, 8.61 mmoles) and triethylamine (1.2 ml, 8.61 mmoles) in acetonitrile (8.6 ml) was stirred at room temperature for 10 minutes and then refluxed (bath temperature 115-125°) for 4 hours under a nitrogen atmosphere. It was cooled to room temperature and extracted with several portions of petroleum ether containing 2% triethylamine (total volume of extracts 100 ml). The volatiles were removed under reduced pressure, the residue was taken in petroleum ether (50 ml) and filtered. The filtrate was concentrated under reduced pressure to afford 0.715 g (93%) of **8** as an oil; ir (neat): 1665 cm^{-1} (CH=COSi); ^{1}H nmr (deuteriochloroform): δ 4.66-4.84 (m, 1H, C=CH), 2.22-2.49 (m, 5H, CHN and CH_2N), 1.12-2.12 (m, 10H, CH_2), 0.66-0.97 (m, 6H, CH_3), 0.11 (s, 9H, $SiCH_3$). This material is unstable and was used as soon as possible in the next step without purification.

1-*p*-Toluenesulfonyl-6,7,8,9-tetrahydro-*N*,*N*-di-*n*-propyl-1*H*-benz[*g*]indol-7-amine (**10**).

To a well stirred, cold (bath temperature <-10°) and under a nitrogen atmosphere mixture of **4** (0.265 g, 0.856 mmole) and **8** (0.715 g, 2.653 mmoles) in dichloromethane (25 ml), titanium tetrachloride (0.480 ml, 4.4 mmoles) was added and stirring was continued for 1 hour at the same temperature. Then, it was poured into an ice-cold mixture of saturated sodium bicarbonate solution (100 ml) and dichloromethane (25 ml), stirred for 30 minutes, filtered through celite, the two phases were separated and the aqueous extracted with dichloromethane (3 x 25 ml). The combined organic extracts were washed with concentrated sodium chloride solution, dried (potassium carbonate) and the solvent evaporated under reduced pressure. The residue was dissolved in 2-propanol (21.6 ml), to this concentrated sulfuric acid (1.5 ml) was added and the mixture was immediately refluxed (bath temperature 115-125°) for 1 hour under a nitrogen atmosphere. It was cooled to room temperature, water (23 ml) was added, filtered and the filtrate concentrated under reduced pressure to half of its volume. To this, water (23 ml) was added, basified with triethylamine under cooling and extracted with dichloromethane (4 x 25 ml). The combined organic extracts were washed with saturated sodium chloride solution, dried (potassium carbonate) and the solvent evaporated under reduced pressure. The residue was mixed with fumaric acid (0.47 g) in water (54 ml) and stirred at room temperature for 2 hours. Ethyl acetate (50 ml) was then added and stirring was continued until the precipitate was dissolved. The two phases were separated and the aqueous phase extracted with ethyl acetate (2 x 25 ml). The combined organic extracts were washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent evaporated under reduced pressure. The residue was twice flash chromatographed on silica gel with eluent first ethyl acetate->ethyl acetate containing 2% triethylamine and then ethyl acetate-petroleum ether (1:3) to afford 0.083 g (23%) of **10** as a viscous oil; ^{1}H nmr (deuteriochloroform): δ 7.67 (d, 1H, C-2-H, J = 3.8 Hz), 7.52 (d, 2H, $HArSO_2$, J = 8.2 Hz), 7.13-7.31 (m, 3H, C-4-H and $HArSO_2$), 6.97 (d, 1H, C-5-H, J = 8 Hz), 6.58 (d, 1H, C-3-H, J = 3.8 Hz), 2.89-3.37 (m, 4H, C-6-H_2 and C-9-H_2), 2.37-2.68 (m, 8H, $ArCH_3$, NCH and NCH_2), 1.84-2.21 (m, 2H, C-8-H_2), 1.21-1.74 (m, 4H, CH_2), 0.74-1.11 (m, 6H, CH_3). An analytical sample was prepared by conversion to the hydrochloride salt and recrystallization from 2-propanol-ether-petroleum ether, mp 209-211°.

Anal. Calcd. for $C_{25}H_{32}N_2O_2S{\bullet}HCl$: C, 65.13; H, 7.21; N, 6.08. Found: C, 64.72; H, 7.28; N, 5.89.

6,7,8,9-Tetrahydro-*N*,*N*-di-*n*-propyl-1*H*-benz[*g*]indole-7-amine (**1**).

A mixture of **11** (0.148 g, 0.349 mmole), ammonium chloride (0.039 g, 0.729 mmole) and Mg (0.424 g, 17.44 mg-atoms) in methanol (26 ml) was stirred for 4 hours under a nitrogen atmosphere while the temperature was kept below 20°. Then, it was poured into an ice-cold mixture of water (120 ml), ammonium chloride (2.4 g) and dichloromethane (60 ml), stirred for 15 minutes, filtered through celite, the two phases were separated and the aqueous phase was extracted with dichloromethane (2 x 20 ml). The combined organic extracts were washed with concentrated sodium chloride solution, dried (potassium carbonate) and the solvent was evaporated under reduced pressure. The residue was flash chromatographed on silica gel with ethyl acetate-petroleum ether (1:1) as the eluent to afford 0.084 g (91%) of **1** as a viscous oil which solidifies on refrigerating, mp 71-73°; ^{1}H nmr (deuteriochloroform): δ 7.95 (br s, 1H, NH), 7.38 (d, 1H, C-4-H, J = 8.6 Hz), 7.08-7.12 (m, 1H, C-2-H; after addition of deuterium oxide it became d, J = 3.0 Hz), 6.85 (d, 1H, C-5-H, J = 8.6 Hz), 6.45-6.49 (m, 1H, C-3-H; after addition of deuterium oxide it became d, J = 3.0 Hz), 2.78-3.10 (m, 4H, C-6-H_2 and C-9-H_2), 2.35-2.66 (m, 5H, NCH and NCH_2), 1.18-1.71 (m, 6H, C-8-H_2 and CH_2), 0.70-1.01 (m, 6H, CH_3), ms: m/z 270 (31) [$M^{+\bullet}$], 241 (38) [$M-C_2H_5$]$^+$,

170 (100) [M-N(n-Pr)2]$^+$, 143 (33) [M-$_2$HC=CH(n-Pr)$_2$]$^{+\bullet}$; hrms: Calcd. for $C_{18}H_{26}N_2$: 270.2096. Found: 270.2090.

1-(*p*-Toluenesulfonyl)-6-[3-[1-(*p*-toluenesulfonyl)]pyrrolyl]-indole (**11**).

To a solution of **4** (0.108 g, 0.349 mmole) in 2-propanol (9.4 ml), concentrated sulfuric acid (0.6 ml) was added and the mixture was immediately refluxed (bath temperature 115-125°) for 1 hour under a nitrogen atmosphere. Then, it was cooled (ice bath), water (20 ml) was added, basified with triethylamine and extracted with ether (4 x 20 ml). The combined organic extracts were washed with water, saturated sodium chloride solution and dried (sodium sulfate). The volatiles were removed under reduced pressure and the residue was flash chromatographed on silica gel with ethyl acetate-petroleum ether (1:4) as the eluent to afford 0.054 g (63%) of **11** as a solid. An analytical sample was prepared by recrystallization from dichloromethane-petroleum ether, mp 186-188°; ^{1}H nmr (deuteriochloroform): δ 8.06 (s, 1H, indole C-7-H), 7.63-7.90 (m, 4H, $HArSO_2$), 7.10-7.54 (m, 9H, $HArSO_2$, indole C-2-H, C-4-H and C-5-H and pyrrole C-2-H and C-5-H), 6.53-6.68 (m, 2H, indole C-3-H and pyrrole C-3-H), 2.37 (s, 3H, CH_3), 2.28 (s, 3H, CH_3).

Anal. Calcd. for $C_{26}H_{22}N_2O_4S_2$: C, 63.65; H, 4.52; N, 5.71. Found: C, 63.32; H, 4.47; N, 5.61.

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