carbamoyl chloride (DECC) and in the presence of triethylamine. After 1 h of stirring at 28 °C, the mixture was refluxed for 4 h. Removal of the solvent under reduced pressure gave a solid residue, which was washed with H_2O, dried, and recrystallized.

7-Chloro-4-[α-[*N*-ethyl-*N*-[(4-methyl-1-piperazinyl)carbonyl]amino]-4-hydroxy-*m*-toluidino]quinoline (13a). 10a (1.5 g, 46 mmol), MPCC HCl (1.1 g, 55 mmol), and Et_3N (3 mL) gave the title compound in 91% yield (1.78 g), after recrystallization from EtOH–ether, mp 190–191 °C. Anal. ($C_{24}H_{28}N_5O_2Cl$) C, H, N, Cl.

7-Chloro-4-[α-[*N*-ethyl-*N*-[(4-methyl-1-piperazinyl)carbonyl]amino]-4-methoxy-*m*-toluidino]quinoline (13b). The reaction of 0.48 g (14 mmol) of **10b**, 0.31 g (15 mmol) of MPCC HCl, and 2 mL of Et_3N in $CHCl_3$ gave 0.6 g (91%) of the title compound, after recrystallization from $CHCl_3$–ether, mp 145 °C. Anal. ($C_{25}H_{30}N_5O_2Cl$) C, H, N, Cl.

7-Chloro-4-[α-[*N*-[(4-methyl-1-piperazinyl)carbonyl]amino]-4-hydroxy-*m*-toluidino]quinoline (14a). 11a (0.85 g (28 mmol), MPCC HCl (0.6 g, 31 mmol), and 5 mL of Et_3N were reacted in THF. After recrystallization from $CHCl_3$–ether, 0.6 g (55%) of the title compound was obtained, mp 170–171 °C. Anal. ($C_{22}H_{24}N_5O_2Cl$) C, H, N, Cl.

7-Chloro-4-[α-[*N*-[(4-methyl-1-piperazinyl)carbonyl]amino]-4-methoxy-*m*-toluidino]quinoline (14b). The reaction of 0.78 g (25 mmol) of **11b**, 0.55 g (27.5 mmol) of MPCC HCl, and 4 mL of Et_3N in $CHCl_3$ gave 1 g (95%) of **14b**, after recrystallization from alcohol–ether, mp 197–198 °C. Anal. ($C_{23}H_{26}N_5O_2Cl$) C, H, N, Cl.

7-Chloro-4-[α-[*N*-ethyl-*N*-(diethylcarbamoyl)amino]-4-hydroxy-*m*-toluidino]quinoline (15a). 10a (1.3 g, 40 mmol), DECC (0.6 g, 44 mmol), and Et_3N (3 mL), on reaction in $CHCl_3$, gave the title product in 80% yield (1.3 g, mp 207–208 °C, after recrystallization from MeOH). Anal. ($C_{23}H_{27}N_4O_2Cl$) C, H, N, Cl.

7-Chloro-4-[α-[*N*-ethyl-*N*-(diethylcarbamoyl)amino]-4-methoxy-*m*-toluidino]quinoline (15b). 10b (0.95 g, 28 mmol) was reacted with 0.39 g (31 mmol) of DECC and 3 mL of Et_3N in $CHCl_3$: 1.1 g (90%) of the title compound was obtained, mp 134–135 °C, after recrystallization from $CHCl_3$–ether. Anal. ($C_{24}H_{29}N_4O_2Cl$) C, H, N, Cl.

7-Chloro-4-[α-[*N*-(diethylcarbamoyl)amino]-4-hydroxy-*m*-toluidino]quinoline (16a). The reaction of 0.9 g (30 mmol) of **11a**, 0.44 g (33 mmol) of DECC, and 4 mL of Et_3N in THF gave 0.78 g (65%) of the title compound, mp 225–226 °C, after recrystallization from MeOH. Anal. ($C_{21}H_{24}N_4O_2Cl$) C, H, N, Cl.

7-Chloro-4-[α-[*N*-(diethylcarbamoyl)amino]-4-methoxy-*m*-toluidino]quinoline (16b). 11b (0.77 g, 25 mmol), DECC (0.35 g, 28 mmol), and Et_3N (4 mL) were reacted in $CHCl_3$: 0.86 g (85%) of the title compound was obtained after recrystallization from EtOH–ether, mp 227–228 °C. Anal. ($C_{22}H_{26}N_4O_2Cl$) C, H, N, Cl.

Acknowledgment. This paper is dedicated to the memory of the late Associate Professor P. N. Natarajan who initiated this work but, due to unforeseen circumstances, was unable to see its completion. The authors gratefully acknowledge Professor G. Lämmler and Dr. I. Sänger of the Institute of Parasitology, Justus-Liebig University, Giessen, for carrying out antifilarial studies (in vivo) on the final compounds. Special thanks are also due to Associate Professor Mulkit Singh and Dr. S. L. Leung for their generous assistance in this work. Lastly, M.L.G. thanks the National University of Singapore, Singapore, for awarding her a Research Scholarship award.

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3-Phenylpiperidines. Central Dopamine-Autoreceptor Stimulating Activity

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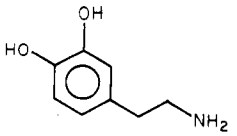
Thirty compounds related to the selective dopamine–autoreceptor agonist 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine have been synthesized and tested for central dopamine–autoreceptor stimulating activity. The 3-(3-hydroxyphenyl)piperidine moiety seems indispensable for high potency and selectivity. Introduction of an additional hydroxyl group into the 4 position of the aromatic ring gives a compound with dopaminergic activity but lacking selectivity for autoreceptors. 3-(3-Hydroxyphenyl)-*N*-*n*-propylpyrrolidine, 3-(3-hydroxy)-*N*-*n*-propylperhydroazepine, and 3-(3-hydroxyphenyl)quinuclidine were all inactive. The most potent compounds were the *N*-isopropyl-, *N*-*n*-butyl-, *N*-*n*-pentyl-, and *N*-phenethyl-substituted 3-(3-hydroxyphenyl)piperidine derivatives. None of the compounds investigated seemed to have central noradrenaline- or serotonin-receptor stimulating activity.

In recent years much interest has been focused on the physiology and pharmacology of the dopamine (DA) autoreceptors.[1,2] In animal experiments, low doses of DA-receptor agonists, for example, apomorphine, have been shown to act preferentially on the autoreceptors, thereby reducing nerve impulse flow, transmitter-synthesis rate, and release in the CNS.[3] Functionally, stimulation of DA autoreceptors results in, among other things, a decrease in locomotor activity and exploratory behavior (cf. ref 4).



DA

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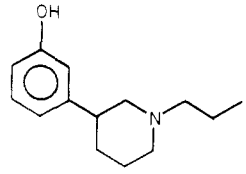
In man, low doses of apomorphine have been reported to alleviate a number of psychotic and dyskinetic conditions.[5] Consequently, it has been suggested that compounds with selective DA-autoreceptor stimulating activity may be of therapeutical value.[1-3]

In our current search for new, selective monoamine-receptor active agents, the synthesis of the DA analogue 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (3-PPP; **21**) was



21

undertaken. When screened in our in vivo biochemical test,[6,7] compound **21** reduced the tyrosine hydroxylation rate in the presynaptic DA neurons of the rat brain, thereby producing the expected effect of a centrally acting DA-receptor agonist. However, compound **21**, in contrast to other DA-receptor agonists (e.g., phenethylamines,[6] 2-aminotetralins,[7] and 2-aminoindans[8]), failed to induce any behavioral stimulation (increased locomotion, stereotypies, etc.) even when given at doses manyfold those having pronounced biochemical effects. Taken together, the results indicated that **21** could be an agent selectively acting on the DA autoreceptors. Further experimental evidence supporting this interpretation has recently been published.[9]

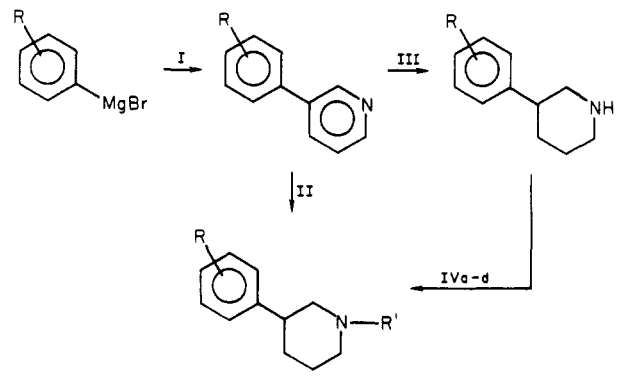
The interesting selectivity of **21** initiated the present investigation of a series of 3-phenylpiperidines and related compounds. Structural variation includes the nitrogen-containing ring and the N substituent, as well as the position and nature of the aromatic substituent(s).

The compounds were tested in rats using biochemical and behavioral methods previously described.[6,7] The compounds synthesized and the biological data obtained are presented in Tables I and II.

Chemistry. Julia et al.[10] have previously reported the synthesis of a number of 3-phenylpiperidines by a route involving addition of the anion of the appropriate phenylacetonitrile derivative to an α,β-unsaturated ester, followed by a reductive ring closure and finally reduction of the resulting lactam.

We chose to use the route depicted in Scheme I because of the greater accessibility of bromobenzene derivatives as compared to their phenylacetonitrile analogues and because of the poor yield in the Michael addition reaction. Thus, the dichlorobis(triphenylphosphine)nickel(II)[11] catalyzed cross coupling of the appropriate arylmagnesium bromide to 3-bromopyridine[12] (pathway I) afforded most

Scheme I[a]



[a] R = H, 3-OCH_3, 4-OCH_3, 3,4-$(OCH_3)_2$, 3-CH_3, 3-F.

of the arylpyridines in Table I in good yields. However, the coupling reaction between 2-methoxyphenylmagnesium bromide and 3-bromopyridine gave **2** in a very low yield. Therefore, 3-(2-methoxyphenyl)piperidine (**32**) was synthesized according to the route of Julia et al.[10] The pyridine nitrogen was quaternized by reaction with an alkyl halide, followed by hydrogenation of the pyridine ring to the piperidine derivatives (pathway II). Nitrogen-unsubstituted arylpiperidines were produced by hydrogenation of the appropriate arylpyridine (pathway III). Most of the N-alkylated phenylpiperidines were prepared from the corresponding secondary amines by one of four different methods: acylation with the appropriate acyl chloride, followed by $LiAlH_4$ reduction of the crude amide (pathway IVa); direct N-alkylation using an alkyl halide (pathway IVb) or a $NaBH_4$–carboxylic acid complex[13] (pathway IVc); enamine formation with cyclohexanone, followed by catalytic hydrogenation (pathway IVd). Finally, demethylation of the methoxy compounds using 48% aqueous HBr afforded the desired phenols.

For the target compounds possessing functional groups not compatible with the reaction conditions employed for synthesis according to Scheme I, some other reaction sequences were designed (Scheme II). Oxidation of 3-(3-methylphenyl)pyridine (**6**) with $KMnO_4$, followed by esterification of the crude amino acid in HCl-saturated methanol, afforded 3-[3-(methoxycarbonyl)phenyl]pyridine (**8**). Catalytic hydrogenation of compound **8** gave 3-[3-(methoxycarbonyl)phenyl]piperidine (**41**). N-Acylation of **41** with propionyl chloride, followed by $LiAlH_4$ reduction of the resulting amide ester, gave 3-[3-(hydroxymethyl)-phenyl]-*N*-*n*-propylpiperidine (**42**). Alternatively, the ester function of the intermediate amide ester was selectively hydrolyzed to give compound **43**. The carboxylic acid function of **43** was then converted to a benzyl carbamate via a modified Curtius rearrangement, followed by reaction of the resulting isocyanate with benzyl alcohol. Hydrogenolysis of the benzylic C–O bond of the carbamate, which was followed by spontaneous formation of an amino function from the carbamic acid formed, and finally reduction of the amide function gave 3-(3-aminophenyl)-*N*-*n*-propylpiperidine (**44**) in low yield. 3-(3-Methoxycarbonyl)-*N*-*n*-propylpiperidine (**45**) was prepared from compound **41** via a direct N-alkylation with a $NaBH_4$–propionic acid complex (Scheme II). Hydrolysis of the ester function of **45** and treatment of the resulting carboxylic acid with thionyl chloride, followed by addition of ammonia, afforded 3-(3-carbamoylphenyl)-*N*-*n*-propyl-

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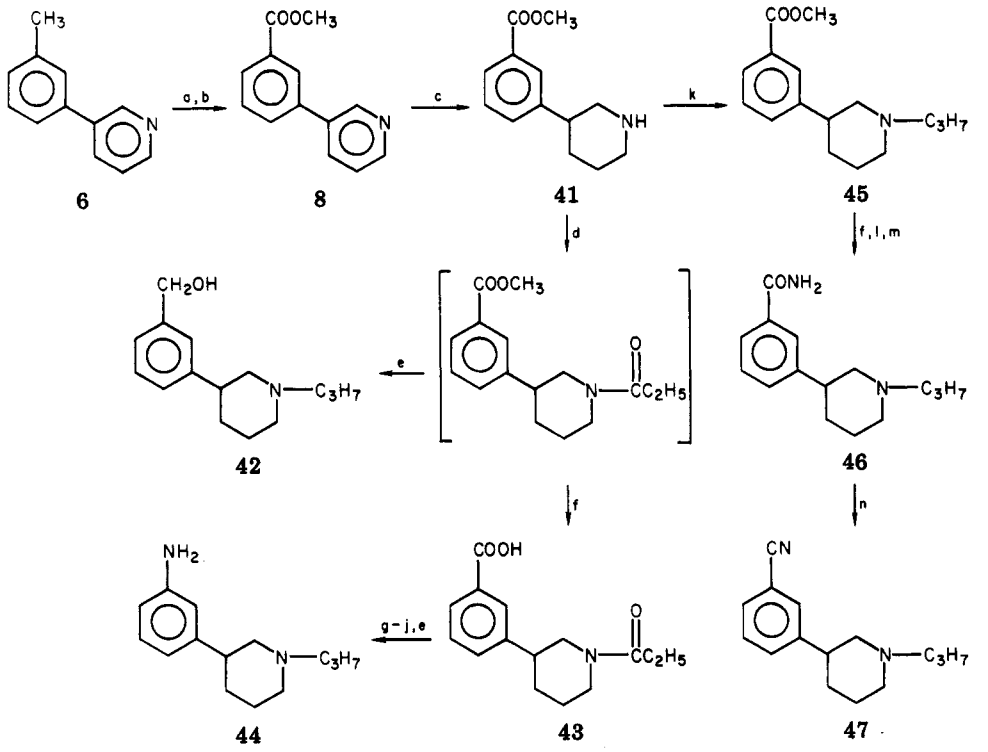
Scheme II[a]



[a] Reagents: a = $KMnO_4$; b = CH_3OH, HCl; c = H_2, PtO_2; d = C_2H_5COCl, $(C_2H_5)_3N$; e = $LiAlH_4$; f = $NaOH/CH_3OH/H_2O$; g = $ClCOOC_2H_5$; h = NaN_3; i = $PhCH_2OH$; j = H_2, Pd/C; k = C_2H_5COOH, $NaBH_4$; l = $SOCl_2$; m = NH_3; n = $POCl_3$, DMF.

piperidine (46). Dehydration of compound 46 with $POCl_3$ gave 3-(3-cyanophenyl)-*N*-*n*-propylpiperidine (47).

The tertiary pyrrolidine derivatives were prepared (methods IVa or IVb; see above) from 3-(3-methoxyphenyl)pyrrolidine (48), the preparation of which is reported elsewhere.[14]

3-(3-Hydroxyphenyl)-*N*-*n*-propylperhydroazepine (58) was obtained by a ring-forming procedure. Alkylation of the anion of 3-methoxyphenylacetonitrile with ethyl 4-iodobutyrate afforded ethyl 5-cyano-5-(3-methoxyphenyl)pentanoate. Reduction of the cyano group to a primary amine by catalytic hydrogenation over Raney Ni, followed by conversion of the carboxylic ester function to the acyl chloride and subsequent ring closure in a boiling triethylamine–toluene mixture, gave 6-(3-methoxyphenyl)perhydroazepin-2-one. Reduction of this lactam with $LiAlH_4$, followed by alkylation of the secondary amine thus formed with a $NaBH_4$–propionic acid complex and finally demethylation in 48% aqueous HBr, yielded the desired compound 58.

Addition of 3-methoxyphenylmagnesium bromide to 3-quinuclidinone gave 3-(3-methoxyphenyl)quinuclidin-3-ol (59), which on treatment with aqueous 48% HBr underwent both dehydration and demethylation to afford 3-(3-hydroxyphenyl)quinuclidin-2-ene (60). Hydrogenation of compound 60 afforded 3-(3-hydroxyphenyl)quinuclidine (61).

Pharmacology. The in vivo biochemical test method utilizes the well-established phenomenon of receptor-mediated feedback inhibition of the presynaptic neuron.[15-17] Thus, the synthesis rate of the catecholamines DA and noradrenaline (NA) is inhibited by agonists activating dopaminergic and α-adrenergic receptors, respectively, and the synthesis rate of 5-hydroxytryptamine (5-HT) is similarly inhibited by 5-HT-receptor agonists. The Dopa accumulation was determined as previously described.[6,7] This accumulation is an indicator of the DA-synthesis rate in the DA-predominated parts (i.e., limbic system and corpus striatum) and the NA-synthesis rate in the NA-dominated remaining hemispheral portions (mainly cortex). The 5-HT accumulation was similarly determined, being an indicator of the 5-HT-synthesis rate in the three brain parts.

Results and Discussion

Previous studies on compounds having pre- as well as postsynaptic DA-receptor stimulating activity demonstrated that at doses giving a half-maximal decrease of the DA-synthesis rate (ED_{50}), no significant postsynaptic DA-receptor activation (stimulation of the motility, stereotypies, etc.) occurred in the reserpinized rat.[7,8] Thus, these ED_{50} values are considered to represent doses eliciting predominantly autoreceptor stimulation.

The ED_{50} values for the present series of compounds are shown in Table I. With only one notable exception, compound 38, none of the compounds produced any significant postsynaptic DA-receptor activation in the reserpinized rat at any dose tested (gross behavioral observations). This suggests a higher autoreceptor selectivity for the present series of dopaminergic compounds as compared to those previously investigated by us.[6-8]

The active compounds have very similar potencies when tested in the limbic system and in striatum. This may indicate that the presynaptic DA receptors in these two

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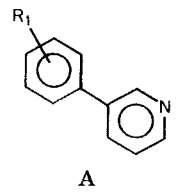
Table I. Physical and Biological Data of the Compounds Studied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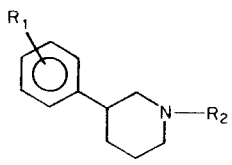
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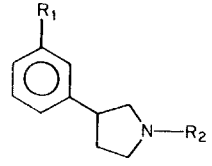
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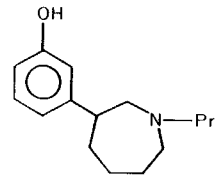
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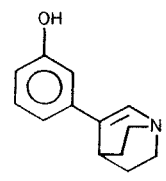
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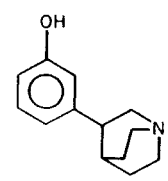
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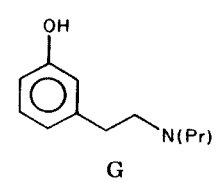
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no.	general structure	R_1	R_2	prepn method	yield, %	bp (mmHg) or mp, °C	recrystn solvents[a]	formula	ED_{50},[b-d] μmol/kg limbic	ED_{50},[b-d] μmol/kg striatum
1	A	H		I	66	85 (0.01)		$C_{11}H_9N$[e]	NT[f]	
2	A	2-OMe		I	3	120–123	A	$C_{12}H_{11}NO\cdot HCl$[g,h]	NT	
3	A	3-OMe		I	73	119–120	B	$C_{12}H_{11}NO\cdot(HOOC)_2$[h]	NT	
4	A	4-OMe		I	32	55–57	*i*	$C_{12}H_{11}NO$[j]	NT	
5	A	3,4-$(OMe)_2$		I	60	209–210	B	$C_{13}H_{13}NO_2\cdot HCl$[h]	NT	
6	A	3-Me		I	75	186–187.5	A	$C_{12}H_{11}N\cdot HCl$[h]	NT	
7	A	3-F		I	34	155–156	A	$C_{11}H_8FN\cdot(HOOC)_2$	NT	
8	A	3-COOMe		*k*	56	208–209	A	$C_{13}H_{11}NO_2\cdot HCl$	NT	
9	A	3-OH		V	47	181–182.5	B	$C_{11}H_9NO\cdot HCl$	I[l]	I[l]
10	B	H	*n*-Pr	III, IVc	30	172–173	B	$C_{14}H_{21}N\cdot HCl$[m]	I	I
11	B	2-OMe	H	*n*	72	173–174	B	$C_{12}H_{17}NO\cdot HCl$[o]	NT	
12	B	2-OMe	*n*-Pr	IVa	84	162–164	A	$C_{15}H_{23}NO\cdot HCl$	NT	
13	B	2-OH	*n*-Pr	V	67	85–90	A	$C_{14}H_{21}NO\cdot HBr\cdot H_2O$	I	I
14	B	3-OMe	H	III	93	137.5–138.5	B	$C_{12}H_{17}NO\cdot HCl$[p]	NT	
15	B	3-OH	H	V	45	166–168	B	$C_{11}H_{15}NO\cdot HBr$	25	25
16	B	3-OMe	Me	II	68	153–154	B	$C_{13}H_{19}NO\cdot HCl$[q]	NT	
17	B	3-OH	Me	V	70	169–170	B	$C_{12}H_{17}NO\cdot HBr$	2.8	2.5
18	B	3-OMe	Et	II	46	149–150	B	$C_{14}H_{21}NO\cdot HCl$[r]	NT	
19	B	3-OH	Et	V	60	158–159	B	$C_{13}H_{19}NO\cdot HBr$	5.7	6.3
20	B	3-OMe	*n*-Pr	II	70	155–156	B	$C_{15}H_{23}NO\cdot HBr$	I	I
21	B	3-OH	*n*-Pr	V	86	146–147.5	C	$C_{14}H_{21}NO\cdot HBr$	3.6	3.6
22	B	3-OMe	*i*-Pr	IVb	80	157–158	C	$C_{15}H_{23}NO\cdot HCl$	NT	
23	B	3-OH	*i*-Pr	V	88	185–186	D	$C_{14}H_{21}NO\cdot HBr$	1.0	0.9
24	B	3-OMe	*n*-Bu	IVa	88	130–131	B	$C_{16}H_{25}NO\cdot HCl$	NT	
25	B	3-OH	*n*-Bu	V	73	123–124	B	$C_{15}H_{23}NO\cdot HBr$	1.1	0.9
26	B	3-OH	*n*-pentyl	IVb, V	28	90–95	B	$C_{16}H_{25}NO\cdot HCl\cdot 0.25H_2O$	1.2	0.9
27	B	3-OH	neopentyl	IVc, V	35	155–156	*i*	$C_{16}H_{25}NO\cdot HCl$	>2.8[s]	>2.8[s]
28	B	3-OMe	cyclohexyl	IVd	44	144–146	B	$C_{18}H_{27}NO\cdot HCl$	NT	
29	B	3-OH	cyclohexyl	V	37	186–188	B	$C_{17}H_{25}NO\cdot HBr$	~45	~45
30	B	3-OMe	CH_2Ph	IVa	79	174–176	B	$C_{19}H_{23}NO\cdot HCl$[t]	NT	
31	B	3-OH	CH_2Ph	V	70	102–105 dec	B	$C_{18}H_{21}NO\cdot HBr$	25[u]	24[u]
32	B	3-OMe	$(CH_2)_2Ph$	IVc	53	180–181	B	$C_{20}H_{25}NO\cdot HCl$[v]	NT	
33	B	3-OH	$(CH_2)_2Ph$	V	42	125–128	*i*	$C_{19}H_{23}NO$[x]	0.2	0.3
34	B	4-OH	*n*-Pr	III, IVa, V	54	179–180	B	$C_{14}H_{21}NO\cdot HBr$	I	I
35	B	3,4-$(OMe)_2$	H	III	91	220–221	B	$C_{13}H_{19}NO_2\cdot HCl$[y]	NT	
36	B	3,4-$(OH)_2$	H	V	70	221–222	B	$C_{11}H_{15}NO_2\cdot HBr$	NT	
37	B	3,4-$(OMe)_2$	*n*-Pr	IVa	77	170–171	B	$C_{16}H_{25}NO_2\cdot HCl$[z]	NT	
38	B	3,4-$(OH)_2$	*n*-Pr	V	85	209.5–210.5	B	$C_{14}H_{21}NO_2\cdot HBr$[aa]	10	13
39	B	3-F	*n*-Pr	III, IVb	23	160–163	B	$C_{14}H_{20}FN\cdot HCl$	I	I
40	B	3-Me	*n*-Pr	III, IVa	47	170–171.5	E	$C_{15}H_{23}N\cdot HCl$	I	I
41	B	3-COOMe	H	III	82	190–192	A	$C_{13}H_{17}NO_2\cdot HCl$	NT	
42	B	3-CH_2OH	*n*-Pr	*k*	76	135–136	B	$C_{15}H_{23}NO\cdot HCl$	I	I

44	B	3-NH_2	*n*-Pr	*k*	4	*bb*	*i*	$C_{14}H_{22}N_2 \cdot 2HCl$[cc]	I	I
45	B	3-COOMe	*n*-Pr	IVc	72	188–189	B	$C_{16}H_{23}NO_2 \cdot HCl$	I	I
46	B	3-$CONH_2$	*n*-Pr	*k*	85	193–194	B	$C_{15}H_{22}N_2O \cdot HCl$	I	I
47	B	3-CN	*n*-Pr	*k*	32	180–181	F	$C_{15}H_{20}N_2 \cdot HCl$	I	I
48	C	3-OMe	H	*dd*	75	92–94 (0.3)		$C_{11}H_{15}NO$[ee]	NT	
49	C	3-OH	H	V	80	112–114	B	$C_{10}H_{13}NO \cdot HBr$[ff]	I	I
50	C	3-OMe	*n*-Pr	IVa	83	85–86 (0.1)		$C_{14}H_{21}NO$	NT	
51	C	3-OH	*n*-Pr	V	80	128–129	B	$C_{13}H_{19}NO \cdot HBr$	~45	~45
52	C	3-OMe	*i*-Pr	IVb	72	125–126	C	$C_{14}H_{21}NO \cdot HCl$	NT	
53	C	3-OH	*i*-Pr	V	93	146–148	C	$C_{13}H_{19}NO \cdot HBr$	I	I
58	D			*k*	3[gg]	148–150	B	$C_{15}H_{23}NO \cdot HCl$	I	I
60	E			*k*	46	208–210	B	$C_{13}H_{15}NO \cdot HBr$	I[hh]	I[hh]
61	F			*k*	47	167–169	B	$C_{13}H_{17}NO \cdot HBr$	I	I
62	G[ii]								0.9	0.8

[a] Recrystallization solvents: A, MeOH–ether; B, EtOH–ether; C, 2-PrOH–ether; D, 2-PrOH–MeOH–ether; E, EtOAc–acetone; F, EtOH–diisopropyl ether. [b] Estimated dose giving a half-maximal decrease of the Dopa level in the rat brain part; maximal reduction of the Dopa level was empirically found to be (for all the compounds tested including 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. [c] No significant effect was obtained in the hemispheral portions. [d] No significant reduction in the 5-HTP accumulation was obtained. [e] Literature[12] bp 130–140 °C (0.2 mmHg). [f] Not tested. [g] Material insufficient for elemental analysis; MS (70 eV), *m/z* 185 (M^+). [h] Reported[21] as part of an isomeric mixture. [i] No recrystallization. [j] Literature[22] mp 64–65. [k] See Experimental Section. [l] Inactive; compounds with an ED_{50} value >45 μmol/kg have been considered inactive. [m] Literature[23] mp 164 °C. [n] Reduction ($LiAlH_4$) of 5-(2-methoxyphenyl)piperidin-2-one according to ref 10. [o] Literature[10] mp 158 °C. [p] Literature[10] mp 138 °C. [q] Literature[10] mp 160 °C. [r] Literature[10] mp 145 °C. [s] The biochemical data did not allow a proper evaluation of the ED_{50} values. [t] Literature[10] mp 173 °C. [u] **31** produced a slight increase of the 5-HTP values in all the three brain areas at doses >10 μmol/kg. [v] Literature[10] mp 178 °C. [x] Literature[10] mp 131 °C. [y] Literature[24] mp 218–220 °C. [z] The base has been reported[18] without physical data. [aa] Literature[18] mp 211 °C. [bb] Could not be crystallized. [cc] Anal. Calcd for $C_{14}H_{22}N_2 \cdot 2HCl$: C, 57.73; H, 8.31; N, 9.62. Found: C, 54.85; H, 8.8; N, 8.45. MS (70 eV), *m/z* 218 (M^+). [dd] Reduction ($LiAlH_4$) of 4-(3-methoxyphenyl)-2-pyrrolidinone according to ref 14. [ee] Literature[14] bp 96–98 °C (0.09 mmHg). [ff] Literature[14] mp 110–112 °C. [gg] Calculated from 3-methoxyphenylacetonitrile. [hh] **60** was inactive at 10 μmol/kg but produced deathly convulsions at 45 μmol/kg. [ii] Previously reported.[6]

Table II. Motor Activity in Reserpinized Rats after Administration of Compounds **21**, **38**, and Apomorphine

treatment	motor act.[a]	ED_{50},[b] μmol/kg sc limbic	striatum
control (0.9% saline)	15 ± 5 (N = 4)		
21 (100 μmol/kg sc)	55 ± 4 (N = 3)	3.6	3.6
38 (100 μmol/kg sc)	522 ± 83 (N = 3)	10	13
apomorphine (2 μmol/kg sc)	624 ± 51 (N = 4)	0.19[c]	0.22[c]

[a] Accumulated counts 0–60 min postinjection. [b] See Table I, footnote *b*; included for comparison. [c] From ref 7.

brain areas are identical or very similar.

The 3-phenylpiperidines may be regarded as phenethylamine congeners. They are conformationally flexible molecules with free rotation around the bond between the rings. However, as seen by inspection of molecular models, small interactions between adjacent hydrogens of the two rings may occur. Assuming a chair conformation of the piperidine ring, the ethylamine moiety should be in an extended trans (anti) conformation, which is the conformation of the ethylamine chain in, for example, the semirigid 2-aminotetralins.

The structurally related compounds 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (**21**) and 3-hydroxy-*N*,*N*-di-*n*-propylphenethylamine (**62**)[6] (included here as a reference) were of the same order of potency in the biochemical test (Table I), both being somewhat more active than their 3,4-dihydroxy analogues (Table I and ref 6). Furthermore, as indicated by the biochemical data, **21** and **62** (as well as the other active compounds) had equal efficacies for the DA autoreceptors. These data may suggest that the DA autoreceptors are similarly affected by the phenethylamine and 3-phenylpiperidine derivatives.

The postsynaptic DA receptors, however, seem to have different structural requirements, since they were activated by the phenethylamine **62**[6] but not by the analogous 3-phenylpiperidine **21**. Thus, it could be speculated that part of the piperidine ring, not included in the phenethylamine derivatives, prevents a proper interaction with the postsynaptic DA receptors. Interestingly, introduction of an additional hydroxyl group into the 4 position of the phenyl moiety, as in **38**, seems to outweigh the effect of the piperidine ring. Compound **38** readily antagonized the reserpine-induced immobility in rats, an effect considered to result from central postsynaptic DA-receptor stimulation. This is in accordance with the demonstration that **38** is capable of reversing reserpine-induced muscle rigidity and, thus, possesses potential antiparkinsonian activity.[18]

The difference in selectivity between 3-hydroxy- and 3,4-dihydroxy-substituted 3-phenylpiperidines is clearly demonstrated when comparing the abilities of **21** and **38** to antagonize reserpine-induced immobility in rats (Table II). At a dose about 30 times the biochemically determined ED_{50} value, the motor activity elicited by **21** differed only slightly from that of controls. In contrast, the locomotor stimulation induced by compound **38** was pronounced at a dose less than 10 times the ED_{50} value. Thus, compound **38** seems to possess a profile, with respect to pre- or postsynaptic receptor stimulation, similar to several other DA-receptor agonists.[7,8]

(18) Nedelec, L.; Guillaume, J.; Dumont, C.; Ger. Offen. 2 621 536, 1976; *Chem. Abstr.* **1976**, *86*, P106398*b*.

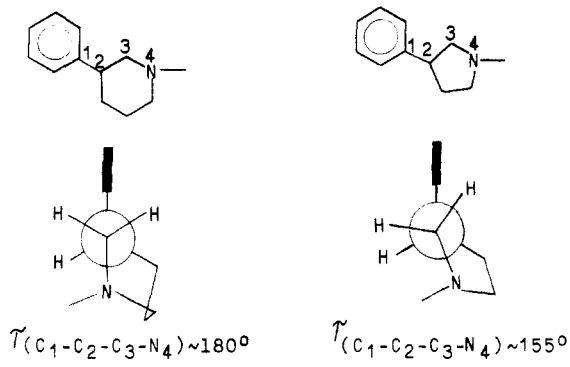

Figure 1. τ values for 3-phenylpiperidines and 3-phenylpyrrolidines demonstrating different orientations of the nitrogens.

Variation of the position of the hydroxyl group on the aromatic ring, giving the 2-hydroxy and 4-hydroxy isomers **13** and **34**, resulted in inactive compounds. A number of compounds with substituents other than hydroxyl in the 3 position of the aromatic ring were also studied. The selection of these substituents was done primarily to obtain a spread in the physicochemical parameters and partly on the basis of their synthetic accessability. All derivatives in the resulting set of compounds were inactive (Table I). Taken together, the results discussed above indicate that monosubstitution with a 3-hydroxy group (or a group convertible in vivo to a 3-hydroxy substituent) is an essential requirement in the 3-phenylpiperidine series to obtain a selective DA-autoreceptor stimulating compound.

The pyrrolidine analogue of compound **21**, 3-(3-hydroxyphenyl)-*N*-*n*-propylpyrrolidine (**51**), was of very weak potency in our tests. In compound **51** the ethylamine chain is part of a five-membered ring, giving a maximal τ value (defined in Figure 1) of about 155°. In contrast, the 3-phenylpiperidines may attain τ values at approximately 180°, which corresponds to the generally preferred conformation for most DA-like substances (see, e.g., Giesecke[19]). The differences in dopaminergic activity between the pyrrolidine (e.g., **51**) and piperidine derivatives (e.g., **21**) may thus be due to the different spatial positions of the nitrogens in relation to the aromatic ring and the hydroxyl group, as reflected by the different τ values for these compounds.

Exchanging the piperidine ring for a perhydroazepine (**58**), quinuclidinene, (**60**) or a quinuclidine ring (**61**) gives inactive compounds. These rings are much bulkier than piperidine and, thus, the inactivity of **58**, **60**, and **61** may not be entirely attributed to unfavorable conformations of their phenethylamine moieties. As expected, 3-(3-hydroxyphenyl)pyridine (**9**) (Table I) showed no dopaminergic activity.

In the present series of compounds, the structure–activity relation for the N substituent seems to be complex. the *N*-isopropyl- (**23**), *N*-*n*-butyl- (**25**), *N*-*n*-pentyl- (**26**), or *N*-phenethyl-substituted derivatives were the most potent compounds (Table I). In contrast to this, it has been shown that one of the N substituents in the 2-amino-5-hydroxytetralin series must be smaller than *n*-butyl and should preferably be an *n*-propyl for high DA-autoreceptor stimulating activity.[7] However, the other N substituent could be varied considerably without significant loss in activity.[7] Consequently, in receptor mapping terms, the N substituent in the 2-aminotetralin series on which less sterical restrictions are imposed may correspond to the N substituent or the 3-phenylpiperidines.

3-(3-Hydroxyphenyl)-*N*-phenethylpiperidine (**33**), which was the most potent of the compounds tested, seemed to differ from the other active derivatives in being more toxic; rats injected with **33** (20 μmol/kg) exhibited severe convulsions, followed by death.

A more detailed pharmacological evaluation is required to assess the precise profile of the new compounds presented here. However, the Dopa level in the hemispheral portions and the 5-HTP level in any one of the three brain areas studied were not decreased by the compounds tested. These results suggest that none of the compounds possesses NA- or 5-HT-receptor stimulating effects at the administered doses.

In conclusion, the present results indicate that the 3-(3-hydroxyphenyl)piperidine moiety is indispensable for high and selective DA-autoreceptor stimulating activity. Contraction of expansion of the piperidine ring to a pyrrolidine or a perhydroazepine ring, respectively, gives inactive compounds. So far, the optimal structure for the N substituent is less defined. However, the *N*-isopropyl, *N*-*n*-butyl, *N*-*n*-pentyl, and *N*-phenethyl derivatives are the most potent compounds of those investigated.

Recently, Goodale et al.[20] reported that 6,7-dihydroxy-2-(dimethylamino)tetralin also seemed to act selectively on DA autoreceptors. Interestingly, this compound and compound **21** have no obvious structural features in common separating them from their less selective analogues. Thus, the enigma of selectivity remains to be further clarified.

Experimental Section

Chemistry. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus; ^{1}H NMR spectra (recorded on a Varian EM-360 spectrometer or on a Perkin-Elmer 157G spectrophotometer) and mass spectra (recorded at 70 eV on a LKB 9000 spectrometer) were in agreement with expected data. The elemental analyses (C, H, and N) for the new substances (Elementaranalystjänst, Chemical Center, Lund, Sweden, or the Microanalytical Laboratory, Agricultural College, Uppsala, Sweden) were within ±0.4% of the theoretical values. For purity tests, TLC was performed on fluorescent silica gel plates developed in at least two different solvents. For all the compounds, only one spot (visualized by UV light and I_2 vapor) was obtained.

3-(3-Methoxyphenyl)pyridine (3). Method I. 3-Methoxyphenylmagnesium bromide, prepared from 3-bromoanisole (131.5 g, 0.70 mol) and Mg (15.5 g, 0.64 mol) in dry THF (600 mL) was added to a solution of 3-bromopyridine (83.8 g, 0.53 mol), dichlorobis(triphenylphosphine)nickel(II)[11] (5.5 g, 0.008 mol), and dry THF (1000 mL). The reaction vessel was immersed in an ice–water bath, and the temperature was kept below 10 °C during the addition. When the addition was complete, the reaction mixture was allowed to reach room temperature and then stirred under N_2 for 24 h. The resulting mixture was poured into ice-cold dilute HCl and extracted with ether. The aqueous layer was neutralized with a saturated K_2CO_3 solution and extracted with ether. Drying (K_2CO_3) and evaporation of the ether afforded **3** as an oil. Distillation in vacuo and chromatography of the fraction boiling from 97 to 105 °C at 0.05 mmHg on a silica column with ether–light petroleum (1:2) as eluant gave pure **3**. The base was precipitated as the oxalate.

3-(3-Methoxyphenyl)piperidine (14). Method II. To a solution of 3-(3-methoxyphenyl)pyridine (**3**; 22.0 g, 99 mmol) in

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(24) Sugimoto, N.; Kugita, H. *J. Pharm. Soc. Jpn.* **1955**, *75*, 183.

MeOH (250 mL) were added PtO_2 (2 g) and concentrated HCl (30 mL). The mixture was hydrogenated at 50 psi in a Parr apparatus. After complete hydrogenation, the catalyst was filtered off (Celite), the solvent was evaporated, and the residue was made alkaline with 1 M NaOH. Extraction with ether, followed by drying (K_2CO_3) and evaporation of the ether, afforded the crude amine, which was precipitated as the hydrochloride. Two recrystallizations gave pure **14**·HCl.

3-(3-Methoxyphenyl)-*N*-*n*-propylpiperidine (20). Method III. 3-(3-Methoxyphenyl)pyridine (**3**; 3.0 g, 16 mmol) and bromopropane (2.0 g, 16 mmol) were dissolved in dry acetone (50 mL) and heated at 110 °C in a high-pressure steel vessel. After 20 h the reaction was interrupted and the solvent was evaporated. The residual quaternary *N*-*n*-propyl-3-(3-methoxyphenyl)-pyridinium bromide was hydrogenated (PtO_2) in MeOH (250 mL) at room temperature and atmospheric pressure. The hydrogen uptake ceased after 24 h. The catalyst was filtered off and the solvent was evaporated. The resulting crude hydrobromide of **20** was recrystallized twice, affording pure **20**·HBr.

***N*-*n*-Butyl-3-(3-methoxyphenyl)piperidine (24). Method VIa.** Butyryl chloride (2.0 g, 19 mmol) in dry toluene (5 mL) was slowly added to a solution of 3-methoxyphenylpiperidine (**14**; 2.45 g, 13 mmol) and triethylamine (1.92 g, 19 mmol) in dry toluene (25 mL) at 5 °C. The mixture was stirred at room temperature for 30 min, whereupon the triethylammonium chloride that formed was filtered off and the solvent was evaporated. The crude *N*-butyryl-3-(3-methoxyphenyl)piperidine (2.82 g), dissolved in dry THF (30 mL), was added to a suspension of $LiAlH_4$ (2.0 g, 53 mmol) in dry THF (30 mL) under N_2. After refluxing for 3 h, the mixture was hydrolyzed, the precipitate was filtered off, and the solvent was evaporated. The residue was chromatographed using an alumina column with ether–light petroleum (1:1) as eluant. The pure product was precipitated as the hydrochloride.

***N*-Isopropyl-3-(3-methoxyphenyl)piperidine (22). Method IVb.** A mixture of 3-(3-methoxyphenyl)piperidine (**14**; 5.0 g, 26 mmol), 2-bromopropane (4.8 g, 39 mmol), K_2CO_3 (7.2 g, 52 mmol), and acetonitrile (50 mL) was refluxed until TLC indicated that no starting material remained (24 h). Ether (50 mL) was added, and the mixture was filtered. Evaporation of the ether layer yielded an oil, which was eluted through an alumina column with ether as eluant. The pure base was converted to its hydrochloride.

***N*-Phenethyl-3-(3-methoxyphenyl)piperidine (32). Method IVc.** $NaBH_4$ (1.9 g, 50 mmol) was added in portions to a solution of phenylacetic acid (22.7 g, 167 mmol) in dry benzene (150 mL). The temperature was kept below 15 °C. After 2 h a solution of 3-(3-methoxyphenyl)piperidine (**14**; 1.9 g, 10 mmol) in dry benzene (100 mL) was added, and the mixture was refluxed for 3 h. The reaction mixture was partitioned between 2 M NaOH (200 mL) and ether (200 mL). The organic layer was dried (K_2CO_3) and evaporated. The resulting oil was purified on an alumina column eluted with ether–light petroleum (1:1). The pure base was converted to its hydrochloride.

***N*-Cyclohexyl-3-(3-methoxyphenyl)piperidine (28). Method IVd.** A mixture of 3-(3-methoxyphenyl)piperidine (**14**; 1.5 g, 8 mmol), cyclohexanone (1.5 g, 15 mmol), and dry toluene (125 mL) was refluxed in a Dean–Stark apparatus for 2 h. The volatiles were evaporated, and the residual enamine was dissolved in MeOH. The enamine was hydrogenated (PtO_2) at 50 psi for 24 h. Filtration, followed by evaporation of the volatiles, gave the crude product as an oil, which was purified on an alumina column eluted with ether. The pure base was precipitated as the hydrochloride.

Demethylation of Methoxy Compounds. Method V. The phenols were obtained by heating the appropriate methoxy compound in aqueous 48% HBr for 2 h at 120 °C under N_2. The hydrobromic acid was evaporated in vacuo, and the residue was recrystallized at least twice.

3-[3-(Methoxycarbonyl)phenyl]pyridine (8). A mixture of 3-(3-methylphenyl)pyridine (**6**; 30 g, 177 mmol) potassium permanganate (67.5 g, 427 mmol), and H_2O (825 mL) was refluxed overnight with stirring. The hot mixture was filtered, acidified (concentrated HCl), and evaporated in vacuo. After drying in the air, the solid was dissolved in HCl-saturated MeOH (2500 mL). The resulting solution was refluxed for 24 h, the MeOH was evaporated, and the residue was made alkaline with a saturated K_2CO_3 solution. Extraction with ether, followed by drying (K_2CO_3) and evaporation of the ether, gave an oil, which was distilled in vacuo. The fraction obtained at 90–135 °C at 0.2 mmHg was chromatographed on a silica column using ether as eluant. Evaporation of the ether gave the pure product as a solid, which was converted into the hydrochloride.

3-[3-(Hydroxymethyl)phenyl]-*N*-*n*-propylpiperidine (42). The HCl salt of 3-[3-(methoxycarbonyl)phenyl]piperidine (**41**; 5.54 g, 22 mmol) was partitioned between a saturated K_2CO_3 solution and ether. To the dried ether layer (K_2CO_3) was added triethylamine (2.23 g, 22 mmol) and propionyl chloride (2.05 g, 22 mmol). Stirring for 1 h, followed by filtration and evaporation of the ether, gave an oil, which was chromatographed twice using an alumina column with ether as eluant. Evaporation of the ether gave 4.8 g of 3-[3-(methoxycarbonyl)phenyl]-*N*-propionylpiperidine as an oil, which could not be crystallized. Part of this amide ester (2.0 g, 7 mmol) was dissolved in dry THF (50 mL) and added to a suspension of $LiAlH_4$ (3.0 g, 79 mmol) in dry THF (50 mL). The mixture was refluxed for 3 h, quenched by the addition of H_2O (3 mL), 15% NaOH (3 mL), and H_2O (9 mL), and filtered. Evaporation of the volatiles gave **42** as an oil. The base was converted to its hydrochloride.

3-(3-Carboxyphenyl)-*N*-propionylpiperidine (43). The amide ester [3-[3-(methoxycarbonyl)phenyl]-*N*-propionylpiperidine] left from the synthesis of compound **42** (2.8 g, 10 mmol) was dissolved in MeOH (40 mL). NaOH pellets (2.5 g, 62 mmol) and H_2O (20 mL) were added. The reaction mixture was stirred until TLC indicated that no starting material remained (4 h). The MeOH was evaporated. The alkaline aqueous layer was washed with ether, acidified with concentrated HCl, and extracted with $CHCl_3$. Evaporation of the dried ($MgSO_4$) solution gave the product (2.1 g, 62% yield from compound **41**) as an oil, which crystallized upon standing, mp 125–126 °C. Anal. ($C_{15}H_{19}NO_3$) C, H, N.

3-(3-Aminophenyl)-*N*-*n*-propylpiperidine (44). Ethyl chloroformate (4.34 g, 40 mmol) was slowly added to a cooled (−10 °C) solution of compound **43** (9.75 g, 36 mmol) and triethylamine (3.56 g, 33 mmol) in acetone (115 mL). After the solution stirred at −10 °C for 1.5 h, a solution of sodium azide (3 g, 46 mmol) in H_2O (10 mL) was added dropwise, and the mixture was stirred at −10 °C for another hour. The reaction mixture was poured into ice–water and extracted with toluene. The toluene extract was dried ($MgSO_4$) and heated until a small sample run on IR indicated that the reaction (the conversion of the acyl azide to the isocyanate) was complete. Evaporation of the toluene gave the isocyanate as an oil. The isocyanate was boiled with benzyl alcohol until no starting material remained (IR; 24 h). Evaporation of the unreacted benzyl alcohol gave an oil (7.5 g), which was chromatographed on an alumina column with ether as eluant. Evaporation of the ether gave 3.0 g of the benzyl carbamate as an oil. This was dissolved in MeOH (100 mL) and hydrogenated (10% Pd/C) at room temperature and atmospheric pressure. Removal of the catalyst and evaporation of the MeOH gave an oily residue, which was passed through an alumina column eluted with ether–MeOH (9:1). Evaporation of the volatiles afforded an oil (1.1 g), which was reduced with $LiAlH_4$ (1.0 g, 26 mmol) in THF. Reflux for 3 h, followed by hydrolysis of the reaction mixture, removal of the precipitate formed, and evaporation of the solvent, gave crude **44**, which was converted to its dihydrochloride by dissolving the base in MeOH and saturating the solution with HCl. Evaporation of the MeOH gave the salt as an oil, which could not be crystallized.

3-(3-Carbamoylphenyl)-*N*-*n*-propylpiperidine (46). A suspension of 3-[3-(methoxycarbonyl)phenyl]-*N*-*n*-propylpiperidine (**45**; 5.0 g, 19.1 mmol) in 10% NaOH solution (150 mL) and MeOH (50 mL) was refluxed until reaction was completed as shown by TLC (1.5 h). The reaction mixture was acidified by 10% HCl and evaporated in vacuo. The solid residue was triturated with MeOH and filtered. Evaporation of the MeOH afforded the crude amino acid hydrochloride as white crystals.

The amino acid hydrochloride was heated in thionyl chloride (10 mL) at 50 °C for 1.5 h. After the addition of more thionyl chloride (5 mL), the heating was continued for 1 h. Evaporation of the excess thionyl chloride gave an oil which crystallized on standing. The solid acyl chloride that formed was dissolved in $CHCl_3$ (100 mL), and NH_3 was slowly bubbled through the solution for 1 h. The reaction mixture was evaporated, and the solid

residue was triturated with CH_2Cl_2 (25 mL). The NH_4Cl was filtered off, and the solvent was evaporated to afford **46**·HCl as slightly yellow crystals.

3-(3-Cyanophenyl)-*N*-*n*-propylpiperidine (47). 3-(3-Carbamoylphenyl-*N*-*n*-propylpiperidine hydrochloride (**46**·HCl; 1 g, 3.5 mmol) was dissolved in DMF (25 mL), and $POCl_3$ (1 mL) was added with stirring. The mixture was heated at 80 °C for 3 h in a N_2 atmosphere. Evaporation of the reaction mixture gave a dark oily residue, which was dissolved in H_2O. The water solution was alkalinized with a saturated Na_2CO_3 solution and extracted several times with CH_2Cl_2. The combined organic layers were evaporated under reduced pressure. The residue was chromatographed on a silica column with MeOH as eluant. Evaporation of the MeOH, addition of ether to the remaining solid, filtration of the insoluble SiO_2, and addition of ethereal HCl to the ether solution afforded **47**·HCl.

3-(3-Hydroxyphenyl)-*N*-*n*-propylperhydroazepine (58). In the following reaction sequence, several intermediates were noncrystalline, but each was homogenous by TLC and was characterized by NMR, IR, and MS.

3-Methoxyphenylacetonitrile (35 g, 238 mmol) in THF (50 mL) was added to a freshly prepared solution of lithium diisopropylamide (238 mmol) in THF (100 mL) under argon. The mixture was kept at −70 °C for 1.5 h, whereafter a solution of ethyl 4-iodobutyrate (58 g, 238 mmol) in THF (50 mL) was added. After another hour at −70 °C, the mixture was allowed to reach room temperature. Addition of 10% HCl (100 mL), followed by separation and evaporation of the organic layer, gave an oily residue, which was partitioned between H_2O and CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), and evaporated, affording an oil, which was distilled in vacuo to yield 39 g (63%) of ethyl 5-cyano-5-(3-methoxyphenyl)pentanoate (**54**), bp 175–185 °C (1 mmHg).

A solution of **54** (10 g, 38.3 mmol) in EtOH (300 mL) was hydrogenated at 50 psi over Raney Ni (15 g) in a Parr apparatus. Removal of the catalyst by filtration, followed by evaporation of the EtOH, gave an oil, which was dissolved in ether and treated with ethereal HCl to yield 7.7 g (67%) of ethyl 5-amino-5-(3-methoxyphenyl)pentanoate (**55**) as the hydrochloride.

A mixture of **55**·HCl (7.0 g, 23.2 mmol) and 20% NaOH (150 mL) was refluxed for 1 h. The reaction mixture was acidified with concentrated HCl and evaporated. The oily residue was taken up in EtOH, the NaCl was filtered off, and the EtOH was evaporated. The amino acid hydrochloride thus obtained was dissolved in CH_2Cl_2 (75 mL), thionyl chloride (10 mL) was added, and the resulting solution was stirred at ambient temperature for 1 h. Evaporation of the volatiles afforded an oily residue, which was dissolved in toluene (30 mL) and triethylamine (10 mL). The solution was refluxed for 48 h, the volatiles were evaporated, and the residue was partitioned between EtOAc and H_2O. The organic layer was dried (Na_2SO_4) and evaporated, affording 4 g of the crude lactam. This was dissolved in THF (40 mL) and added to a suspension of $LiAlH_4$ (1.0 g, 26 mmol) in THF (50 mL) under N_2. After refluxing for 1 h, the reaction mixture was hydrolyzed, the precipitate was filtered off, and the THF was evaporated. The residue oil (2.8 g) was chromatographed on a silica column with MeOH as eluant and 0.8 g (20%) of 3-(3-methoxyphenyl)perhydroazepine (**56**) was obtained as an oil.

N-Alkylation of compound **56** (0.8 g, 4.5 mmol) with $NaBH_4$ (0.76 g, 20 mmol) and propionic acid (4.25 g, 63 mmol) was performed according to the procedure described in method IVc (above). The crude tertiary amine was chromatographed on a silica column with MeOH as eluant. The oily residue was dissolved in ether, filtered, and treated with ethereal HCl to afford 0.7 g (62%) of **57**·HCl as an oil, which could not be crystallized. **57**·HCl (0.7 g) was demethylated in 48% aqueous HBr (20 mL) by heating at 120 °C for 2 h. Evaporation of the HBr in vacuo afforded the crude **58**·HBr. The aminophenol was purified by extractions and was precipitated as the hydrochloride, affording 0.43 g of pure **58**·HCl.

3-(3-Methoxyphenyl)quinuclidin-3-ol (59). A solution of 3-quinuclidinone (12.5 g, 100 mmol) in dry THF was added dropwise to a solution of 3-methoxyphenylmagnesium bromide [prepared from 3-bromoanisole (44.0 g, 240 mmol) and Mg (7.3 g, 300 mmol)] in THF (300 mL) at 0 °C. The reaction mixture was stirred for 24 h at room temperature. Most of the THF was evaporated on a rotary evaporator. To the residue were added, in succession, saturated aqueous solutions of NH_4Cl (100 mL) and $(NH_4)_2HPO_4$ (200 mL). The precipitate that formed was filtered and then triturated with $CHCl_3$ (100 mL). After having been made strongly alkaline by addition of 50% NaOH (50 mL), the filtrate was extracted with $CHCl_3$ (4 × 10 mL). The $CHCl_3$ extracts and the $CHCl_3$ from the trituration were combined, dried (K_2CO_3), and evaporated to dryness to leave a grayish solid product, which after three recrystallizations from EtOH–acetone had a mp of 149–150 °C: yield 7.8 g (33%). Anal. ($C_{14}H_{19}NO_2$) C, H, N.

3-(3-Hydroxyphenyl)quinuclidin-2-ene (60). A solution of **59** (0.5 g, 2.1 mmol) in 48% aqueous HBr (25 mL) was heated at 120 °C under N_2 for 2 h. Evaporation of the HBr in vacuo afforded the crude **60**·HBr, which was recrystallized twice.

3-(3-Hydroxyphenyl)quinuclidine (61). A solution of **60**·HBr (0.46 g, 1.6 mmol) in MeOH (30 mL) was hydrogenated over 5% Pd/C (0.2 g). The catalyst was filtered (Celite), and the MeOH was evaporated. The crude product thus obtained was chromatographed on a silica column eluted with $CHCl_3$–MeOH (9:1), affording pure **61**·HBr.

Pharmacology. Animals used in the biochemical and motor activity experiments were male rats of Sprague–Dawley strain (Anticimex, Stockholm) weighing 200–350 g. All substances to be tested were dissolved in saline immediately before use, occasionally with the addition of a few drops of glacial acetic acid and/or moderate heating in order to obtain complete dissolution. 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 neutral pH.

Biochemistry. The biochemical experiments and the spectrophotometric determinations of Dopa and 5-HTP were performed as previously described.[6,7] Separate dose–response curves based on 4–6 dose levels for each substance (sc administration) and brain area were constructed (cf. ref 8). From these curves the ED_{50} value (Table I), the dose yielding a half-maximal decrease of the Dopa level, was estimated.

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.[6,7] Six hours prior to the motility testing (carried out between 1 and 6 p.m.), the rats were intraperitoneally injected with reserpine (10 mg/kg). The test compounds were administered subcutaneously in the neck region. Immediately after drug administration the rats were placed in the test cages (one rat per cage) and put into the motility meters where motor activity was 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 II.

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