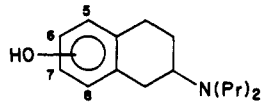
Communications to the Editor

8-Hydroxy-2-(di-*n*-propylamino)tetralin, a New Centrally Acting 5-Hydroxytryptamine Receptor Agonist

Sir:

We are currently investigating the pharmacological properties of 2-aminotetralins and related compounds using biochemical and behavioral methods recently published.[1,2] It has been previously shown that 5-hydroxy- (1), 6-hydroxy- (2) and 7-hydroxy-2-(di-*n*-propylamino)-tetralin (3) exhibit considerable dopamine (DA) receptor stimulating activity.[3,4] In this series, the 5-hydroxy isomer 1 is the most active compound, being a highly active central DA-receptor agonist.

Now we report the pharmacological properties of 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT; 4) which are consistent with the characterization of this compound as a central 5-hydroxytryptamine (5-HT) receptor agonist, devoid of DA-receptor stimulating activity. The DA-receptor-active 2-aminotetralins (1–3) are included for comparative purposes in this study. We are also presenting the resolution of 4 and the testing results for the enantiomers.

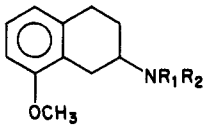


1, 5-OH
2, 6-OH
3, 7-OH
4, 8-OH

The compounds were tested in reserpinized rats according to biochemical and behavioral methods previously described.[1,2] The enantiomers of compound 4 were also tested in nonpretreated animals.

The in vivo biochemical test method utilizes the well-established phenomenon of receptor-mediated feedback inhibition of the presynaptic neuron.[5-7] Thus, the synthetic rate of the catecholamines DA and noradrenaline (NA) is inhibited by agonists activating dopaminergic and α-adrenergic receptors, respectively, and the synthetic rate of 5-HT is similarly inhibited by 5-HT-receptor agonists. The Dopa accumulation, after decarboxylase inhibition by means of 3-hydroxybenzylhydrazine (NSD 1015), was thus determined, being an indicator of the DA-synthesis rate in the DA-predominated parts (i.e., limbic system, corpus striatum) and the NA-synthesis rate in the NA-dominated remaining hemispheral portions (mainly cortex). The 5-HTP accumulation was similarly determined, being an indicator of the 5-HT synthesis rate in the three brain parts.

8-Hydroxy-2-(di-*n*-propylamino)tetralin (4) was prepared from the hydrochloride of compound 5[8] (mp 148.5–149.5 °C) by demethylation in 48% aqueous HBr: yield 89%; mp 221.5–222 °C.[9] Using the same method we also prepared 1·HBr,[2] 2·HBr[10] (yield 39%; mp 190–191 °C), and 3·HBr[10] (yield 21%; mp 181–182 °C).



5, R_1 = *n*-Pr; R_2 = *n*-Pr
6, R_1 = *n*-Pr; R_2 = H
7, R_1 = H; R_2 = CH_2-Ph

Attempts to resolve 5 and 6 failed when L(+)-tartaric acid or (+)-dibenzoyl-D-tartaric acid was used as resolving agent. Separation of the diastereomeric tartaric acid salts of 7 by means of fractional crystallization was, however, successful. Hot ethanol solutions of D(−)-tartaric acid and of 7 were mixed and allowed to stand at room temperature overnight. The crystals thus formed were recrystallized four times from ethanol until the specific rotation of (−)-7·HCl was constant: yield 12%; mp 240–241 °C; $[\alpha]^{22}_D$ −62.5° (*c* 1.01, MeOH). The free amine, obtained from the combined mother liquors, was treated with L(+)-tartaric acid as described above to give (+)-7·HCl: yield 23%; mp 239–240 °C; $[\alpha]^{22}_D$ +63.3° (*c* 1.01, MeOH).

In order to determine the enantiomeric purity, (+)-7 and (−)-7 were converted to *O*-methylmandelamides by reacting them with an excess of (*R*)-(−)-2-methoxy-2-phenylacetyl chloride and triethylamine in benzene. In the 100-MHz ^{1}H NMR spectra of the (*R*)-(−)-*O*-methylmandelamides, the diastereotopic methine protons α to the methoxy groups were differently shifted (5.36 and 5.44 ppm, respectively). By estimation of the relative areas of these signals, the percent enantiomeric excess (% ee) was calculated to be 90% ee for (+)-7 and 87% ee for (−)-7.

Acylation of (+)-7 with propionyl chloride, followed by reduction of the formed amide with $LiAlH_4$ and hydrogenolysis (10% Pd/C) of the benzylic C–N bond, gave (+)-6·HCl: yield 84%; mp 236–237 °C; $[\alpha]^{22}_D$ +78.3° (*c* 1.05, MeOH). Subsequent acylation with propionyl chloride, followed by reduction with $LiAlH_4$, afforded (+)-5·HCl: yield 88%; mp 164–165 °C, $[\alpha]^{22}_D$ +77.1° (*c* 1.04, MeOH). Similarly, (−)-7 was converted, via (−)-6·HCl [yield 81%; mp 235–236.5 °C; $[\alpha]^{22}_D$ −77.0° (*c* 1.03, MeOH)], to (−)-5·HCl: yield 85%; mp 164–164.5 °C, $[\alpha]^{22}_D$ −76.1° (*c* 1.00, MeOH).

The methyl ethers (+)-5 and (−)-5 were cleaved using 48% aqueous HBr to give (+)-4·HBr [yield 89%; mp

(1) Wikström, H.; Lindberg, P.; Hjorth, S.; Carlsson, A.; Hacksell, U.; Svensson, U.; Nilsson, J. L. G. *J. Med. Chem.* **1978**, *21*, 864.
(2) Hacksell, U.; Svensson, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Wikström, H.; Lindberg, P.; Sanchez, D. *J. Med. Chem.* **1979**, *22*, 1469.
(3) McDermed, J. D.; McKenzie, G. M.; Freeman, H. S. *J. Med. Chem.* **1976**, *19*, 547.
(4) Tedesco, J. L.; Seeman, P.; McDermed, J. D. *Mol. Pharmacol.* **1979**, *16*, 369.
(5) Andén, N.-E.; Carlsson, A.; Häggendal, J. *Annu. Rev. Pharmacol.* **1969**, *9*, 119.
(6) Aghajanian, G. K.; Bunney, B. S.; Kuhar, M. J. In "New Concepts in Neurotransmitter Regulation"; Mandell, A. J., Ed.; Plenum Press: New York, **1973**; p 119.
(7) Neckers, L. M.; Neff, N. H.; Wyatt, R. J. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1979**, *306*, 173.
(8) Ames, D. E.; Evans, D.; Grey, T. F.; Islip, P. J.; Richards, K. E. *J. Chem. Soc.* **1965**, 2636.
(9) The elemental analyses (C, H, and N) for the new substances were within ±0.4% of the theoretical values.
(10) Compounds 2 and 3 were reported in ref 3 as hydriodides.

0022-2623/81/1824-0921$01.25/0

Table I. Monophenolic 2-(Di-*n*-propylamino)tetralins: Effects on Rat Brain in Vivo Dopa and 5-HTP Accumulation

compd	Dopa accumulation: [a] ED_{50}, [b,d] nmol/kg sc		5-HTP accumulation: [a] ED_{50}, [d,e] nmol/kg sc		
	limbic	striatum	limbic	striatum	hemispheres (cortex)
1	11 [f]	9 [f]	I [g]	I	I
2	180 ± 14	170 ± 20	I	I	I
3	27 ± 2	30 ± 1	I	I	I
(±)-4	I [g]	I	48 ± 9	45 ± 5	68 ± 3
(+)-4	I	I	36 ± 5** [h]	48 ± 4* [i]	52 ± 6* [i]
(−)-4	I	I	61 ± 8	75 ± 12	90 ± 16

[a] For experimental details, see ref 1. [b] Dose giving a half-maximal decrease of Dopa formation in the rat brain part, estimated from a dose–response curve comprising four to six dose levels (n = 3–5). The maximal reduction of the Dopa level was empirically found to be 65% from the control level (635 ng of Dopa/g of tissue) for the limbic and 80% from the control level (1670 ng of Dopa/g of tissue) for the striatal brain portions. [c] No significant effect on Dopa accumulation was obtained in the hemispheral portions (cortex). [d] Shown are the ED_{50} values ± SD. [e] Dose giving a half-maximal decrease of 5-HTP formation in the rat brain part, estimated from a dose–response curve comprising four to six dose levels (n = 3–5). The maximal reduction of the 5-HTP level was empirically found to be 50% from the control levels (120 ng of 5-HTP/g of limbic tissue, 75 ng of 5-HTP/g of striatal tissue, and 75 ng of 5-HTP/g of hemispheral tissue). [f] The values were taken from ref 1. [g] Inactive; no significant effect at doses approximately 40 times the ED_{50} for Dopa or 5-HTP accumulation, respectively. [h] Differs from (−)-4: ** = $p < 0.01$. [i] Differs from (−)-4: * = $p < 0.05$.

178.5–179.5 °C, $[\alpha]^{22}_D$ +67.5° (*c* 1.03, MeOH)] and (−)-4 HBr [yield 82%; mp 178.5–179.5 °C, $[\alpha]^{22}_D$ −66.5° (*c* 1.01, MeOH)].

The biochemical and behavioral test results from compounds 1–4 are given in Tables I and II and in the text, respectively.

In accordance with previous observations,[2,3] we found that compounds 1–3 are centrally acting DA-receptor stimulating agents capable of activating the DA autoreceptors (cf., e.g., ref 11) as well as (at higher doses) the postsynaptic DA receptors (Table I and gross behavioral observations, respectively), with the rank order of potency being 1 > 3 > 2. The biochemical (Table I) and behavioral data indicate that compounds 1–3 are devoid of 5-HT activity, whereas compound 4 appears to lack DA effects. In addition, none of the compounds 1–4 affect the Dopa accumulation in the cortical areas of rat brain, suggesting a lack of noradrenaline-receptor stimulatory effects.

Compound 4, in contrast to the other monophenolic isomers (1–3), appears to be a 5-HT-receptor stimulating agent. This is indicated by the marked and selective decrease in brain 5-HTP formation (Table I) and the appearance of a clear-cut behavioral syndrome characterized by flat body posture, forepaw extension and padding ("piano playing"), abducted hindlimbs, occasional tremor in the forebody, and (at higher doses) Straub tail reaction. This syndrome is characteristic for central 5-HT-receptor activation and can thus be induced by all known directly or indirectly acting 5-HT agonists.[12-14] The demonstration that the "5-HT syndrome" induced by compound 4 (0.5 mg/kg, sc) was not blocked by 5-HT depletion by means of reserpine (10 mg/kg, ip, 6 h prior to compound 4) plus the tryptophan hydroxylase inhibitor α-propyldopacetamide[15] (H 22/54, 500 mg/kg, ip, 1 h prior to compound 4) strongly supports the view that compound 4 is a direct 5-HT-receptor stimulating agent (cf., e.g., ref 16).

Interestingly, both enantiomers of compound 4 proved to be effective 5-HT agonists (the potency comparable to that of LSD; unpublished results from this group) as reflected in their behavioral as well as biochemical actions. However, the (+) isomer was significantly more active in the biochemical tests than the (−) isomer (Tables I and II).

In order to investigate the possible difference between the enantiomers of 4 with regard to behavioral 5-HT activity, the following experiment was performed. Twelve male Sprague–Dawley rats (200–230 g), pretreated with reserpine plus H 22/54 as described above, were divided into four groups of three animals. Within each group, one animal was injected with (+)-4 (0.4 mg/kg, sc), one with (−)-4 (0.4 mg/kg, sc), and one with saline. Five to ten minutes later they were ranked blindly within their groups for the intensity of behavioral activity by seven observers independently. All seven observers gave rank one to the animals that were treated with (+)-4 (i.e., they exhibited the most pronounced "5-HT syndrome"), the second rank was given to the (−)-4 treated animals, and the third rank to the saline controls. This was true for all four groups of animals in the experiment. Thus, the gross behavioral observations demonstrate that both enantiomers of compound 4 are effective elicitors of the "5-HT syndrome" in rats and that there was a significantly more pronounced effect ($p < 0.001$) of the (+) than of the (−) isomer of compound 4, i.e., parallel with the biochemical results obtained with the enantiomers (Tables I and II).

The absolute configuration of compound 4 has yet to be experimentally determined. However, for both compound 1 and 2-amino-6,7-dihydroxytetralin it has been established that the dextrorotatory form has the *R* configuration.[17] By analogy, it could be assumed that (+)-4, the more active enantiomer, also has the *R* configuration, i.e., the same absolute configuration as the 2-aminotetralin fragment of the pharmacologically active form of LSD.

The efficacy of both enantiomers of compound 4 suggests that the 5-HT receptor is less stereoselective in its interaction with 2-aminotetralins than the DA receptor, which shows pronounced preference for the (−) isomer of compound 1[3,4,17] and the (+) isomer of 2-amino-6,7-dihydroxytetralin.[17,18]

In conclusion, our results indicate that 8-hydroxy-2-(di-*n*-propylamino)tetralin (4)[19] is a potent and selective

(11) Carlsson, A. In "Pre- and Postsynaptic Receptors"; Usdin, E.; Bunney, W. E., Jr., Eds.; Marcel Dekker: New York, 1975.
(12) Jacobs, B. L. *Life Sci.* **1976**, *19*, 777, and references cited therein.
(13) Gerson, S. C.; Baldessarini, R. J. *Life Sci.* **1980**, *27*, 1435, and references cited therein.
(14) Sloviter, R. S.; Drust, E. G.; Connor, J. D. *J. Pharmacol. Exp. Ther.* **1978**, *206*, 339.
(15) Carlsson, A.; Corrodi, H.; Waldeck, B. *Helv. Chim. Acta* **1963**, *46*, 2271.
(16) Andén, N.-E.; Corrodi, H.; Fuxe, K.; Hökfelt, T. *Br. J. Pharmacol.* **1968**, *34*, 1.
(17) McDermed, J. D.; Freeman, H. S.; Ferris, R. M.; In "Catecholamines: Basic and Clinical Frontiers", Usdin, E.; Kopkin, F. J.; Barchas, J., Eds.; Pergamon Press: New York, 1979; p 568.
(18) Davis, A.; Poat, J. A.; Woodruff, G. N. *Eur. J. Pharmacol.* **1980**, *63*, 237.

Table II. 8-Hydroxy-2-(di-*n*-propylamino)tetralin (4): Effects of the (+) and (-) Isomers on Brain Dopa and 5-HTP Formation

treatment[a]	5-HTP,[b] ng/g			Dopa,[b] ng/g		
	limbic	striatum	hemisph (cortex)	limbic	striatum	hemisph (cortex)
control (0.9% NaCl)	118 ± 2	65 ± 2	72 ± 2	333 ± 13	414 ± 12	51 ± 4[c]
(+)-4 (40 μg/kg sc)	63 ± 2***[d]	40 ± 2***[d]	44 ± 2***[d]	359 ± 18	416 ± 17	55 ± 2
(-)-4 (40 μg/kg sc)	84 ± 2***[e]	53 ± 2***[e]	57 ± 2***[e]	336 ± 4	445 ± 17	53 ± 5

[a] Nonpretreated rats were given (+)-4 or (-)-4 subcutaneously 60 min before death. NSD 1015, 100 mg/kg ip, was given 30 min before death. [b] Shown are the means ± SEM; $n = 4$. Statistics: ANOVA followed by Student's t test. [c] $n = 3$. [d] Differs from control and (-)-4: *** = $p < 0.001$ (ANOVA followed by Student's t test). [e] Differs from (-)-4: *** = $p < 0.001$ (ANOVA followed by Student's t test).

direct 5-HT-receptor agonist devoid of DA- and NA-receptor stimulatory properties, whereas 5-hydroxy-, 6-hydroxy-, and 7-hydroxy-2-(di-*n*-propylamino)tetralin (1–3), while lacking 5-HT and NA effects, show considerable DA-receptor stimulating activity.

Acknowledgment. The authors thank Mrs. Ingrid Bergh, Ms. Kerstin Bingefors, Mrs. Lucia Gaete-Valderrama, Ms. Boel Göransson, Mrs. Gerd Leonsson, Ms. Maria Lindbäck, and Mrs. Barbro Sköldeberg for skillful technical assistance, Dr. Gunnar Blomqvist for the statistical analysis, and Mr. Göran Everitt for the 100-MHz ^{1}H NMR spectra.

(19) After preparation of this manuscript, compound 4 was reported: Feenstra, M. G. P.; Rollema, H.; Dijkstra, D.; Grol, C. J.; Horn, A. S.; Westerink, B. H. C. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1980**, *313*, 213. In accordance with the present results they found that compound 4 (0.1–20 μmol/kg, ip) did not alter the dopamine metabolism (DOPAC, HVA, and dopamine levels) in the rat striatum. No effects on 5-HT systems were reported.

The financial support from AB Hässle, Mölndal, Sweden, Astra Läkemedel AB, Södertälje, Sweden, The Swedish Board for Technical Development, The Swedish Academy of Pharmaceutical Sciences, "Stiftelsen Clas Groschinskys Minnesfond", "Magnus Bergvalls Stiftelse", and the Medical Faculty, University of Gothenburg, are gratefully acknowledged.

Lars-Erik Arvidsson,* Uli Hacksell, J. Lars G. Nilsson
Department of Organic Pharmaceutical Chemistry Biomedical Center, University of Uppsala, S-751 23 Uppsala, Sweden

Stephan Hjorth, Arvid Carlsson
Department of Pharmacology, University of Gothenburg S-400 33 Göteborg, Sweden

Per Lindberg, Domingo Sanchez, Håkan Wikström
Organic Chemistry Unit, Department of Pharmacology University of Gothenburg, S-400 33 Göteborg, Sweden

Received September 2, 1980