Synthesis of 8-Dipropylamino-7,8,9,10-tetrahydrophenanthridines as Potential Serotoninergic Agonists

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A number of 8-dipropylamino-7,8,9,10-tetrahydrophenanthridines have been prepared as analogs of the known serotoninergic agonist 8-hydroxy-2-(dipropylamino)tetralin (8-OH-DPAT) and their affinity for the 5-HT_{1A} receptor subtype evaluated by radioligand binding assay.

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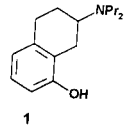
Research on the physiological role of serotonin (5-hydroxytryptamine, 5-HT) has expanded dramatically in recent years following the recognition of this neurotransmitter's importance in the etiology and treatment of a wide variety of medical problems. Multiple 5-HT receptors have now been identified [2-5], and represent attractive targets for the design of new compounds capable of selectively modifying serotoninergic function. The 5-HT_{1A} subtype is of particular interest in view of its implication in anxiety, depression, sleep, appetite regulation, and vascular or cardiovascular disorders [6-11].

8-Hydroxy-2-(dipropylamino)tetralin (8-OH-DPAT, **1**) is the prototypical agonist [12-14] which has been shown to exhibit both high affinity and selectivity for the 5-HT_{1A} receptor [15-18]. 8-OH-DPAT shows little activity, however, when administered orally because of extensive glucoronidation of the hydroxy group both in the case of the parent molecule and its major metabolite [19].



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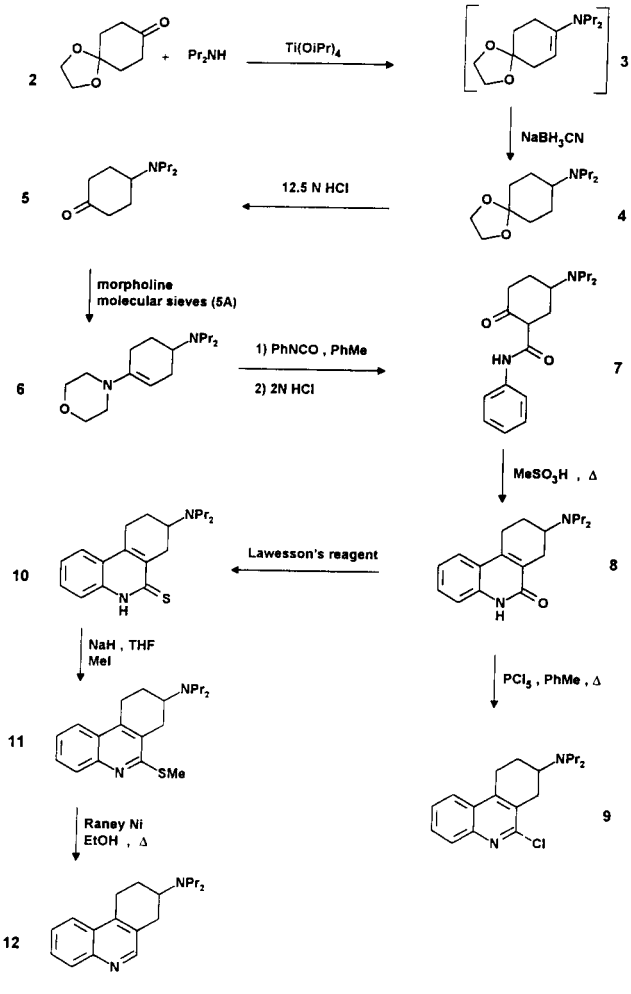
A large number of compounds related to 8-OH-DPAT have been prepared and the structure-activity relationships show, for example, that the 5-, 6-, and 7-hydroxy analogs are dopaminergic rather than serotoninergic agonists [20,21], and that replacement of the 8-hydroxy group by a variety of substituents is compatible with high affinity for the 5-HT_{1A} receptor [22-24].

The benzo ring of 8-OH-DPAT has been replaced by a number of heterocyclic systems, such as thiazolo [25,26], pyrimido [27] or pyrido [28], but all lack a substituent corresponding to the crucial 8-position of 8-OH-DPAT. We now describe the preparation of a number of appropriately substituted phenanthridines, **8-12**, related to 8-OH-DPAT and their evaluation as potential 5-HT_{1A} ligands.

The synthetic route employed for preparing the 8-dipropylamino-7,8,9,10-tetrahydrophenanthridines **8-12** is depicted in the Scheme. Reaction of ketone **2** with dipropylamine in the presence of titanium(IV) isopropoxide gave the enamine **3** which was reduced *in situ* with sodium cyanoborohydride, according to the general procedure described in reference [29], to give compound **4** in 46% overall yield. Acid hydrolysis of the ketal **4** afforded ketone **5** which was converted to the morpholino enamine **6** using molecular sieves as the dehydrating agent. Reaction of compound **6** with phenyl isocyanate, followed by acid hydrolysis, gave the keto amide **7** which was cyclized, without purification, in methanesulfonic acid at reflux to give

Scheme



8-dipropylamino-7,8,9,10-tetrahydrophenanthridin-6(5*H*)-one (**8**) in 30% yield. Use of the more reactive pyrrolidino enamine corresponding to **6** led to lower yields of the phenanthridone **8**. Treatment of compound **8** with phosphorus pentachloride in refluxing toluene gave the 6-chloro derivative **9**, and treatment with Lawesson's reagent afforded thione **10** in good yield. Attempted methylation of compound **10** with iodomethane in the presence of triethylamine or di*iso*propylethylamine was unsatisfactory, and compound **11** was finally obtained, albeit in moderate yield, by methylation of the anion generated using sodium hydride in tetrahydrofuran. Desulfurization of compound **11** was accomplished with Raney nickel to afford the tetrahydrophenanthridine **12**, unsubstituted at the **6**-position.

Compounds **8-12** were evaluated as 5-HT_{1A} ligands by their ability to displace tritiated 8-OH-DPAT from rat cerebral cortex preparations using the method described by Sleight and Peroutka [30]. None of the compounds tested showed significant affinity for the 5-HT_{1A} receptor even at micromolar concentrations. Further work is in progress to determine whether the lack of affinity of the above molecules is due to the nature of the heterocycle, or to the presence of an additional ring with respect to 8-OH-DPAT.

EXPERIMENTAL

Melting points were determined in open capillaries using an Electrothermal 9200 Apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 510P FT spectrometer. The ^{1}H nmr spectra were recorded using a Bruker AC-200 spectrometer and chemical shifts (δ) are reported in ppm relative to tetramethylsilane. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualized using a uv lamp or Dragendorff's reagent (Prolabo). E. Merck silica gel 60 F (70-230 mesh) was used for column chromatography. The elemental analyses were carried out using a Carlo Erba Model 1106 elemental analyser. All reagents were employed as received from commercial suppliers. Solvents were purified and dried using standard methods.

8-Dipropylamino-1,4-dioxaspiro[4.5]decane (**4**).

A mixture of 30 g (192 mmoles) of 1,4-dioxaspiro[4.5]decan-8-one, 26.3 ml (192 mmoles) of dipropylamine, and 71.4 ml (240 mmoles) of titanium(IV) isopropoxide was stirred at room temperature for 1 hour. The viscous solution was diluted with 200 ml of ethanol, 8.1 g (129 mmoles) of sodium cyanoborohydride was added and the reaction mixture was stirred at room temperature for 24 hours. After adding 50 ml of water, the resulting inorganic precipitate was filtered and washed with ethanol. The filtrate and washings were evaporated under reduced pressure, dissolved in 50 ml of ethyl acetate, filtered to remove the remaining solids, evaporated and purified by distillation to give 21.5 g (46%) of compound **4** as a pale yellow oil, bp 110-115°/0.1 mm; ^{1}H nmr (deuteriochloroform): δ 0.86 (t, J = 7.3 Hz, 6H, CH_3), 1.36-1.81 (m, 12H, CH_2), 2.41 (t, J = 7.6 Hz, 4H, CH_2N), 2.58 (br s, 1H, CH), 3.94 (s, 4H, CH_2O ring).

Anal. Calcd. for $C_{14}H_{27}NO_2$: C, 69.67; H, 11.27; N, 5.80. Found: C, 69.28; H, 11.01; N, 5.92.

4-Dipropylaminocyclohexanone (**5**) [31].

A mixture of 21.5 g (89 mmoles) of compound **4**, 40 ml of water, and 10 ml of 12.5 *N* hydrochloric acid was stirred for 2 days at room temperature. The solution was then made alkaline with 30 ml of 5 *N* sodium hydroxide, extracted with 3 x 50 ml of diethyl ether, dried (magnesium sulfate), filtered and evaporated. The crude mixture was then purified by distillation to afford 15.8 g (90%) of **5** as a colorless oil, bp 90-95°/0.1 mm; ir (sodium chloride): 1718 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 0.87 (t, J = 7.3 Hz, 6H, CH_3), 1.35-1.53 (m, 4H, CH_2), 1.68-1.82 (m, 2H, CH_2), 1.98-2.08 (m, 2H, CH_2), 2.24-2.48 (m, 8H, CH_2), 2.89-3.00 (m, 1H, CH).

Anal. Calcd. for $C_{12}H_{23}NO$: C, 73.05; H, 11.75; N, 7.10. Found: C, 72.70; H, 11.69; N, 7.03.

4-Dipropylamino-1-morpholino-1-cyclohexene (**6**).

This experiment was carried out under an argon atmosphere. About 40 g of molecular sieves (Linde 5A) were added to 19.7 g (100 mmoles) of ketone **5** and 10.5 g (120 mmoles) of morpholine in 40 ml of dry toluene. The reaction mixture was stirred until no free ketone could be detected by ir spectroscopy. The mixture was then filtered, evaporated and the product purified by vacuum distillation to afford 18.7 g (70%) of enamine **6** as a pale yellow oil, bp 110-120°/0.1 mm; ir (sodium chloride): 1648 cm^{-1} (C=C-N); ^{1}H nmr (deuteriochloroform): δ 0.86 (t, J = 7.3 Hz, 6H, CH_3), 1.35-1.53 (m, 4H, CH_2CH_2N), 1.88-2.25 (m, 6H, CH_2), 2.37-2.45 (m, 4H, CH_2CH_2N), 2.66-2.89 (m, 5H, CH_2N ring and CH), 3.71-3.76 (m, 4H, CH_2O ring), 4.63 (br s, 1H, =CH).

Anal. Calcd. for $C_{16}H_{30}N_2O$: C, 72.13; H, 11.35; N, 10.51. Found: C, 71.76; H, 11.14; N, 10.32.

8-Dipropylamino-7,8,9,10-tetrahydrophenanthridin-6(5*H*)-one (**8**).

A solution of 13.5 g (50.7 mmoles) of enamine **6** in 15 ml of dry toluene was added dropwise, with stirring, to a solution of 5 ml (46 mmoles) of phenyl isocyanate in 20 ml of dry toluene. This addition was carried out under an argon atmosphere, at room temperature. The reaction was monitored by ir spectroscopy and 25 ml of 2 *N* hydrochloric acid was added with vigorous stirring when the isocyanate absorption band was no longer apparent. After 24 hours at room temperature the mixture was basified with 25 ml of 2 *N* sodium hydroxide and extracted with dichloromethane. The organic layer was washed with brine, dried (magnesium sulfate), filtered, and evaporated to give compound **7** as an orange oil which was used without further purification for the next step. Compound **7** was then refluxed in 15 ml of methanesulfonic acid for 5 hours and the cyclization monitored by tlc using chloroform:methanol:ammonia solution 32% (90:9:1) as eluent. After cooling to room temperature, the mixture was slowly poured into 60 ml of 4 *N* sodium hydroxide at 0° and extracted with dichloromethane, dried (magnesium sulfate), filtered, and evaporated to give a brown solid which was washed with methanol, diethyl ether, and dried under reduced pressure to give 4 g (30%) of **8** as a white solid, mp 248-250°; ir (potassium bromide): 1657 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 0.91 (t, J = 7.3 Hz, 6H, CH_3), 1.41-3.22 (m, 15H, CH_2 and CH), 7.19-7.69 (m, 4H, aromatic H), 10.16 (s, 1H, NH).

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.48; H, 8.69; N, 9.29.

A methanolic solution of 1 g (3.4 mmoles) of compound **8** was treated with tartaric acid and the salt precipitated by the addition of diethyl ether to afford 1.4 g (91%) of the tartrate of compound **8** as a white solid, mp 218-220°; ir (potassium bromide): 1647 cm^{-1} (C=O); ^1H nmr (deuterated methanol): δ 1.02-1.35 (m, 6H, CH_3), 1.75-3.80 (m, 15H, CH_2 and CH), 4.39 (s, 2H, C*H*OH), 7.23-7.76 (m, 4H, aromatic H).

Anal. Calcd. for $C_{23}H_{32}N_2O_7 \cdot 0.8H_2O$: C, 59.68; H, 7.32; N, 6.05. Found: C, 59.50; H, 7.38; N, 5.68.

6-Chloro-8-dipropylamino-7,8,9,10-tetrahydrophenanthridine (**9**).

A mixture of 1.1 g (5.4 mmoles) of phosphorus pentachloride and 1.5 g (5 mmoles) of compound **8** in 60 ml of dry toluene was refluxed for 2 hours. The solution was allowed to cool to room temperature, the solvent was evaporated under reduced pressure and the resulting product was purified by silica gel chromatography using dichloromethane:methanol:32% ammonia solution (95:4:1) as the eluent to afford 1.1 g (67%) of compound **9** as a pale yellow solid, mp 87-89°; ^1H nmr (deuteriochloroform): δ 0.92 (t, J = 7.3 Hz, 6H, CH_3), 1.43-3.49 (m, 15H, CH_2 and CH), 7.50-7.99 (m, 4H, aromatic H).

Anal. Calcd. for $C_{19}H_{25}N_2Cl$: C, 72.02; H, 7.95; N, 8.84; Cl, 11.19. Found: C, 71.71; H, 8.01; N, 8.82; Cl, 11.05.

Treatment of 0.3 g (1 mmole) of compound **9** with an ethanolic solution of hydrogen chloride gave, after addition of a mixture of diethyl ether and ethyl acetate, 0.3 g (91%) of the hydrochloride salt of **9** as a white solid, mp 168-170°; ^1H nmr (deuterium oxide): δ 1.02 (m, 6H, CH_3), 1.56-3.46 (m, 15H, CH_2 and CH), 7.24-7.56 (m, 4H, aromatic H).

Anal. Calcd. for $C_{19}H_{26}N_2Cl_2 \cdot 0.5H_2O$: C, 62.98; H, 7.51; N, 7.73; Cl, 19.57. Found: C, 62.59; H, 7.46; N, 7.66; Cl, 19.56.

8-Dipropylamino-7,8,9,10-tetrahydrophenanthridine-6(5*H*)-thione (**10**).

To a suspension of 3 g (10 mmoles) of compound **8** in 100 ml of dry toluene was added 4 g (10 mmoles) of Lawesson's reagent and the suspension was refluxed for 10 hours with vigorous stirring. The mixture was allowed to cool to room temperature, the solvent was evaporated under reduced pressure, and the residue purified by silica gel chromatography using dichloromethane:methanol: 32% ammonia solution (95:4:1) as the eluent to afford 2.5 g (78%) of **10** as a yellow solid, mp 190-192°; ^1H nmr (deuteriochloroform): δ 0.93 (t, J = 7.3 Hz, 6H, CH_3), 1.55 (m, 4H, CH_2), 1.70-2.20 (m, 4H, CH_2), 2.61 (m, 4H, CH_2), 2.75-3.41 (m, 3H, CH_2 and CH), 7.33-7.81 (m, 4H, aromatic H), 11.72 (s, 1H, NH).

Anal. Calcd. for $C_{19}H_{26}N_2S$: C, 72.56; H, 8.33; N, 8.91; S, 10.20. Found: C, 72.26; H, 8.31; N, 8.82; S, 10.28.

Treatment of 2.5 g (7.8 mmoles) of compound **10** with an ethanolic solution of hydrogen chloride gave 1.3 g (45%) of the hydrochloride salt of **10** as a yellow solid, mp 281-283°; ^1H nmr (deuterium oxide): δ 1.01 (t, J = 7.3 Hz, 6H, CH_3), 1.75-3.71 (m, 15H, CH_2 and CH), 7.13-7.45 (m, 4H, aromatic H).

Anal. Calcd. for $C_{19}H_{27}N_2SCl \cdot 0.3H_2O$: C, 64.04; H, 7.81; N, 7.86. Found: C, 64.18; H, 7.68; N, 7.78.

6-Methylthio-8-dipropylamino-7,8,9,10-tetrahydrophenanthridine (**11**).

A suspension of 2.5 g (7.8 mmoles) of compound **10** in 20 ml of dry tetrahydrofuran was added in portions with stirring, at room temperature, to 0.8 g (20 mmoles) of sodium hydride (60% in mineral oil, previously washed with hexane) in 10 ml of dry tetrahydrofuran. After 30 minutes 0.5 ml (8 mmoles) of iodomethane was introduced and the reaction mixture stirred at room temperature for a further 5 hours. Excess sodium hydride was destroyed by the addition of methanol, the solvents were evaporated under reduced pressure and the crude product was extracted with dichloromethane. The extracts were washed with brine, dried (magnesium sulfate), filtered and evaporated. The resulting product was purified by silica gel chromatography using dichloromethane:ethyl acetate (50:50) as eluent to give 0.8 g (30%) of compound **11** as a pale yellow oil; ^1H nmr (deuteriochloroform): δ 0.93 (t, J = 7.3 Hz, 6H, CH_3), 1.45-1.58 (m, 4H, CH_2), 1.60-2.20 (m, 2H, CH_2), 2.53-2.60 (m, 4H, CH_2), 2.71 (s, 3H, SCH_3), 2.65-3.45 (m, 5H, CH_2 and CH), 7.39-7.64 (m, 2H, aromatic H), 7.84-7.97 (m, 2H, aromatic H).

Treatment of 0.7 g (2.3 mmoles) of compound **11** with an ethanolic solution of hydrogen chloride followed by addition of diethyl ether gave 0.4 g (42%) of the dihydrochloride salt of **11** as a pale yellow solid, mp 170-172°; ^1H nmr (deuterated methanol): δ 1.09 (t, J = 7.3 Hz, 6H, CH_3), 1.81-2.63 (m, 6H, CH_2), 3.07 (s, 3H, SCH_3), 3.15-4.07 (m, 9H, CH_2 and CH), 7.76-8.00 (m, 2H, aromatic H), 8.23-8.34 (m, 2H, aromatic H).

Anal. Calcd. for $C_{20}H_{30}N_2SCl_2 \cdot H_2O$: C, 57.27; H, 7.69; N, 6.68; Cl, 16.90. Found: C, 57.59; H, 7.40; N, 6.82; Cl, 16.53.

8-Dipropylamino-7,8,9,10-tetrahydrophenanthridine (**12**).

A large excess of Raney nickel was refluxed with 2.1 g (6.4 mmoles) of compound **11** in 60 ml of ethanol for 5 hours. The mixture was allowed to cool to room temperature, filtered through celite, evaporated and purified by silica gel chromatography using dichloromethane:methanol (95:5) as eluent to give 0.8 g (44%) of **12** as a pale yellow solid, mp 49-52°; ^1H nmr (deuteriochloroform): δ 0.92 (t, J = 7.3 Hz, 6H, CH_3), 1.79-3.48 (m, 15H, CH_2 and CH), 7.49-7.68 (m, 2H, aromatic H), 7.89-8.07 (m, 2H, aromatic H), 8.64 (s, 1H, N=CH ring).

Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.96; H, 9.41; N, 9.87.

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[31] The preparation of compound **5** by hydrolysis of the 2,2-dimethyltrimethylene ketal is described in reference [27] but no physical or spectroscopic data are given, other than the presence of a carbonyl band at 1710 cm^{-1} in the ir spectrum.