NMR ($CDCl_3$ + TFA) δ 7.5–6.6 (8 H, m), 5.4 (1 H, s), 5.1–3.4 (12 H, m, s), 3.1 (3 H, s). Anal. ($C_{20}H_{24}N_2O$·2HCl) C, H, N, Cl.

Acknowledgment. We thank David St. Maurice, William Kuipers, and members of the analytical chemistry staff for excellent analytical services, Lenore Bookless for typing the manuscript, Dr. Stephen J. Riggi for his encouragement to pursue the molecular modelling approach, and Dr. Garland Marshall for his invaluable assistance and technical support with the computer graphics.

Registry No. 1, 3963-62-0; 2, 90065-24-0; (±)-3, 90065-25-1; (±)-3·HCl, 90065-26-2; (±)-4a, 90065-27-3; (±)-4a·2HCl, 90065-28-4; (±)-4b, 90065-29-5; (±)-4b·2HCl, 90083-49-1; (±)-4c, 90065-30-8; (±)-4c·2HCl, 90083-50-4; (±)-5, 90065-31-9; (±)-5·2HCl, 90065-32-0; (±)-6, 90065-33-1; (±)-6·2HCl, 90065-34-2; (±)-7a, 90065-35-3; (±)-7a·2HCl, 90065-36-4; (±)-7b, 90065-37-5; (±)-7b·2HCl, 90065-38-6; (±)-8·2HCl, 90065-39-7; (–)-9, 90130-07-7; (–)-9·0.5-(–)-DOBT, 90191-34-7; (–)-9·2HCl, 90191-35-8; (+)-10, 90130-08-8; (+)-10·D-tartarate, 90191-38-1; (+)-10·0.5(+)-DOBT, 90191-36-9; (+)-10·2HCl, 90191-37-0; (±)-11, 90065-40-0; (±)-11·2HCl, 90065-41-1; (±)-12a, 90065-42-2; (±)-12a·2HCl, 90065-43-3; (±)-12b, 90065-44-4; (±)-12c, 90065-45-5; (±)-12d, 90065-46-6; (±)-2e, 90065-47-7; (±)-13, 90065-48-8; (±)-13·2HCl, 90065-49-9; (±)-14, 90065-50-2; (±)-14·2HCl, 90065-51-3; (±)-15, 90065-52-4; (±)-15·2.5HCl, 90065-53-5; (±)-16, 90065-54-6; (±)-16·2HCl, 90065-55-7; (±)-17, 90065-56-8; (±)-17·2HCl, 90065-57-9; (±)-18, 90065-58-0; (±)-18·2HCl, 90065-59-1; $MeNH_2$, 74-89-5; $EtNH_2$, 75-04-7; Me_2NH, 124-40-3; EtOC(O)C(O)OEt, 95-92-1; (±)-1,2,3,4-tetrahydro-2-formyl-1-[(dimethylamino)methyl]-4-phenylisoquinoline, 90065-60-4; (±)-*cis*-1,3,4,6,7,11b-hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline-3,4-dione, 90065-61-5; (±)-*cis*-1,3,4,6,7,11b-hexahydro-2-ethyl-7-phenyl-2*H*-pyrazino[2,1-*a*]isoquinoline-3,4-dione, 90083-51-5; (±)-*trans*-1,3,4,6,7,11b-hexahydro-2-methyl-7-phenyl-2*H*-pyrazino[2,1-*a*]-isoquinoline-3,4-dione, 90065-62-6; (±)-*cis*-1,3,4,6,7,11b-hexahydro-7-phenyl-2-propionyl-2*H*-pyrazino[2,1-*a*]isoquinoline, 90065-63-7.

C_1-Methylated 5-Hydroxy-2-(dipropylamino)tetralins: Central Dopamine-Receptor Stimulating Activity

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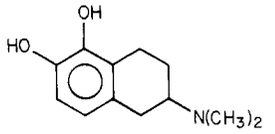
C_1-Methylated derivatives of the potent dopaminergic agonist 5-hydroxy-2-(di-*n*-propylamino)tetralin (**6**) have been synthesized and tested for central dopamine (DA) receptor stimulating activity, by using biochemical and behavioral tests in rats. Both *cis*- and *trans*-5-hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin (**4** and **3**) may be classified as central DA-receptor agonists, albeit of lower potency than **6**. The results obtained indicate that both **4** and **3** display DA-autoreceptor stimulation capacity. However, only one of the isomers, *trans*-**3**, is able to elicit clear-cut postsynaptic DA receptor agonist actions at larger doses. 5-Hydroxy-1,1-dimethyl-2-(*n*-propylamino)tetralin (**5**) was found to be inactive.

In 1972 Cannon et al.[1] reported that 5,6-dihydroxy-2-(dimethylamino)tetralin (**1**, "M7") possesses a potency



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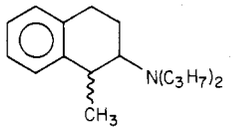

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comparable to that of apomorphine in eliciting emesis in the dog and compulsive gnawing in the mouse, thereby demonstrating high dopaminergic potency.

Cannon's study initiated the synthesis and testing of a large number of related compounds, and several subsequent papers have discussed structure–activity relationships of 2-aminotetralins;[2] particularly well documented are changes in biological effects resulting from variations of the N-substituents[3] and of the position(s) of the phenolic hydroxyl groups(s).[4] However, to our knowledge only one 2-aminotetralin that is alkyl substituted in the nonaromatic ring has been tested for dopaminergic activity. This compound, 1-methyl-2-(di-*n*-propylamino)tetralin (**2**), showed moderate potency in eliciting stereotyped behavior in the rat.[3a] A considerably higher dopaminergic potency might be expected from phenolic analogues of **2**.[5] We have therefore synthesized and tested the *cis*-1-methyl, *trans*-1-methyl, and 1,1-dimethyl derivatives (**4**, **3**, and **5**, respectively, Table I) of the potent DA-receptor agonist 5-hydroxy-2-(di-*n*-propylamino)tetralin (**6**),[3b] which is included here as a reference.

Chemistry. The stereoselective syntheses of *cis*- and *trans*-5-methoxy-1-methyl-2-(di-*n*-propylamino)tetralin (**14** and **12**) are outlined in Scheme I.

trans-2-Amino-5-methoxy-1-methyltetralin (**9**) was conveniently prepared from the oxime of 5-methoxy-1-

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(1) Cannon, J. G.; Kim, J.-C.; Aleem, M. A.; Long, J. P. *J. Med. Chem.* **1972**, *15*, 348.
(2) For recent reviews, see: Long, J. P.; Rusterholz, D. R.; Flynn, J. R.; Cannon, J. G. *Adv. Biosci.* **1979**, *18*, 73. Cannon, J. G.; Long, J. P.; Bhatnagar, R. *J. Med. Chem.* **1981**, *24*, 1113. Nilsson, J. L. G.; Arvidsson, L. E.; Hacksell, U.; Johansson, A.; Svensson, U.; Carlsson, A.; Hjorth, S.; Lindberg, P.; Sanchez, D.; Wikström, H. *Acta Pharm. Suec. Suppl.* **1983**, *2*, 37.
(3) See, for example: (a) McDermed, J. D.; Mc Kenzie, G. M.; Phillips, A. P. *J. Med. Chem.* **1975**, *18*, 362. (b) Hacksell, U.; Svensson, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Wikström, H.; Lindberg, P.; Sanchez, D. *J. Med. Chem.* **1979**, *22*, 1469. (c) Ginos, H. Z.; Stevens, J. M.; Nichols, D. E. *J. Med. Chem.* **1979**, *22*, 1323.
(4) See, for example ref 3a and Arvidsson, L. E.; Hacksell, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Sanchez, D.; Lindberg, P.; Wikström, H. *J. Med. Chem.* **1981**, *24*, 921.
(5) Compare ref 3a and Rusterholz, D. B.; Long, H. P.; Flynn, H. P.; Cannon, J. G.; Lee, T.; Pease, H. P.; Clemens, H. A.; Wong, D. T.; Bymaster, F. P. *Eur. J. Pharmacol.* **1979**, *55*, 73.

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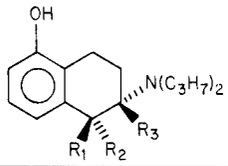
Table I. Physical and Biological Data of the Compounds Studied



no.	R_1	R_2	R_3	yield,[a] %	mp, °C	formula	Dopa accumulation: ED_{50},[b,c] nmol/kg limbic	striatum	motor act. accumulated:[i] counts/60 min
3	CH_3	H	H	32	197–198[d]	$C_{17}H_{27}NO\cdot HBr$	660	725	406 ± 47
4	H	CH_3	H	67	206–207[d]	$C_{17}H_{27}NO\cdot HBr$	670	800	52 ± 7
5	CH_3	CH_3	H	66	144–146[e]	$C_{18}H_{29}NO\cdot HBr$	I[f]		
6	H	H	H				11[h]	9[h]	688 ± 63[k]

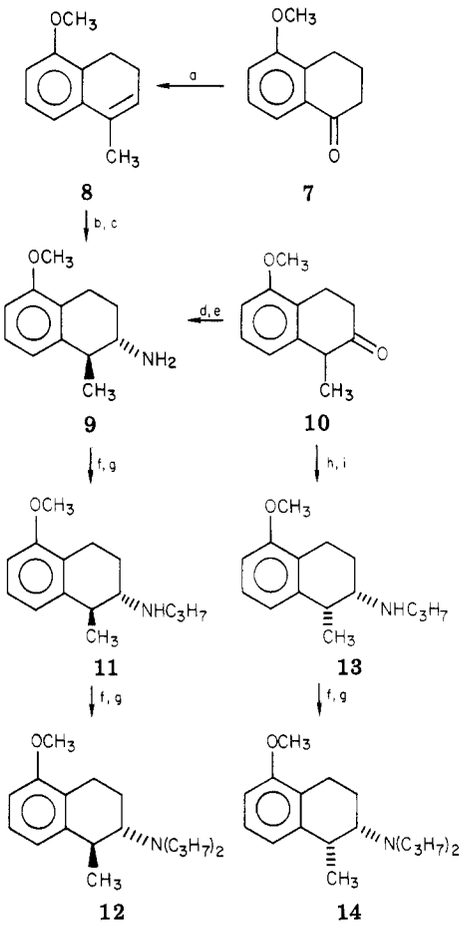
[a] Yield in the demethylation step. [b] Graphically estimated dose giving a half-maximal decrease of the dopa level in rat brain; maximal reduction of the Dopa level was empirically found to be (for all the compounds tested, as well as for apomorphine) 65% from the control level (635 ng of dopa/g of tissue) for the limbic and 80% from the control level 1670 ng of dopa/g of tissue) for the striatal brain portions. The shapes of the dose–response curves were all similar to those of apomorphine. In each point of the curves, SEM was less than 15% of the mean value (see Experimental Section). [c] No effects were obtained in the hemispheral portions. [d] No recrystallization. See Experimental Section. [e] From EtOH. [f] Inactive; compounds with and ED_{50} value greater than 5000 nmol/kg have been considered as inactive. [g] From EtOH–ether. [h] From ref 3b. [i] For details, see Experimental Section. [k] From ref 13d.

methyl-2-tetralone (**10**)[6] by reduction with sodium sand[7] in 2-propanol. This reaction gave a 2:8 mixture of cis and trans isomers from which the pure trans isomer **9** was obtained by fractional crystallization of the hydrochlorides. The trans configuration of **9** was confirmed by use of an alternative synthetic sequence; addition of the methylmagnesium iodide to 5-methoxy-1-tetralone (**7**) gave 3,4-dihydro-2-methoxy-1-methylnaphthalene (**8**).[8] Hydroboration of compound **8**, followed by treatment of the resulting organoborane adduct with hydroxylamine-*O*-sulfonic acid, gave a product identical with **9**. The hydroboration–amination sequence used is known[9] to give stereospecific cis-hydroamination and thus establishes the trans relationship of the methyl and amino substituents of **9**. The primary amine **9** was converted to the tertiary amine **12** by a repetitive N-acylation–reduction procedure.

cis-5-Methoxy-1-methyl-2-(di-*n*-propylamino)tetralin (**13**) was obtained by reductive amination of ketone **10** (Scheme I). Use of platinum oxide as hydrogenation catalyst gave a 7:3 mixture of the diastereomeric amines **13** and **11**, from which fractional crystallization of the hydrochlorides afforded compound **11** of more than 95% isomeric purity. Exchange of platinum oxide for palladium on carbon as catalyst improved the stereoselectivity of the reduction; the ratio of cis/trans isomers increased to 96:4. The tertiary amine **14** was prepared from **13** via N-acylation, followed by reduction of the resulting amide.

The isomeric purity of the cis and trans isomers was examined by gas chromatography (GC) and by ^1H NMR of methanol-d_4 solutions of the hydrochlorides or hydrobromides. In the ^1H NMR spectra of the cis isomers (**13**, **14**, and **4**), the C_1-methyl appears as a doublet more than 0.05-ppm upfield from the absorption due to the C_1-methyl of the corresponding trans isomers (**11**, **12**, and **3**). The

Scheme I[a]



[a] Reagents: a = CH_3MgI; b = $NaBH_4$, $BF_3\cdot(C_2H_5)_2O$; c = H_2NOSO_3H; d = $H_2NOH\cdot HCl$, NaOAc; e = Na, 2-PrOH; f = C_2H_5COCl, $(C_2H_5)_3N$; g = $LiAlH_4$; h = $C_3H_7NH_2$; i = H_2, PtO_2 or H_2, Pd/C.

^1H NMR spectra did not reveal any isomeric impurities. However, GC showed a small contamination (less than 5%) of trans isomer in all the cis derivatives. GC was also used to ascertain the absence of any contamination of the highly potent compound **6** in compounds **3** and **4**.

5-Methoxy-1,1-dimethyl-2-(di-*n*-propylamino)tetralin (**17**) was prepared from 5-methoxy-1,1-dimethyl-2-tetralone

(6) Cornforth, J. W.; Robinson, R. J. *J. Chem. Soc.* **1949**, 1855.
(7) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. I, p 1023.
(8) Dehydration of the intermediate 5-methoxy-1-methyltetralin-1-ol occurred spontaneously. This contrasts with the behavior of 1-methyltetralin-1-ol, which is reported to be stable under the conditions used. English, J.; Cavaglieri, G. J. *J. Am. Chem. Soc.* **1943**, *65*, 1085.
(9) Rathke, M. W.; Inoue, N.; Varma, K. R.; Brown, H. C. *J. Am. Chem. Soc.* **1966**, *88*, 2870. See also: Wiley, R. A.; Pearson, D. A.; Schmidt, V.; Wesche, S. B.; Roxon, J. J. *J. Med. Chem.* **1983**, *26*, 1077.

(15)[10] via reductive amination, N-acylation, and $LiAlH_4$ reduction. The phenols presented in Table I were all prepared from the corresponding methoxy compounds via demethylation in 48% aqueous HBr.

Pharmacological Results and Discussion

The compounds were tested biochemically for DA-receptor stimulating activity in reserpinized rats as previously described.[11] In this in vivo biochemical screening method, we utilized the ability of DA-receptor agonists to decrease the Dopa-synthesis rate in the presynaptic neurons. The reduced Dopa accumulation (as compared to controls) is measured after administration of the aromatic-L-amino acid decarboxylase inhibitor *m*-hydroxybenzylhydrazine hydrochloride (NSD 1015, 100 mg/kg). Motor activity recordings were carried out as previously described[11] with motility meters. The results obtained in the biochemical and motor activity tests are presented in Table I.

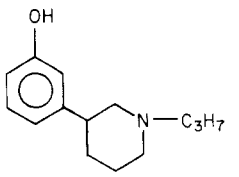
Compounds **3** and **4** reduced the Dopa accumulation in the striatum and in the limbic system, whereas compound **5** was inactive in the biochemical test.

At doses equal to the ED_{50} values, no behavioral or locomotor effects characteristic for postsynaptic dopaminergic stimulation (locomotor activity, stereotypies, etc.) were observed in the reserpine/NSD 1015 treated rats. Thus, compounds **3** and **4** seem to resemble the unsubstituted analogue **6**, as well as several other DA-receptor stimulants,[12] because of its predominant action on DA autoreceptors in low doses. The decreases in Dopa accumulation induced by **3** and **4** were antagonized by haloperidol pretreatment (0.32 mg/kg ip; 30 min before), thereby confirming DA receptor involvement.

The Dopa accumulation in the hemispheral portion and the 5-HTP accumulation (not shown) in the hemispheral, limbic, and striatal portions of the brain were not affected by the compounds tested. These results suggest that none of these compounds possess central noradrenalin- or serotonin-receptor stimulatory effects, respectively, at the administered doses.

Recently, some 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]-quinolines have been shown to be central and/or peripheral DA-receptor agonists.[13] These compounds may be viewed as C_1-alkyl-substituted 2-aminotetralin congeners. In the octahydrobenzo[*f*]quinoline series, only the trans isomers are potent DA-receptor agonists.[13d] This contrasts with the biochemical equipotency observed here for the cis and trans isomers **4** and **3**.

Compounds **3** and **4** were also tested for their ability to counteract akinesia resulting from severe monoamine, particularly DA, depletion by means of combined reserpine and α-methyl-*p*-tyrosine pretreatment in rats. Activity in this test may be considered to mainly detect direct postsynaptic DA receptor stimulation and is reflected in increased locomotion and the induction of stereotyped behaviors. Interestingly, only the trans-isomer **3** was active in this test. The cis-isomer **4** failed, even at doses more than 40 times its biochemical ED_{50}, value, to elicit significant motor-activity stimulation. Thus, the present results indicate that compound **4**, although able to activate the DA autoreceptors, appears to lack prominent postsynaptic DA-receptor stimulatory capacity. This is a pharmacological profile that is similar to that observed for racemic 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (3-PPP, **18**).[14] However, the apparent selectivity of racemic



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18 seems to be caused by the opposing effects of the *R* and *S* forms on postsynaptic DA receptors.[15] Therefore, it is important to note that compound **4** is a racemic mixture and that the final classification of its effects has to be done by using the enantiomers.

Experimental Section

Chemistry. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. ^1H NMR spectra were recorded on a Perkin-Elmer R 12B spectrometer, on a JEOL FX 100 spectrometer, or on a Bruker WP 200 spectrometer. IR spectra recorded on a Perkin-Elmer 157G spectrophotometer and mass spectra recorded at 70 eV on a LKB 9000 spectrometer were all in accordance with the assigned structures. The elemental analyses (C, H, and N) for all new compounds (Agricultural College, Uppsala, Sweden) were within ±0.4% of the theoretical values. For purity tests, TLC was performed on fluorescent silica gel or alumina plates. For all the compounds, only one spot (visualized by UV light and I_2 vapor) was obtained. GC was performed on a Varian 2700 instrument with a flame-ionization detector. A glass column (3 m) with 3% OV-25 on 100-120 mesh Gas-Chrom Q was used throughout. The relative amounts of each component in the isomeric mixtures were determined by estimation of the relative peak areas in GC.

***trans*-2-Amino-5-methoxy-1-methyltetralin (9). Method 1.** A mixture of 5-methoxy-1-methyl-2-tetralone (**10**)[6] (prepared via alkylation of the pyrrolidine enamine of 5-methoxy-2-tetralone according to Stork et al.[16]) (4 g, 21 mmol), hydroxylamine hydrochloride (3 g, 42 mmol), and sodium acetate (5.6 g, 68 mmol) in EtOH (100 mL) was refluxed for 1 h. The EtOH was evaporated in vacuo, and the residue was partitioned between ether and H_2O. The dried ($MgSO_4$) ether layer was evaporated in vacuo, affording yellowish, slightly oily crystals, which were rinsed with ether. The 5-methoxy-1-methyl-2-tetralone oxime thus obtained was sufficiently pure to use in the next step without further purification. To the above oxime (3.65 g, 18 mmol) in dry 2-

(10) Cornforth, J. W.; Cornforth, R. H.; Robinson, R. *J. Chem. Soc.* **1942**, 689.

(11) Wikström, H.; Lindberg, P.; Martinson, P.; Hjorth, S.; Carlsson A.; Hacksell, U.; Svensson, U.; Nilsson, J. L. G. *J. Med. Chem.* **1978**, *21*, 864, and ref 3b.

(12) See, for example, ref 3b and Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, J. L. G.; Wikström, H.; Lindberg, P.; Sanchez, D.; Hjorth, S.; Carlsson, A.; Paalzow, L. *J. Med. Chem.* **1981**, *24*, 429.

(13) (a) Cannon J. G.; Hatheway, G. J.; Long, J. P.; Sharabi, F. M. *J. Med. Chem.* **1976**, *19*, 987. (b) Cannon, J. G.; Suarez-Gutierrez, C.; Lee, T.; Long J. P.; Costall, B.; Fortune, D. H.; Naylor, R. C. *J. Med. Chem.* **1979**, *22*, 341. (c) Cannon, J. G.; Lee, T.; Goldman, H. D.; Long, J. P.; Flynn, J. R.; Verimer, T.; Costall, B.; Naylor, R. J. *J. Med. Chem.* **1980**, *23*, 1. (d) Wikström, H.; Sanchez, D.; Lindberg, P.; Arvidsson, L.-E.; Hacksell, U.; Johansson, A.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1982**, *25*, 925.

(14) (a) Hjorth, S.; Carlsson, A.; Wikström, H.; Lindberg, P.; Sanchez, D.; Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, J. L. G. *Life Sci.* **1981**, *18*, 1225. (b) Hacksell, U.; Arvidsson, L.-E.; Svensson, K.; Nilsson, J. L. G.; Sanchez, D.; Wikström, H.; Lindberg, P.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1981**, *24*, 1475.

(15) (a) Hjorth, S.; Carlsson, A.; Clark, D.; Svensson, K.; Wikström, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L.-E.; Johansson, A.; Nilsson, J. L. G. *Psychopharmacology* **1983**, *81*, 89. (b) Wikström, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L.-E.; Johansson, A.; Thorberg, S. O.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Clark, D.; Carlsson, A. *J. Med. Chem.*, in press.

(16) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrel, R. *J. Am. Chem. Soc.* **1963**, 207.

propanol (300 mL) was added sodium sand[7] (17.4 g, 760 mmol) according to the method described by Miller et al.[17] for trans reduction of 2-[3,4-(methylenedioxy)phenyl]cyclobutanone oxime. The reaction mixture was quenched by the addition of 20% HCl, the 2-PrOH was evaporated in vacuo, and the residue was partitioned between H_2O and ether. The aqueous phase was alkalinized with 10% NaOH and extracted several times with ether. The combined ether layers were dried and evaporated in vacuo, whereafter the oily residue was dissolved in ether and treated with ethereal HCl. The precipitated hydrochloride was recrystallized twice from EtOH–ether, affording 1.05 g (22% as calculated from **10**) of pure **9**·HCl, mp 256–257 °C. Anal. ($C_{12}H_{17}NO$·HCl) C, H, N.

Method 2. 5-Methoxy-1-tetralone (**7**; 5 g, 28 mmol) dissolved in 50 mL of dry ether was slowly added at −30 °C to methylmagnesium bromide, which was prepared from methyl iodide (12 g, 85 mmol) and magnesium (2.1 g, 85 mmol) in dry ether (50 mL). The reaction mixture was allowed to reach room temperature and was then refluxed for 30 min. A saturated NH_4Cl solution was added, the organic layer was separated, and the aqueous layer was extracted with two 100-mL portions of ether. The combined ether extracts were passed through a short alumina column and evaporated in vacuo. The residue was distilled in vacuo, affording 1,2-dihydro-4-methyl-8-methoxynaphthalene (**8**), bp 95 °C (0.5 mmHg), yield 2.6 g (54%).

The following hydroboration was performed according to the method described by Rathke et al.[9] To 96% $NaBH_4$ (0.25 g, 6.3 mmol) in diglyme (10 mL) was added a solution of compound **8** (2.6 g, 15 mmol) in diglyme (10 mL). The mixture was cooled to 0 °C, and boron trifluoride etherate (1.2 g, 8.3 mmol) was added. Stirring for 3 h at room temperature, followed by the addition of a solution of hydroxylamine-*O*-sulfonic acid (1.9 g, 17 mmol) in diglyme (15 mL) and subsequent heating at 100 °C for 3 h, completed the reaction. After the mixture was cooled and concentrated HCl (10 mL) was added, the mixture was partitioned between H_2O and ether. The aqueous phase was alkalinized with 10% NaOH and extracted several times with ether. The crude amine resulting from evaporation of the combined and dried (K_2CO_3) ether extracts was precipitated as the hydrochloride and recrystallized from EtOH–ether: yield 0.2 g (7% as calculated from **7**) of pure **9**·HCl, mp 256–257 °C.

***trans*-5-Methoxy-1-methyl-2-(*n*-propylamino)tetralin (11).** Propionyl chloride (1.5 g, 16 mmol) in dry ether (20 mL) was added to a solution of **9** (0.88 g, 4.6 mmol) and triethylamine (1.5 g, 15 mmol) in dry ether (250 mL). After 30 min at room temperature, the reaction mixture was filtered, and the ether was evaporated. The resulting crude amide was passed through an alumina column eluted with ether. The purified amide dissolved in dry THF (20 mL) was added to a suspension of $LiAlH_4$ (1.0 g, 26 mmol) in dry THF (30 mL) under N_2. After stirring under reflux for 3 h, the reaction mixture was hydrolyzed, the precipitate was filtered off, and the solvent was evaporated. The oily residue was chromatographed on an alumina column with ether–light petroleum (1:1) as eluant: yield 0.82 g (76%) of pure **11**. The hydrochloride was precipitated and recrystallized from EtOH–ether: mp 172–174 °C; GC (225 °C) homogeneous, t_R = 1.3 min; ^{1}H NMR (MeOH-d_4) δ 1.00 (t, 3 H), 1.35 (d, 3 H), 1.55–3.73 (m, 10 H) 3.81 (s, 3 H), 6.75–6.87 (m, 2 H), 7.12–7.24 (m, 1 H); MS (70 eV), m/z 233 (60), 204 (50), 175 (64). Anal. ($C_{15}H_{23}NO$·HCl) C, H, N.

***trans*-5-Methoxy-1-methyl-2-(di-*n*-propylamino)tetralin (12).** This compound was prepared from **11** (0.80 g, 3.4 mmol) according to the procedure described above. The amine was converted into the hydrochloride, yielding 0.52 g (40%) of **12**·HCl: mp 130–131 °C (from EtOH–ether); GC (215 °C) homogeneous, t_R = 2.05 min; ^{1}H NMR (MeOH-d_4) δ 0.98 (t, 6 H), 1.38 (d, 3 H), 1.63–3.70 (m, 14 H), 3.82 (s 3 H), 6.75–6.91 (m, 2 H), 7.14–7.25 (m, 1 H); MS (70 eV), m/z 275 (8), 246 (100), 175 (21). Anal. ($C_{18}H_{29}NO$·HCl) C, H, N.

***cis*-5-Methoxy-1-methyl-2-(*n*-propylamino)tetralin (13). Method 1.** To a solution of 5-methoxy-1-methyl-2-tetralone (**10**; 2.0 g, 10.5 mmol) in absolute EtOH (50 mL) were added acetic acid (1.9 g, 31.5 mmol), *n*-propylamine (1.85 g, 31.5 mmol), and 4 Å molecular sieves. The mixture was heated in a closed flask at 80 °C for 1 h. The molecular sieves were removed by filtration, and the solution was hydrogenated (PtO_2) at atmospheric pressure. The catalyst was filtered off (Celite), and the volatiles were evaporated. Dilute HCl (50 mL) was added to the solid residue. The resulting acidic solution was washed with ether, alkalinized with 5% NaOH, and extracted twice with ether. The ether extracts were combined, dried (K_2CO_3), and evaporated. The resulting crude base was eluted through an alumina column with ether–light petroleum (1:4) as eluant, affording an oil of 71% isomeric purity (GC). The hydrochloride was prepared and recrystallized three times from MeOH–ether: yield 500 mg (17%); mp 225–230 °C; GC (225 °C) isomeric purity >95%, t_R = 1.6 min; ^{1}H NMR (MeOH-d_4) δ 1.06 (t, 3 H), 1.24 (d, 3 H), 1.68–3.58 (m, 10 H), 3.80 (s, 3 H), 6.71–6.81 (m, 2 H), 7.07–7.20 (m, 1 H); MS (70 eV), m/z 233 (57), 204 (52), 175 (62). Anal. ($C_{15}H_{23}NO$·HCl) C, H, N.

Method 2. A solution of **10** (10.0 g, 52.6 mmol), *n*-propylamine (6.2 g, 105.4 mmol), and *p*-toluenesulfonic acid monohydrate (25 mg, 0.1 mmol) in 300 mL of dry benzene was refluxed under nitrogen in a Dean–Stark apparatus. After 24 h no more water was formed, and the volatiles were evaporated in vacuo. The residue was quickly dissolved in 100 mL of dry ethanol and hydrogenated at atmospheric pressure with palladium (10%) on activated carbon as catalyst. The catalyst was filtered off (Celite), and the volatiles were evaporated in vacuo. The residue was chromatographed through a short alumina column eluted with ether–light petroleum (1:1). The amine was converted into the hydrochloride, yielding 8.8 g (62%) of **13**·HCl after one recrystallization from MeOH/ether. The crude **13**·HCl had an isomeric purity of 96% (GC).

***cis*-5-Methoxy-1-methyl-2-(di-*n*-propylamino)tetralin (14).** Compound **13** (350 mg, 1.5 mmol) was N-acylated and then reduced according to the procedure described above for the preparation of **11**. The hydrochloride was prepared from the amine and recrystallized from EtOH–ether to give 200 mg (42%) of **14**·HCl: mp 170.5–171.5 °C; GC (215 °C) isomeric purity >95%, t_R = 2.45 min; ^{1}H NMR (MeOH-d_4) δ 1.05 (t, 6 H), 1.32 (d, 3 H), 1.64–3.66 (m, 14 H), 3.80 (s, 3 H), 6.71–6.82 (m, 2 H), 7.10–7.20 (m, 1 H); MS (70 eV), m/z 275 (28), 246 (100), 176 (69). Anal. ($C_{18}H_{29}NO$·HCl) C, H, N.

5-Methoxy-1,1-dimethyl-2-(*n*-propylamino)tetralin (16). The reductive amination of 5-methoxy-1,1-dimethyl-2-tetralone (**15**;[10] 9.2 g, 45 mmol) was accomplished as described above for the preparation of **13** (method 1). The pure base was converted into the hydrochloride and recrystallized from EtOH: yield 6.8 g (53%); mp 270–272 °C. Anal. ($C_{16}H_{25}NO$·HCl) C, H, N.

5-Methoxy-1,1-dimethyl-2-(di-*n*-propylamino)tetralin (17). This compound was prepared from **16** (2.9 g, 9 mmol) according to the procedure described above for the preparation of compound **11**. The pure base was converted into the hydrochloride and recrystallized from EtOH–ether: yield 1.97 g (69%); mp 228–230 °C. Anal. ($C_{19}H_{31}NO$·HCl) C, H, N.

Demethylation of Methoxy Compounds. The phenols were obtained by heating the appropriate methoxy compound in 48% aqueous HBr for 2 h at 120 °C under N_2, and the volatiles were evaporated in vacuo.

***trans*-5-Hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin (3).** The crude **3**·HBr resulting from demethylation of **12**·HCl was purified by TLC using precoated TLC plates (silica gel 60 F_{254}, Merck) eluted with $CHCl_3$–MeOH (9:1): GC (225 °C) homogeneous, t_R = 2.0 min; IR (KBr) ν 3200 (O–H stretch) cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 0.98 (t, 6 H), 1.37 (d, 3 H), 1.60–3.60 (m, 14 H), 6.59–6.77 (m, 2 H) 6.95–7.10 (m, 1 H); MS (70 eV), m/z 261 (37), 232 (100), 161 (91).

***cis*-5-Hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin (4).** The crude **4**·HBr resulting from demethylation of **14**·HCl was purified as described above for **3**·HBr: GC (225 °C) isomeric purity >95%, t_R = 2.3 min; IR (KBr) ν 3136 (OH–H stretch) cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 1.05 (t, 6 H), 1.31 (d, 3 H), 1.50–3.74 (m, 14 H), 6.44–6.69 (m, 2 H), 6.81–7.07 (m, 1 H); MS (70 eV), m/z 261 (36), 232 (100), 161 (82).

Pharmacology. Biochemistry. Animals used in the biochemical and motor activity experiments were male rats of Sprague–Dawley strain (Anticimex, Stockholm), weighing 200–350 g.

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All substances to be tested were dissolved in saline immediately before use. Reserpine was dissolved in a few drops of glacial acetic acid and made up to volume with 5.5% glucose. Injection volumes were 5 or 10 mL/kg, and injection solutions had approximately neutral pH.

The biochemical experiments and the spectrophotometric determinations of Dopa were performed as previously described.[11] Separate dose–response curves based on four to six dose levels for each substance (subcutaneous administration) and brain area were constructed (cf. ref 11). From these curves, the dose of the drug yielding a half-maximal decrease of the Dopa level, the ED_{50} value (presented in Table I), was graphically estimated. In each point of the curves, the SEM was less than 15% of the mean value.

Motor Activity. The motor activity was measured by means of photocell recordings ("M/P 40 Fc Electronic Motility Meter", Motron Products, Stockholm) as previously described.[11]

The rats were treated with reserpine (10 mg/kg ip) and DL-α-methyl-*p*-tyrosine methyl ester hydrochloride (tyrosine hydroxylase inhibitor; 250 mg/kg ip) 6 and 1 h, respectively, prior to the motility testing (carried out between 1 and 6 p.m.). The different compounds under investigation were then administered subcutaneously in the neck region ($n = 4$), in a dose of 1 mg/kg (3000 nmol/kg: compounds **3** and **6**) or 10 mg/kg (30 000 nmol/kg; compound **4**). Controls received isotonic saline.

Immediately after drug administration, the rats were placed in the test cages (one rat per cage) and put into the motility meters. Motor activity was then followed and recorded for the subsequent 60 min. Each box was equipped with a semitransparent mirror that allowed gross behavior observations of the animals during the experiments. The motor activity results are shown in Table I.

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Registry No. **3**, 90295-42-4; **3**·HBr, 90295-43-5; **4**, 90295-44-6; **4**·HBr, 90295-45-7; **5**·HBr, 90295-46-8; **7**, 33892-75-0; **8**, 90295-47-9; **9**, 90295-48-0; **9**·HCl, 90295-49-1; **9** *N*-propionyl deriv., 90295-50-4; **10**, 42263-75-2; **11**, 90295-51-5; **11**·HCl, 90295-52-6; **12**, 90365-41-6; **12**·HCl, 90365-42-7; **13**, 90295-53-7; **13**·HCl, 90295-54-8; **14**, 90365-43-8; **14**·HCl, 90365-44-9; **15**, 4003-87-6; **16**, 90295-55-9; **16**·HCl, 90295-56-0; **17**, 78950-90-0; **17**·HCl, 90295-57-1; 5-methoxy-1-methyl-2-tetralone oxime, 90295-58-2; propionyl chloride, 79-03-8; *n*-propylamine, 107-10-8.

[(Arylcarbonyl)oxy]propanolamines. 1. Novel β-Blockers with Ultrashort Duration of Action

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Novel [(arylcarbonyl)oxy]propanolamines were synthesized and investigated as potential ultrashort-acting β-adrenergic receptor blockers. Many of these analogues exhibited good potency and short duration. The *N*-ureidoalkyl analogue **85** (ACC-9089) has a potency equal to propranolol and a duration of action of about 21 min in the dog. It has been selected as a candidate for further clinical study. Structure–activity relationships and structure–duration relationships for these new β-blockers are also discussed.

In certain clinical situations, drugs with very short biological half-lives may be preferred over their longer acting counterparts. Intravenous infusion of an ultrashort-acting drug into a patient will allow rapid achievement of a steady-state therapeutic effect,[5] a rapid alteration of the desired effect in a dose–titration manner, and a rapid termination of undesirable responses should they occur. An ultrashort-acting drug is also useful for testing the patient response and tolerance to the therapy before using a long-acting compound.

The wide clinical indications of β-adrenergic blocking agents and the dangerous side effect of inducing cardiac failure during surgery[6] or after myocardial infarction[7] suggest a need for an ultrashort-acting β-blocker. A more detailed discussion of the pharmacological rationale for an ultrashort-acting β-blocker has recently been published.[8]

We felt that an ideal ultrashort-acting β-blocker should have the following profile: (1) Duration. The duration of β-blocking activity in patients should last from 10 to 30 min after termination of the infusion of the drug. A duration of action of about 15 min seems to be most desirable. A duration longer than 30 min or shorter than 10 min is less desirable since the former would prevent strict control of activity over an ever-changing situation and the latter would make precise minute to minute control too difficult to achieve. Our approach to try to achieve short duration of action was to incorporate into the skeleton of the β-blocker a "metabolically unstable" ester function that on breakdown in vivo by esterases would lead to products that are devoid of β-blocking activity. Esterases are widely distributed in body fluids and tissues.[9] (2) Toxicity. Due to the fast breakdown of the drug, the compound has to be replenished continuously to maintain a constant drug level in the blood. It is thus obvious that the cumulative

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