cis- and *trans*-4-*n*-Propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo(*f*)quinolines

JOSEPH G. CANNON*x, CECILIA KOBLE-SUAREZ*, JOHN PAUL LONG‡, MUSTAFA ILHAN‡, AND RANBIR K. BHATNAGAR‡

Received May 4, 1984, from the *Division of Medicinal Chemistry and Natural Products, College of Pharmacy and the ‡Department of Pharmacology, College of Medicine, The University of Iowa, Iowa City, IA 52242. Accepted for publication February 11, 1985.

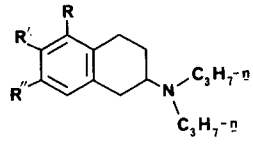
Abstract □ *cis*- and *trans*-4-*n*-Propyloctahydrobenzo(*f*)quinolines **4a,b** were prepared for further assessment of dopaminergic effects of non-oxygenated dopamine congeners. The trans isomer **4b** exhibited marked dopamine-like effects in the cat cardioaccelerator nerve assay and in a rat rotation model. Compound **4b** produced dose-related lowering of blood pressure in the cat. The cis isomer **4a** was inactive in these assays. Both compounds were inactive in a dopamine binding assay, but both appeared active in a spiroperidol binding assay. Both compounds are active α_1- and α_2-adrenoceptor antagonists. Compound **4b** provides evidence that α_2-adrenoceptors and dopamine receptors are different entities, since this compound is an α_2 antagonist and a dopamine receptor agonist at presynaptic sites.

A prior communication[1] described the pronounced activity of *N,N*-di-*n*-propyl-2-aminotetralin (**1**) in inducing emesis in dogs, contralateral circling in unilaterally lesioned rats, and inhibition of prolactin release in rats. These results are consistent with postsynaptic dopamine receptor stimulating activity in the central nervous system, and they seemed remarkable because the molecule **1** lacks phenolic group(s) which have been associated with maximal dopaminergic effects in 2-aminotetralins.[2] In contrast, **1** was extremely weak in a [^{3}H]dopamine binding assay and in a haloperidol binding assay, compared to the catechol congeners **2** and **3**. Compound **1** failed to induce stereotyped behavior following intracerebral administration in rats,[3,4] but it elicited weak stereotyped behavioral responses following subcutaneous injection.[4]

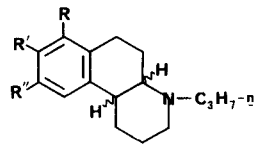
To further assess these findings, members of another non-oxygenated ring system, *cis*- and *trans*-4-*n*-propyloctahydrobenzo(*f*)quinolines **4a,b**, were selected for study. The trans catechol congeners, **5** and **6**, of this ring system have prominent dopaminergic actions.[2] McDermed and co-workers[5] described the preparation of compound **4** and its *N*-ethyl homologue, and assigned cis ring-fusion geometry to the products without experimental evidence. The McDermed group did not report biological data on these compounds. Our group[6] reported that the *N*-methyl homologues of **4a,b** lacked dopaminergic agonist effects in a variety of assays, but that the compounds antagonized apomorphine-induced emesis in dogs. These *N*-methyl compounds potentiated stimulation of the cardioaccelerator nerve in the cat in vitro, but not in vivo.

Bach and co-workers[7] found that compound **7** exhibits no dopamine-like effects in either the prolactin release assay or the rat rotational model. Compound **8**, however, displayed weak dopamine-like actions in these assays. The patent literature[8] reported, inter alia, derivatives of **9** of a *trans*-hexahydronaphth-(1,2-*b*)-1,4-oxazine where R = alkyl and R^1–R^4 = H, and indicated that the (*R,R*)-enantiomers have dopaminergic effects whereas the (*S,S*)-enantiomers have α-adrenoceptor antagonizing action.

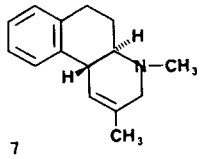
Chemistry—Preparation of **4a–b** followed a sequence utilized previously in these laboratories for oxygen-substituted octahydrobenzo(*f*)quinolines.[9] In the present study, separation of cis and trans ring-fused isomers was effected by HPLC rather than by fractional crystallization, as had been done in earlier studies.[9] Establishment of cis and trans geometry was based on the magnetic nonequivalence of the N—CH_2 protons in the *cis*- and *trans*-*N*-benzyl derivatives.[9] Spectral (IR, NMR) data on all intermediates and final compounds were consistent with the proposed structures.



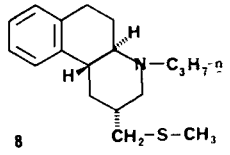
1 R = R′ = R″ = H
2 R = R′ = OH; R″ = H
3 R = H; R′ = R″ = OH



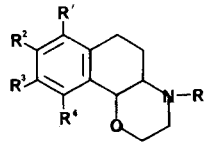
4 R = R′ = R″ = H
a = cis
b = trans
5 R = R′ = OH; R″ = H
6 R = H; R′ = R″ = OH



7



8



9

Results and Discussion

Only compound **4b** inhibited the effects of stimulation of the cardioaccelerator nerve in cats (Table I). The ID_{50}, 1.62 μM/kg, indicated a potency 0.03 (0.007–0.022) times that of apomorphine (ID_{50}: 0.022 μM/kg). The decrease in blood pressure produced by **4b** was dose related, and this effect is typical of dopamine receptor agonists. The cardiovascular effects of **4b** were antagonized by 100 μg/kg iv of haloperidol.

In rats with unilateral denervation of the caudate nucleus, compound **4a** was inactive at doses up to 15 μM/kg, and only **4b** was active in inducing rotations. It was 0.33 (0.17–0.67)

0022-3549/85/0600-0672$01.00/0

Table I—Influence of 4a, 4b, and Apomorphine on the Cardiovascular System of Anesthetized Cats

Compound	Intravenous Dose, μM/kg	Cat Cardioaccelerator Nerve-ID_{50}, μM/kg	Decrease in Arterial Pressure, %	Decrease in Heart Rate, %
4a	1.1	inactive	−6.9 ± 1	−1.8 ± 2.6
	3.8	inactive	−12.4 ± 7	−3.7 ± 0.3
4b	0.28	1.62[a]	−13.8 ± 3	−14 ± 9
	0.84	(1.09–3.22)[b]	−29.6 ± 6.3	−10 ± 1.5
	2.50		−28.7 ± 1.6	−6 ± 2
Apomorphine	0.01	3.48×10^{-2}[a]	−0.05 ± 0.02	−0.05 ± 0.03
	0.033	$(2.7 \times 10^{-2}$–$4.5 \times 10^{-2})$[b]	−21.1 ± 7.7	−5.7 ± 3.1
	0.099	$(2.7 \times 10^{-2}$–$4.5 \times 10^{-2})$[b]	−22.4 ± 4.3	−9.7 ± 4.9

[a] Inhibition of cardioaccelerator nerve stimulation was significantly antagonized by intravenous administration of haloperidol, 100 μg/kg. [b] Confidence limits (95%) of the calculated ID_{50} dose.

times as active as apomorphine as determined by the 3 × 3 parallel-line bioassay of Finney. Apomorphine (1 mg/kg) produced 1053 ± 75 rotations in 1 h. The duration of action of **4b** was approximately the same as that of apomorphine (~1.5 h). The induced rotations were inhibited by pretreatment with 0.5 mg/kg of haloperidol.

Binding assays indicated that **4a** was quite inactive and **4b** had some activity when [^{3}H]dopamine was the radioligand. The IC_{50} values (nM) were as follows: **4a**, 3350 ± 78; **4b**, 411 ± 30; apomorphine, 0.333 (0.071–0.988). Similarly, **4b** appeared to be more active than **4a** when [^{3}H]spiroperidol was used as the radioligand. The IC_{50} values (nM) were as follows: **4a**, 7750 ± 65; **4b**, 2950 ± 27; apomorphine, 794 (180–2900). These values represent the mean from 3–5 experiments with either the 1 SEM or confidence intervals (for apomorphine) as indicated. Although it is apparent that the trans isomer **4b** has a much higher affinity than **4a** for sites that bind [^{3}H]dopamine and [^{3}H]spiroperidol, **4b** is about 4 times less potent than apomorphine in displacing [^{3}H]spiroperidol and about 1000 times less potent than apomorphine in displacing [^{3}H]dopamine from their binding sites in the striatal membrane.

Compounds **4a**, **4b**, and yohimbine were assayed for their ability to antagonize clonidine-induced inhibition of transmurally stimulated rat vas deferens and guinea pig ilea. The pA_2 values are shown in Table II. Compounds **4a** and **4b** are active α_2-adrenoceptor antagonists. The experimental compounds also exhibit α_1-adrenoceptor antagonist activity. The pA_2 values using the isolated rabbit aorta and epinephrine as the α_1-adrenoceptor agonist are as follows: **4a**, 5.96 ± 0.42; **4b**, 6.30 ± 0.11.

Table III illustrates the inhibitory action of the compounds on reflex activation of the sympathetic nervous system (stimulation of the central stump of the sciatic nerve) and the antagonistic action of the compounds **4a** and **4b** when epinephrine was used as the vasopressor agent. The data cited above indicate unusual receptor involvement for **4a** and **4b**. The involvement of dopamine receptors on the cat cardioaccelerator nerve terminal indicates agonist properties for the trans isomer **4b**, as suggested by the antagonist properties of haloperidol (100 μg/kg). In the same dosage, α_1- and α_2-adrenoceptor antagonist properties were observed for both **4a** and **4b**. The compounds were approximately equally effective as antagonists of these two receptors. Since only **4b** was active as an antagonist of the reflex-induced pressor response, interaction at sites other than α_1- and α_2-adrenoceptors must be assumed. Perhaps the **4b** antagonist action is related to dopaminergic action.

It is widely accepted that α_2- and dopamine receptors are not identical entities, at least on a functional basis. However, this conclusion is based largely on the use of data involving antagonists, and possible multireceptor involvement of these antagonists is always a hindrance to drawing conclusions concerning mechanisms of action. Pharmacological effects described for **4b** represent direct experimental evidence supporting the concept that α_2-adrenoceptors and dopamine receptors are distinct and separate entities.

Table II—pA_2 Values Determined for α_2-Receptors Using In Vitro Preparations

Compound	Rat Vas Deferens	Guinea Pig Ilea
4a	6.77 ± 0.10	7.27 ± 0.13
4b	6.77 ± 0.04	7.50 ± 0.11
Yohimbine	7.65 ± 0.04	7.76 ± 0.06

Table III—Inhibition of Vasopressor Responses in the Cat Induced by Central Sciatic Nerve Stimulation and Intravenous Epinephrine

Compound	Dose, μmol/kg	Inhibition of Pressor Responses, %[a]	Inhibition of Vasopressor Responses, %[b]
4a	0.44	3.4 ± 3.4	47.2 ± 18.0
	1.3	19.0 ± 11.6	74.2 ± 9.8
	4.4	14.7 ± 8.4	Reversed
4b	0.15	33.5 ± 13.8	—
	0.44	68.3 ± 9.0	46.0 ± 15.0
	1.3	96.0 ± 1.8	82.7 ± 12.6
	4.4	100	Reversed

[a] Induced by stimulation of the central stump of the sciatic nerve. [b] Induced by intravenous epinephrine.

In summary, **4a** and **4b** exhibit multireceptor involvements. However, only the trans isomer **4b** appears to be an effective dopamine receptor agonist. Both **4a** and **4b** are α_1- and α_2-adrenoceptor antagonists. In addition, **4b** may be a selective agonist for the postsynaptic dopamine receptors in the caudate nucleus of rats.

Experimental Section

Cat Cardioaccelerator Nerve Preparation—This assay was used to determine activity at presynaptic (DA-2) receptors. Cats were anesthetized with pentobarbital sodium (30 mg/kg ip) and were intubated. Respiration was maintained with a Harvard respirator. Systemic arterial pressure was monitored with a Statham P23A pressure transducer from a cannula positioned in the femoral artery. Mean heart rate was obtained from phasic arterial blood pressure pulses with a Beckman type 9857 cardiotachometer. A femoral vein was cannulated for drug administration. After bilateral vagotomy, the right cardioaccelerator nerve trunk was exposed via a midsternal incision. The nerve trunk was placed on a bipolar electrode for stimulation. The nerve trunk was stimulated with a Grass 48 stimulator using the following parameters: 2 Hz, 5-ms pulse duration, 20 V. These parameters produced reproducible chronotropic responses which were sensitive to β-adrenoceptor antagonism. Blood pressure and heart rate were continuously recorded on a Beckman R511A recorder.

To test for potential cardiosympathetic inhibitory activity, agents were administered in a bolus injection at various logarithmic doses. If the cardioinhibitory effect was reversed by haloperidol (0.24 μmol/kg), it was assumed that the inhibitory effect was mediated by a presynaptic dopamine receptor mechanism.

Cat Blood Pressure Responses—Anesthetized cats were prepared as described above, except that no midsternal incisions were made. Intravenous epinephrine (1 or 2 μg/kg) was used to produce vasopressor responses and, after repeated injections, produced stable responses; **4a** or **4b** was administered intravenously. After 5 min, control doses of epinephrine were repeated. Succeeding doses of the experimental compound were increased by 0.48 logarithmic intervals. Five animals were used to assay each compound.

Reflex sympathetic neuronal activation of the cardiovascular system was induced by stimulating the central stump of a sectioned sciatic nerve in five cats. After vasopressor responses became stable, **4a** or **4b** was administered intravenously in cumulative doses varied by 0.48 logarithmic intervals.

Rotational Behavior in Rats—Drug-induced rotation in the contralateral direction is indicative of a direct central dopaminergic receptor postsynaptic agonist. The nigrostriatal pathway in female Sprague–Dawley rats (170–180 g) was unilaterally denervated with 6-hydroxydopamine hydrobromide (8 μg/4 μL of 0.02% ascorbic acid) at an infusion rate of 4 μL/4 min. A stainless-steel 27-gauge cannula was lowered into the nigrostriatal projection at coordinates 4.4 mm posterior from bregma, 1 mm lateral and 7.5 mm vertical from top of the dura with the incisor bar at −2.3 mm. Rotational behavior was assessed with methamphetamine (5 mg/kg) 7 d after surgery and with apomorphine 14 d after surgery. Turning behavior was shown to be dose dependent with apomorphine (0.0625, 0.25, 1.0 mg/kg). Experimental compounds were administered subcutaneously, and the circling responses were recorded automatically and were expressed as turns/0.5 h. The dose–response curves were determined after the responses to apomorphine had become consistent. Six animals were used for each dose of each compound.

pA_2 Values Using Clonidine as the α_2-Adrenoceptor Agonist—pA_2 values for agonist–antagonist interactions were obtained by the method of Arunlakshana and Schild.[10] Results are expressed as mean ± SEM. The paired t test was used to assess the significance of the results and a level of $p < 0.05$ was considered significant.

Dopamine Receptor Binding Studies—[^{3}H]Spiroperidol and [^{3}H]dopamine were used as the radioligands to evaluate interactions with postsynaptic and presynaptic dopamine receptors. Antagonist binding studies were carried out using ^{3}H-spiroperidol on striatal tissue of rat brain according to the method of List and Seeman.[11] Triplicate tubes received 100 μL of varying concentrations of competing drugs, 200 μL of ^{3}H-spiroperidol (final concentrations 2 nM; specific activity, 25.7 Ci/mmol, New England Nuclear Corp., Boston, MA), and 200 μL of tissue suspension (0.2–0.3 mg of protein), all prepared in the incubation buffer. A parallel set of triplicate tubes received 100 μL of incubation buffer instead of the drug, to estimate total binding. Another set of triplicate tubes received 100 μL of 5 μM of d-butaclamol, to yield a final concentration of 1 μM. The samples were incubated at room temperature for 30 min with gentle shaking and 0.4-mL aliquots were filtered under reduced pressure through prewashed Whatman GF/B filters, followed by two 5-mL rinses with incubation buffer. The filters were placed in counting vials, allowed to stand in 10 mL of Aquasol II overnight, and then were counted using a liquid scintillation counter.

The difference between total binding of [^{3}H]spiroperidol and binding in the presence of 1 μM d-butaclamol represented specific binding. IC_{50} values of the competing drugs on radioactive ligand binding were calculated. Similar experiments were repeated at least once on a different day, and the average of at least two IC_{50} values was used for comparison.

Agonist binding studies were carried out using [^{3}H]dopamine as the ligand on the striatal tissue of rat brain as described by Bacopoulos,[12] with some minor modifications. The striata were dissected and stored as described above. The tissue was homogenized with a Teflon pestle in a glass homogenizer in 50 volumes (w/v) of ice-cold 50 nM Tris-HCl buffer pH 7 (room temperature) containing 3 nM of $CaCl_2$, and was incubated at 37°C for 30 min. The binding assays were carried out essentially as described above for antagonist binding, except that the ligand was [^{3}H]dopamine (specific activity, 41.5 Ci/mmol, New England Nuclear Corp.) in a final concentration of 2.5 nM. The k_d of [^{3}H]dopamine binding was 2.5 nM when 10 μM of d-butaclamol was used to determine the specific binding. In the present studies, however, 1 μM d-butaclamol was used for determination of specific binding and the calculation of IC_{50} values of the competing drug as a percent of specific binding.

Chemistry—Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus, and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Where analyses are indicated by the symbols of the elements, analytical results were within ±0.4% of the theoretical values. NMR spectra were recorded on a Varian Associates EM360A spectrometer using tetramethylsilane as the internal standard. Mass spectra were obtained on a Ribermag 10/10 mass spectrometer. Preparative HPLC was done with a Waters 500A Prep HPLC apparatus.

4-Benzyl-1,4,5,6-tetrahydrobenzo(*f*)quinolin-3(2*H*)-one (10)—A mixture of 7.0 g (35 mmol) of 1,4,5,6-tetrahydrobenzo(*f*)quinolin-3(2*H*)-one,[6] 1.1 g (46 mmol) of NaH (1.84 g of 60% mineral oil dispersion), and 200 mL of anhydrous (distilled from $LiAlH_4$) dimethoxyethane was heated under reflux for 3 h. The mixture was cooled to room temperature and 6.6 g (38.6 mmol) of benzyl bromide was added. The resulting mixture was heated under reflux for 2 h, then it was stirred overnight at room temperature. Excess NaH was destroyed by addition of 11 mL of H_2O, and the resulting mixture was evaporated under reduced pressure. The residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was washed twice with H_2O, then with saturated NaCl. It was dried ($MgSO_4$), filtered, and the filtrate was evaporated under reduced pressure to leave a brown oil, for which TLC analysis (SiO_2, EtOAc) showed 3 spots. This material was purified by flash chromatography through a 50 mm i.d. column using 150 g of SiO_2 (35–75 μm) and eluting with 30% EtOAc:70% petroleum ether (bp 37.2–52.5°C). Fractions (50 mL) were collected. Fractions 15–21 contained the product: yield, 5.49 g (54%) of a thick yellow oil. An analytical sample of this material was prepared by preparative TLC (SiO_2, 5% EtOAc in CH_2Cl_2). The purified compound was a thick yellowish oil; MS: m/z 290 (M^+).

Anal.—Calc. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 81.51; H, 6.83; N, 4.84.

This material darkened upon standing at ambient temperature for 24 h, and TLC analysis (SiO_2, 5% EtOAc in CH_2Cl_2) showed 3 spots. The flash-chromatographed material was used immediately in the next step.

***cis*- and *trans*-4-Benzyl-1,2,3,4,4a,5,6,10b-octahydrobenzo(*f*)quinoline Hydrochloride (11 and 12)**—To 4.40 g (15.2 mmol) of **10** in 125 mL of dry benzene was added 18.5 g (5.68 mmol) of a 3.4 M solution of sodium bis-(2-methoxyethoxy)aluminum hydride ("Red-Al") in toluene, and the resulting solution was heated under reflux for 6 h. Excess hydride was destroyed by addition in a dropwise manner of 5.0 mL of H_2O to the cooled solution, and the solid aluminum salts which precipitated were dissolved by addition of 50% KOH. The organic phase was separated, washed three times with H_2O, and dried (Na_2SO_4). Removal of the volatile materials under reduced pressure afforded 3.69 g of a light brown oil which was used at once in the next step.

A mixture of 3.60 g (13.1 mmol) of this oil and 1.5 g (23.8 mmol) of $NaCNBH_3$ in 45 mL of MeCN was stirred at ambient temperature for 16 h. Glacial AcOH was added from time to time to maintain the mixture at approximately pH 6 (pH paper). The mixture was treated with 10 mL of concentrated HCl. Volatile materials were removed under reduced pressure, and the residual paste was taken up in H_2O. This solution was made basic with KOH, and then it was extracted with CH_2Cl_2. This extract was dried (Na_2SO_4) and evaporated to afford 3.62 g of an orange oil. TLC analysis (SiO_2, 30% EtOAc:70% petroleum ether) showed five spots. This material was subjected to preparative HPLC (SiO_2, 5% EtOAc in CH_2Cl_2). Fifteen 500-mL fractions were collected: #1–3 were impurities; #4–6 were subsequently shown to be the cis isomer **11**; #7–14 were a mixture of cis and trans isomers; and the trans isomer **12** was obtained from fraction 15 and by subsequent flushing of the column with 800 mL of EtOAc. Solvents were removed from the eluate fractions under reduced pressure to yield (from #4–6) 1.16 g (32% yield) of the cis product **11**; NMR ($CDCl_3$): δ 1.46–3.33 (m, 12, aliphatic H), 3.87 (s, 2, NCH_2Ar), 7.16 (s, 4, ArH), and 7.43 ppm (s, 5, ArH). The free base **11** was treated with ethereal HCl, and the resulting solid was recrystallized from isopropyl alcohol to give 0.820 g (21% yield) of a white powder; mp 225–227°C. MS: *m/z* 277 (M^+ – HCl).

Anal.—($C_{20}H_{24}ClN$) C, H, N.

From eluate fraction 15 and the EtOAc wash was obtained 0.710 g (20% yield) of trans product **12**; NMR ($CDCl_3$): δ 1.15–3.17 (m, 12, aliphatic H), 3.77 (AB system, J = 14 Hz, $\Delta\nu_{AB}$ = 52 Hz, 2, NCH_2Ar), and 7.06–7.50 ppm (m, 9, ArH). The free base **12** was treated with ethereal HCl and the resulting solid was recrystallized from MeOH:Et_2O to give 0.490 g (12% yield) of white crystals, mp 258–260°C (dec.); MS: *m/z* 277 (M^+ – HCl).

Anal.—($C_{20}H_{24}ClN$) C, H, N.

***cis*-1,2,3,4,4a,5,6,10b-Octohydrobenzo(*f*)quinoline Hydrochloride (13)**—A mixture of 0.650 g (2.07 mmol) of **11** hydrochloride and 0.526 g of 5% Pd/C in 35 mL of MeOH was hydrogenated in a Parr shaker apparatus at an initial pressure of 25 psig for 16 h. The reduction mixture was filtered and the filtrate was evaporated under reduced pressure to leave a white solid residue which was recrystallized from MeOH:Et_2O to afford 0.381 g (82% yield) of white crystals, mp 266–267°C (dec.); MS: *m/z* 187 (M^+ – HCl).

Anal.—($C_{13}H_{18}ClN$) C, H, N.

***trans*-1,2,3,4,4a,5,6,10b-Octahydrobenzo(*f*)quinoline Hydrochloride (14)**—A mixture of 0.394 g (1.26 mmol) of **12** hydrochloride and 0.32 g of 5% Pd/C in 20 mL of MeOH was hydrogenated at an initial pressure of 25 psig for 16 h. The reduction mixture was filtered and the filtrate was evaporated under reduced pressure to leave a white solid residue which was recrystallized from MeOH:Et_2O to afford 0.215 g (76% yield) of a white powder, mp 278–279°C (dec.); MS: *m/z* 187 (M^+ – HCl).

Anal.—($C_{13}H_{18}ClN$) C, H, N.

***cis*-4-*n*-Propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo(*f*)quinoline Hydrochloride (4a)**—The amine alkylation method of Marchini et al.[13] was employed. $NaBH_4$ (1.02 g, 27 mmol) was added in small portions to 6.85 g (92.6 mmol) of propionic acid in 95 mL of dry benzene, maintaining the temperature below 20°C. When H_2 gas evolution ceased, 0.98 g (5.23 mmol) of the free base of **13** in 25 mL of dry benzene was added in one portion, and the resulting mixture was heated under reflux overnight. The cooled mixture was shaken with excess 2 M NaOH. The organic layer was washed three times with H_2O, dried (Na_2SO_4), filtered, and evaporated under reduced pressure to afford 1.14 g (95%) of a light yellow oil. This was treated with ethereal HCl, and the resulting solid was recrystallized from isopropyl alcohol:Et_2O; mp 222–224°C (dec.) [lit.[5] mp 208–209°C (from EtOH:EtOAc)]; MS: *m/z* 229 (M^+ – HCl).

Anal.—($C_{16}H_{24}ClN$) C, H, N.

***trans*-4-*n*-Propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo(*f*)quinoline Hydrochloride (4b)**—The procedure described for **4a** was employed, using 0.76 g (20 mmol) of $NaBH_4$, 4.97 g (67 mmol) of propionic acid, 65 mL of dry benzene, and 0.71 g (3.8 mmol) of the free base of **14** in 20 mL of dry benzene. The HCl salt (0.83 g, 82% yield) was recrystallized from isopropyl alcohol:Et_2O, mp 192–193°C; MS: *m/z* 229 (M^+ – HCl).

Anal.—($C_{16}H_{24}ClN$) C, H, N.

References and Notes

1. Rusterholz, D. B.; Long, J. P.; Flynn, J. R.; Cannon, J. G.; Lee, T.; Pease, J. P.; Clemens, J. A.; Wong, D. T.; Bymaster, F. P. *Eur. J. Pharmacol.* **1979,** *55,* 73–82.
2. Cannon, J. G. *Annu. Rev. Pharmacol. Toxicol.* **1983,** *23,* 103–130.
3. Costall, B.; Naylor, R. J.; Cannon, J. G.; Lee, T. *Eur. J. Pharmacol.* **1977,** *41,* 307–319.
4. Cannon, J. G.; Costall, B.; Laduron, P. M.; Leysen, J. E.; Naylor, R. J. *Biochem. Pharmacol.* **1978,** *27,* 1417–1420.
5. McDermed, J. D.; McKenzie, G. M.; Phillips, A. P. *J. Med. Chem.* **1975,** *18,* 362–367.
6. Cannon, J. G.; Hatheway, G. J.; Long, J. P.; Sharabi, F. M. *J. Med. Chem.* **1976,** *19,* 987–993.
7. Bach, N. J.; Kornfeld, E. C.; Clemens, J. A.; Smalstig, E. B. *J. Med. Chem.* **1980,** *23,* 812–814.
8. Merck and Co., U.S. Patent 4 420 480, **1983;** *Chem. Abstr.* **1984,** *100,* 139126x.
9. Cannon, J. G.; Suarez-Gutierrez, C.; Lee, T.; Long, J. P.; Costall, B.; Fortune, D. H.; Naylor, R. J. *J. Med. Chem.* **1979,** *22,* 341–347.
10. Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol.* **1959,** *14,* 48–58.
11. List, S. J.; Seeman, P. *Proc. Natl. Acad. Sci. USA* **1981,** *78,* 2620–2624.
12. Bacopoulos, N. G. *Biochem. Pharmacol.* **1982,** *31,* 3085–3091.
13. Marchini, P.; Liso, G.; Reho, A.; Liberatore, F.; Moracci, F. M. *J. Org. Chem.* **1975,** *40,* 3453–3456.

Acknowledgments

This work was supported by Grant GM-22365, National Institute of General Medical Sciences.