Resolution and Absolute Configuration of the Potent Dopamine Agonist *N*,*N*-Diethyl-*N'*-[(3α,4aα,10aβ)-1,2,3,4,4a,5,10,10a-octahydro-6-hydroxy-1-propyl-3-benzo[*g*]quinolinyl]sulfamide[1]

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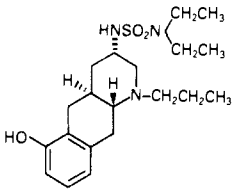
The synthesis and preliminary pharmacological evaluation of the optical antipodes of the title compound (±)-1 (CV 205-502) is presented. The dopaminomimetic activity is shown to reside entirely in the (−) enantiomer. Crystallographic analysis has proven that the absolute configuration of the active (−) enantiomer corresponds to that of its ergoline analogue **3** (CQ 32-084) and of apomorphine (**5**).

In a previous paper[2] we reported the synthesis of two novel dopamine agonists, the racemic octahydrobenzo[*g*]quinolines (±)-1 (CV 205-502) and (±)-2 (205-503). In



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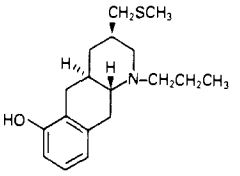

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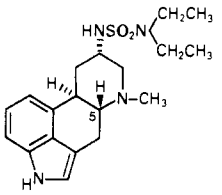
these compounds we combined the important structural features of the ergolines **3** (CQ 32-084) and **4** (pergolide) with those of the specific dopamine agonist apomorphine (**5**).



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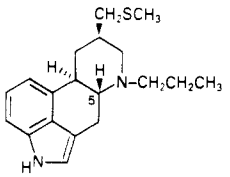

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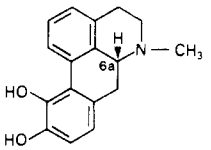

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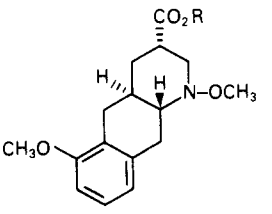
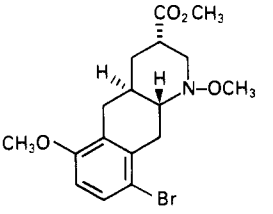
The high potency of (±)-1 and (±)-2 in inhibition of prolactin secretion in rats supported the earlier suggestion[3] that a rigid pyrroleethylamine is the dopaminomimetic pharmacophore of the ergolines. To further strengthen this hypothesis we report here the synthesis and dopaminergic activity of the optical antipodes (+)-1 (206-961) and (−)-1 (206-962) and their absolute configurations.[4]

Initially we failed to resolve the parent compound (±)-1 by fractional crystallization of the dibenzoyl *l*-tartrate, *d*-tartrate or camphorsulfonate-10-*d* salts. Therefore, carboxylic acid (±)-**7**, derived from *tert*-butyl ester (±)-**6**,[2] was resolved with D-(+)-α-methylbenzylamine and L-(−)-α-methylbenzylamine, respectively. The two enantiomeric salts were converted to the free acids, followed by esterification with diazomethane to give (+)-**8** and (-)-**8**. Enantiomeric purity (ee), determined by ^{1}H NMR spectroscopy in comparison to the spectrum of racemic (±)-**8** and on addition of the chiral shift reagent Eu(THFC)$_3$, was found >94% (detection limit) for both enantiomers. Conversion to (±)-1 and (−)-1 followed exactly the reaction sequence developed for the synthesis of racemic (±)-1.[2] The optical antipodes (+)-1 and (−)-1 were evaluated for dopaminomimetic effects in vivo and in vitro in comparison with their racemic counterpart. The results summarized in Table I show that the pharmacological activity of **1** is residing stereoselectively in the (−) enantiomer. Results with the corresponding ergoline **3** and apomorphine (**5**) are shown for comparison.

It remained to determine the absolute configuration of one of the enantiomers. Since the crystals obtained from the α-methylbenzylamine salts of (+)-**7** and (−)-**7** were not suitable for X-ray crystallography, we prepared the brominated derivative (−)-**9** from (−)-**8**. The X-ray crystal structure of (−)-**9**, shown in Figure 1, revealed that the absolute configuration of carbon 10a is *R*, which corresponds to the C5-*R* configuration in the active form of the ergolines and to the C6a-*R* configuration in apomorphine (**5**). In addition, the X-ray structure confirmed the relative configuration derived earlier in the racemic series by ^{1}H NMR spectroscopy.[2] It follows that the active enantiomer (−)-1 has the (3*S*,4a*R*,10a*R*) absolute configuration, which corresponds to the absolute configuration of **3**, therefore providing conclusive evidence that a rigid pyrroleethylamine moiety does indeed represent the dopaminomimetic pharmacophore of the ergolines.



6 R = t-C$_4$H$_9$
7 R = H
8 R = CH$_3$



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Experimental Section

All reactions were followed by TLC carried out on Merck F254 silica gel plates. Solutions were dried over Na_2SO_4 and concentrated on a Buchi rotary evaporator at low pressure (water aspirator). Melting points were determined on a Buchi SMP-20 apparatus and are not corrected. Elemental analyses were within ±0.4% of theoretical values, except where noted. Optical rotations

(1) This paper is dedicated to the memory of Michael I. Goldberg.
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(4) The absolute configuration of all formulas shown corresponds to that of the active (−) enantiomer.

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Table I. Biological Activities[a] of (+)-1 and (−)-1 in Comparison to (±)-1, 3, and Apomorphine (5)

subst	in vivo ID_{50}, μg/kg sc: Basal Prolactin	in vitro IC_{50}, nM					
		SPC[b]	DA[c]	SPFC[d]	5HT[e]	Clon[f]	WB 4101[g]
(+)-1	>3000	>10000	>100000	>10000	>10000	>10000	>10000
(−)-1	1.8	19	75	2300	3200	7400	6000
(±)-1	5	48	190	5100	4600	5600	7800
3	1.4	25	120	26	>5000	480	3300
5	>10000[h]	1350	15	4500	>10000	430	7750

[a] For details, see the Experimental Section. The ID_{50} values for inhibition of basal prolactin are for a time 4 h after injection and were estimated graphically; thus, no confidence intervals are available. In the binding studies, we do not routinely calculate confidence limits of IC_{50}. In those instances where determinations have been repeated at widely separated time intervals, we have found the IC_{50}'s to be reproducible to within a factor of 1.5–2. [b] [^{3}H]Spiperone, calf caudate; dopamine receptors. [c] [^{3}H]Dopamine, calf caudate; dopamine receptors. [d] [^{3}H]Spiperone, rat frontal cortex; serotonin receptors. [e] [^{3}H]Serotonin, whole rat brain; serotonin receptors. [f] [^{3}H]Clonidine, rat brain minus cerebellum; α_2-adrenoceptors. [g] [^{3}H]WB 4101, whole rat brain; α_1-adrenoceptors. [h] Four hours after sc injection, apomorphine has practically no effect on basal secretion of prolactin in male rats. The ID_{50}'s for inhibition of basal prolactin secretion 30 and 60 min after sc injection are 58 and 81 μg/kg, respectively.

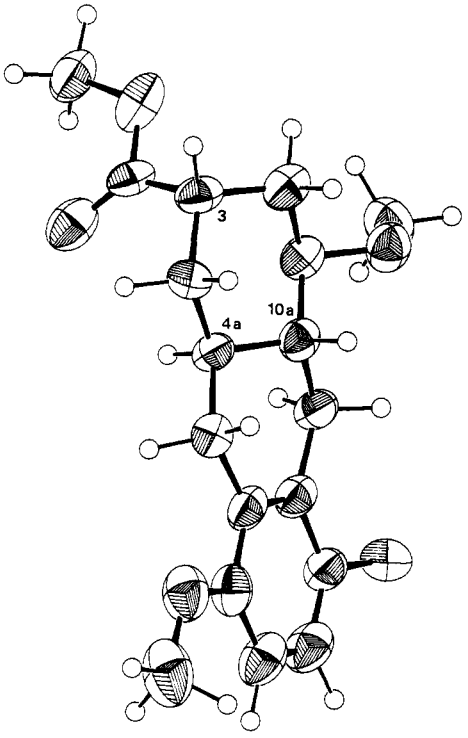

Figure 1. Drawing of (−)-9 (X-ray).

were measured at room temperature on a Perkin-Elmer 241 MC polarimeter. ^{1}H NMR spectra of (+)-1, (−)-1, (±)-7, (+)-8, (−)-8, and (−)-9 were measured on a Bruker Spectrospin 360-MHz (WH-360) or 90-MHz (HX-90) spectrometer using Me_4Si as an internal standard; IR and mass spectra were determined for compounds (±)-7, (+)-1, and (−)-1; all spectral data were consistent with the proposed structures. All other intermediates were identified by TLC by comparison with their racemic counterparts.[2] Abbreviations: Eu(THFC)$_3$, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III).

(±)-(3α,4aα,10aβ)-3-Carboxy-1,2,3,4,4a,5,10,10a-octahydro-1,6-dimethoxybenzo[*g*]quinoline ((±)-7). Compound (±)-3 (15 g, 43.2 mmol; identical with compound **13b** in ref 2) was treated with neat trifluoroacetic acid (150 mL). After 45 min at room temperature the reaction mixture was evaporated, and the residue was reevaporated three times from CH_2Cl_2 to give a brown foam, which was redissolved in CH_2Cl_2 and extracted with 1 N NaOH. The aqueous layer was acidified and reextracted five times with CH_2Cl_2. The organic layers were dried, evaporated, and crystallized from CH_2Cl_2 at −20 °C to yield 11.4 g (90%) of (±)-7; mp 195–196 °C; NMR ($CDCl_3$, 360 MHz) δ 1.43 (td, J = 13, 5 Hz, 1 H), 1.94–2.08 (m, 1 H), 2.15–2.30 (m, 2 H), 2.64 (td, J = 11, 5 Hz, 1 H), 2.76 (dd, J = 10, 3 Hz, 1 H), 2.81 (dd, J = 16, 11 Hz, 1 H), 3.00 (br) and 3.03 (dd, J = 17, 5 Hz, together 2 H), 3.40 (dd, J = 16, 5 Hz, 1 H), 3.69 (s, 3 H), 3.73 (br d, J = 11 Hz, 1 H), 3.80 (s, 3 H), 6.68 (d, J = 8 Hz, 1 H), 6.75 (d, J = 8 Hz, 1 H), 7.12 (t, J = 8 Hz, 1 H); signal of COOH not visible. Anal. ($C_{16}H_{21}NO_4$) C: calcd, 66.0; found, 65.3; H, N, O.[5]

(+)-(3*R*,4a*S*,10a*S*)-3-Carboxy-1,2,3,4,4a,5,10,10a-octahydro-1,6-dimethoxybenzo[*g*]quinoline ((+)-7). To a solution of (±)-4 (22 g, 75.5 mmol) in CH_2Cl_2 was added a solution of L-(−)-α-methylbenzylamine (1.1 equiv) in CH_2Cl_2. The salt was crystallized by addition of Et_2O at −20 °C. The crystals were recovered by filtration and were recrystallized from CH_2Cl_2/Et_2O until melting point was 178–179 °C: $[\alpha]^{20}_D$ (*c* 1, DMF) +70°. The salt was dissolved in CH_2Cl_2 and extracted with 1 N HCl. The organic layer was dried and evaporated to yield 6.1 g (28%) of (+)-7 as the free acid: $[\alpha]^{20}_D$ (*c* 1, DMF) +107°.

(−)-(3*S*,4a*R*,10a*R*)-3-Carboxy-1,2,3,4,4a,5,10,10a-octahydro-1,6-dimethoxybenzo[*g*]quinoline ((−)-7). This was obtained from the combined mother liquors from above after extraction with 1 N HCl by using 1.1 equiv of D-(+)-α-methylbenzylamine. The salt was recrystallized until the melting point was 177–178 °C; $[\alpha]^{20}_D$ (*c* 1, DMF) −68°. The salt was converted to the free acid as above to yield 6.7 g (30%) of (−)-7; $[\alpha]^{20}_D$ (*c* 1, DMF) −107°.

(+)-(3*R*,4a*S*,10a*S*)-1,2,3,4,4a,5,10,10a-Octahydro-1,6-dimethoxy-3-(methoxycarbonyl)benzo[*g*]quinoline ((+)-8). Compound (+)-7 (6 g, 20.5 mmol) in CH_2Cl_2 (50 mL) was esterified by addition of an ethereal solution of diazomethane. The reaction mixture was evaporated and the residue crystallized from CH_2Cl_2/Et_2O/hexane to yield 6.2 g (98%) of (+)-8: mp 133–134 °C; $[\alpha]^{20}_D$ (*c* 1, DMF) 99°. The NMR spectrum exhibited the same resonances as that of the racemic compound,[2] ee > 94% (detection limit), determined with Eu(THFC)$_3$ as the chiral shift reagent.

(−)-(3*S*,4a*R*,10a*R*)-1,2,3,4,4a,5,10,10a-Octahydro-1,6-dimethoxy-3-(methoxycarbonyl)benzo[*g*]quinoline ((−)-8). This was obtaine from (−)-7 (6.5 g, 22.3 mmol) exactly as above: yield 6.6 g (97%) of (−)-8; mp 132–133 °C; $[\alpha]^{20}_D$ (*c* 1, DMF) −98°. The NMR spectrum exhibited the same resonances as that of the racemic compound[2], ee > 94% (detection limit), determined with Eu(THFC)$_3$ as the chiral shift reagent.

(+)-*N*,*N*-Diethyl-*N*′-[(3*R*,4a*S*,10a*S*)-1,2,3,4,4a,5,10,10a-octahydro-6-hydroxy-1-propyl-3-benzo[*g*]quinolinyl]sulfamide ((+)-1) Hydrochloride. Compound (+)-5 (3 g, 9.8 mmol) was converted in six steps[6] to (+)-1 exactly as performed in the racemic series.[2] Compound (+)-1 was crystallized as hydrochloride salt from CH_2Cl_2/Et_2O (overall yield 0.65 g (15%)): mp >245 °C (dec); $[\alpha]^{20}_D$ (*c* 1, DMF) +71°. The NMR spectrum exhibited the same resonances as that of the racemic compound.[2] Anal. ($C_{20}H_{34}N_3O_3SCl$) C: calcd, 55.6; found, 54.4; H, N, O, S; Cl: calcd, 8.2; found, 8.8.[5]

(−)-*N*,*N*-Diethyl-*N*′-[(3*S*,4a*R*,10a*R*)-1,2,3,4,4a,5,10,10a-octahydro-6-hydroxy-1-propyl-3-benzo[*g*]quinolinyl]sulfamide ((−)-1) Hydrochloride. This was obtained as above from (−)-8 (3.2 g, 10.5 mmol). Compound (−)-1 was crystallized as

(5) Despite the deviation in the elemental analysis, the compound was pure according to the ^{1}H NMR spectrum and TLC.

(6) Reaction conditions in these six steps are as follows: (a) Zn, AcOH, H_2O, room temperature; (b) CH_3CH_2CHO, 10% Pd/C, H_2, PrOH, room temperature; (c) $H_2NNH_2 \cdot H_2O$, MeOH, 50 °C; (d) NOCl, THF, −30 °C to reflux, followed by HCl, THF, reflux; (e) Et_2NSO_2Cl, Et_3N, $CHCl_3$, 50 °C; (f) BBr_3, $CHCl_3$, −10 °C.

hydrochloride salt from CH_2Cl_2/Et_2O (overall yield 0.6 g (13%)): mp >245 °C (dec); $[\alpha]^{20}_D$ (c 1, DMF) −72°. The NMR spectrum exhibited the same resonances as that of the racemic compound.[2] Anal. ($C_{20}H_{34}N_3O_3SCl$) C, H, N, O, S, Cl.

(−)-(3*S*,4a*R*,10a*R*)-9-Bromo-1,2,3,4,4a,5,10,10a-octahydro-1,6-dimethoxy-3-(methoxycarbonyl)benzo[*g*]quinoline ((−)-9). A solution of (−)-8 (31 mg, 0.1 mmol) in CH_2Cl_2 (2 mL) was treated with a 0.1 M solution (1.2 mL) of bromine in CH_2Cl_2. After 1 h at room temperature saturated aqueous $NaHSO_3$ was added followed by extraction with 1 N $KHCO_3$. The organic layer was dried and evaporated. The residue was crystallized from diisopropyl ether to yield (−)-9 (20 mg, 52%): mp 129–130 °C; $[\alpha]^{20}_D$ (c 0.2, DMF) −73°; NMR ($CDCl_3$, 360 MHz) δ 1.24 (td, J = 13, 5 Hz, 1 H), 1.85–2.0 (m, 1 H), 2.15 (dd, J = 17, 12 Hz, 1 H), 2.31 (br d, J = 13 Hz, 1 H), 2.43 (td, J = 11, 5 Hz, 1 H), 2.57 (dd, J = 16, 11 Hz, 1 H), 2.66 (dd, J = 11, 3 Hz, 1 H), 2.84 (br s, 1 H), 3.03 (dd, J = 17, 5 Hz, 1 H), 3.46 (dd, J = 16, 5 Hz, 1 H), 3.60 (s, 3 H), 3.73 (s, 3 H), 3.79 (s, 3 H), 3.87 (br d, J = 11 Hz, 1 H), 6.58 (d, J = 8 Hz, 1 H), 7.35 (d, J = 8 Hz, 1 H).

The compound crystallized as thin colorless needles of monoclinic space group symmetry $P1$, unit cell dimensions a = 9.246 (2) Å, b = 9.898 (3) Å, c = 12.749 (3) Å, α = 129.56 (2)°, β = 98.75 (2)°, γ = 95.13 (2)°, V = 862.1 Å^3, Z = 2, d_{calcd} = 1.480 g/cm^3.

Intensity data were collected on an Enraf-Nonius CAD4-F diffractometer by use of monochromatized Cu Kα radiation (λ = 1.5418 Å, μ = 32 cm^{-1}) from a crystal of approximate dimensions 0.1 × 0.1 × 0.5 mm. All accessible symmetry-independent reflections in the range $1.5° \le \theta \le 60°$ were measured in ω–2θ scan mode, variable scan angle $\Delta\omega = [1.0 + 0.14 \tan\theta]°$, variable aperture $A = 3.0 + 0.30 \tan\theta$ mm, scan speed adjusted to obtain a required precision of $\sigma(I)/I$ of 0.02, or a maximum scan time 120 s. A total of 2553 measured reflections yielded 2183 significant [$I > 3\sigma(I)$] diffraction maxima. Data were corrected for Lorentz and polarization effects and put on an absolute scale by Wilson's method,[7] B = 5.40 Å^2.

The structure was solved by direct methods, MULTAN80.[8] A structural model including hydrogens in calculated positions was refined with anisotropic temperature factors for the non-hydrogen atoms, fixed isotropic temperature factors (B = 4.0 Å^2) for the hydrogens, a scale factor, and an isotropic extinction factor (413) parameters). The refinement used a block-diagonal least-squares procedure with weights $w = 1/\sigma^2(F_o)$ (w = 0 for insignificant reflections) and converged to final R values of 0.031 (2183 significant reflections) and 0.52 (all measured reflections). The absolute configuration was determined by the use of the anomalous dispersion effect of the non-hydrogen atoms for Cu Kα radiation. Structure factors for the Bijvoet pairs of reflections were evaluated assuming that the coordinates of the atoms were derived from a right-handed set of axes. The 14 most sensitive pairs of reflections ($\Delta F_c > 4\sigma(F_o)$) were remeasured on the diffractometer with high precision ($\sigma(I)/I < 0.01$). From the good accordance between the signs of F_c and I_o it can be concluded that the refined atomic coordinates correctly represent the absolute configuration of the molecule referred to a right-handed set of axes.

The resulting structure is depicted in Figure 1.

Inhibition of Prolactin Secretion in Male Rats. Adult rats (SIV 50) were used. One day before the experiment, the animals were put into individual cages and kept, as before, in a room with controlled environment (light from 4 a.m. to 6 p.m.). The rats were injected once subcutaneously with test compound, returned to their cages, and decapitated 4 h after treatment. Blood was collected from the trunk and the serum pipetted off after coagulation. One to three groups of three rats per dose were used. For estimation of prolactin levels, the sera of three rats were pooled in equal parts and the concentration was determined by means of an RIA double-antibody method. The concentrations obtained in ng/mL are expressed in terms of the NIH standard rat Prl RP-1, and the dose needed for 50% reduction of serum prolactin levels was estimated graphically.

Binding Studies. Displacement studies were carried out on various brain homogenates as previously described. Typically four to six different concentrations of test compound were incubated in triplicate, and the IC_{50} value, expressed in nM, was determined by appropriately weighted regression analysis. The ligands were as follows: for dopamine receptors, [^{3}H]spiperone[9] and [^{3}H]dopamine,[10] both in calf caudate; for serotonin receptors, [^{3}H]spiperone in rat frontal cortex[11] and [^{3}H]serotonin in whole rat brain;[12] and for α-adrenoceptors,[13] [^{3}H]clonidine in rat brain minus cerebellum and [^{3}H]WB4101 in whole rat brain.

Acknowledgment. We thank M. Kaiser for his capable technical assistance in the synthetic work. We appreciate the valuable help of H. R. Loosli, M. Ponelle, and T. Zardin (NMR spectra); W. Pfirter (analysis); C. Quiqerez (mass spectra); and L. Thielemann (IR spectra). We are further grateful to our colleague U. Briner for pharmacological testing and to Drs. W. Frick and A. Closse for performing the binding studies.

Registry No. (+)-1·HCL, 97805-49-7; (−)-1·HCL, 97805-50-0; (±)-3, 97805-44-2; (±)-7, 87056-73-3; (+)-7, 97805-45-3; (−)-7, 97805-46-4; (+)-8, 97805-47-5; (−)-8, 97805-48-6; (−)-9, 97732-35-9.

Supplementary Material Available: Listings of atomic coordinates of the heavier atoms, with estimated standard deviations and equivalent isotropic B's (Table II), atomic coordinates of the hydrogen atoms (Table III), anisotropic thermal parameters and esd's of the heavier atoms (Table IV), bond distances with esd's (Table V), bond angles with esd's (Table VI), results from Bijvoet pair measurements (Table VII), and observed and calculated structure factors (Table VIII) and X-ray numbering diagrams pertaining to the X-ray structure determination (Figures 2 and 3) (23 pages). Ordering information is given on any current masthead page.

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