trans-Hexahydroindolo[4,3-*ab*]phenanthridines ("Benzergolines"), the First Structural Class of Potent and Selective Dopamine D_1 Receptor Agonists Lacking a Catechol Group

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In contrast to the many selective dopamine (DA) D_2 receptor agonists known, only two prototypes of selective D_1 receptor agonists have been described; both show preference for the periphery due to their catechol partial structures. Our search for non-catechol, selective D_1 agonists was based on the hypothesis that D_1 selectivity could be conferred upon ergolines by annulation with a phenyl ring. The target molecules, *trans*-4,6,6a,7,8,12b-hexahydroindolo-[4,3-*ab*]phenanthridines ("benzergolines"), were efficiently synthesized by using the Ninomiya enamide photocyclization reaction. These compounds were found to be as active as the most potent D_1 agonists in the adenylate cyclase D_1 receptor model, but showed no activity in the ACh release D_2 receptor assay. The acquired subtype selectivity of the novel structures was accompanied by an enhanced potency and efficacy as compared to the corresponding ergolines. This points to a D_1 affinity enhancing, D_2 receptor discriminating role for the additional phenyl group and provides further support for the existence of a D_1 receptor specific accessory aryl binding site. Thus the benzergolines represent the first structural class of potent and selective D_1 agonists lacking a catechol group which should allow an efficient central nervous system penetration. On the basis of these results, the D_1 agonist pharmacophore has to be revised in the sense that potent activity requires neither a catechol function nor an orthogonal conformation of the aromatic rings.

The discovery of two dopamine (DA) receptor subtypes, D_1 and D_2, with different anatomical locations and functional roles,[1,2] and their possible involvement in various physiological and pathophysiological states has stimulated the search for subtype-selective agonists and antagonists. The introduction of bromocriptine[3] for several endocrine indications as well as for Parkinson's disease, more than a decade ago, marked the availability of a selective D_2 agonist for clinical practice. Since then, several other selective D_2 receptor stimulating drugs have entered clinical trials. However, in the field of selective D_1 agonists,[4] the only clinical data obtained so far originates from the experimental drug fenoldopam (SKF 82526,[7] **3**; X = Cl, Y = OH), which is selective for the periphery. In our search for selective D_1 agonists,[8-10] we were looking for new structural types which might possibly also reach the central nervous system (CNS).

Considerable efforts have already been devoted to investigations on structure-activity relationships (SAR) of DA agonists. They reveal that the structural requirements for activation of the D_1 receptor are much more stringent than those for the D_2 subtype. So far, only two structural classes have been found with selectivity for the D_1 receptor, benzazepines of the type SKF 38393[11] (**3**; X, Y = H), and 3',4'-dihydroxynomifensine (**4**; Y = NH_2, R = Me) and its derivatives.[12-15] Both types of structures contain, besides a catechol group, an additional phenyl ring. This aromatic group appears to be responsible for the induction of D_1 selectivity as well as for an increase in affinity/potency at the D_1 site.[16,17] In order to rationalize its contribution to receptor affinity, an interaction with an accessory binding site has been postulated.[19] The exact position of the phenyl group in the molecule seems to be critical. For example in apomorphine (**1**), which shows no subtype preference, the annulated phenyl ring is obviously unable to reach the postulated aryl binding site.

The structures of both types of selective D_1 agonists, **3** and **4**, contain a catechol group. It imparts high activity but is also responsible for the low oral bioavailability of the compounds, for their sensitivity toward oxidation, and for their inability to penetrate efficiently the CNS. Therefore, we were aiming at molecules selective for the D_1 receptor, lacking a catechol function. Ergolines **2** belong to the few potent non-catechol DA agonists. They contain an indole group instead of a hydroxylated phenyl ring but

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(16) Unsubstituted 7,8-dihydroxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine is more potent at the D_2 than at the D_1 receptor; its EC_{50} in the DA-sensitive adenylate cyclase D_1 model is more than 2 orders of magnitude smaller than that of SKF 38393.[11]
(17) 3-(3',4'-dihydroxyphenyl)-1-methylpiperidine,[18] which corresponds to 3',4'-dihydroxynomifensine without an annulated aniline ring, proved to be unselective in our tests systems; D_1, pD_2 = 5.0 (47% maximal stimulation); D_2, pD_2 = 7.5 (92% maximal inhibition).
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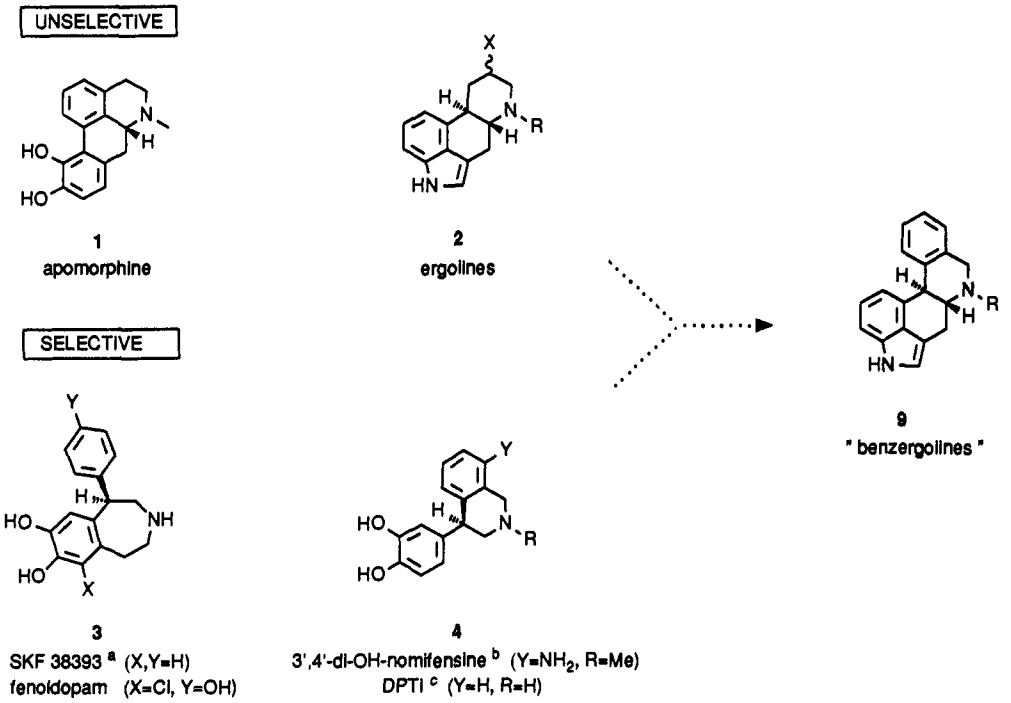
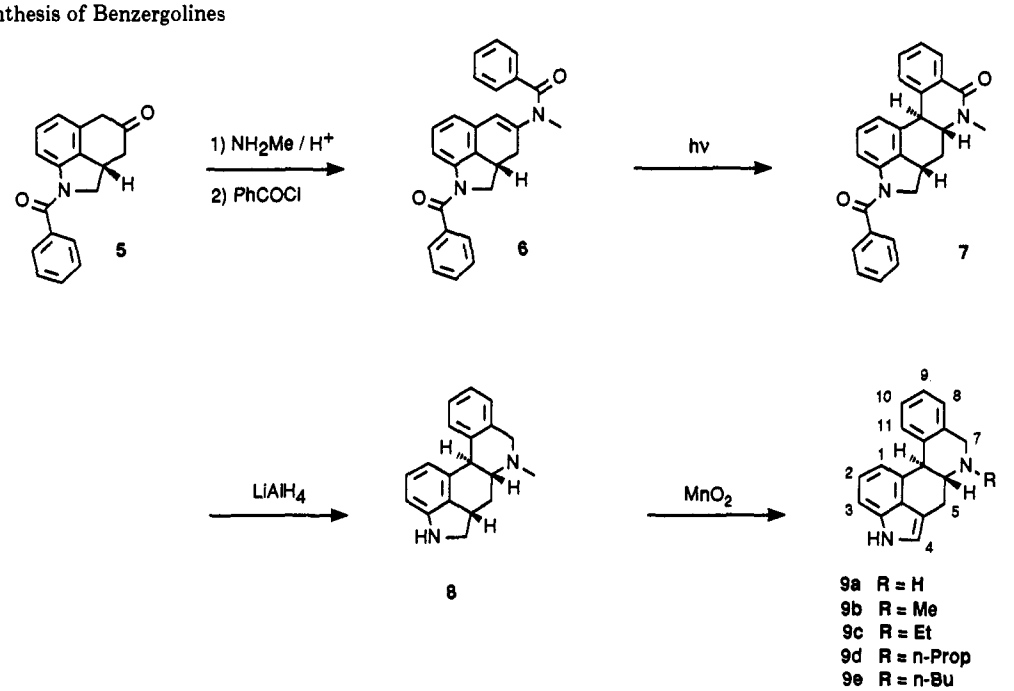
Scheme I. D_1 Receptor Activating Compounds



[a] Absolute configuration of active enantiomer shown.[19] [b] Absolute configuration of active enantiomer shown.[14] [c] 4-(3',4'-Dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline.

Scheme II. Synthesis of Benzergolines



are nevertheless able to stimulate D_1 as well as D_2 receptors.[20] Attempts to achieve D_1 selectivity by modification of the substituent in the 8-position (**2**, X) were unsuccessful.[21] The piperidine ring of the ergolines, according to a concept based on our DA receptor model,[10] should correspond to the piperidine ring of 3,4'-dihydroxynomifensine or its simpler, more active derivative 4-(3',4'-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline (DPTI, **4**; Y = H, R = H). Since, in the case of DPTI, the molecule acquired D_1 selectivity following fusion of a phenyl group to the piperidine ring,[17] it was intriguing to test whether a similar variation in the ergoline series would also induce D_1 selectivity (Scheme I). The structures thus envisaged were *trans*-4,6,6a,7,8,12b-hexahydroindolo[4,3-*ab*]-phenanthridines ("benzergolines", **9**). Here we describe the synthesis and pharmacological evaluation of some representative members of this hitherto unknown chemical class of compounds. For the assessment of the biological activities we used two functional in vitro assays, stimulation of DA-sensitive adenylate cyclase as a model to measure D_1 receptor activation and inhibition of electri-

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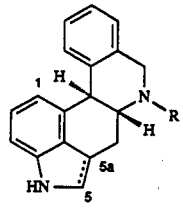
Table I. Biological Data



no.[a]	5,5a-double bond	R	adenylate cyclase[b] potency pD_2	adenylate cyclase[b] max stimltn,[c] % rel to DA	ACH release[b] potency pD_2	ACH release[b] max inhibn,[d] % of control
8	-	Me		0		0
9a	+	H	6.3	82		0
9b	+	Me	6.1	57		0
9c	+	Et	6.0	72		0
9d	+	*n*-Pr	5.7	55		0
9e	+	*n*-Bu		0		0
reference compounds						
apomorphine (1)			6.2	38	7.5	85
6-methylergoline (2; X = H, R = Me)			5.2	24	7.5	30
SKF 38393[a] (3; X, Y = H)			6.6	58		0
DPTI[a,e] (4; Y = H, R = H)			6.0	86		0

[a] Racemic compounds. [b] Mean values of two to three independent experiments performed in triplicate (SE < 10%). [c] Percent of maximal effect of 125 μM DA. [d] Change of S_2/S_1 versus control at 1 μM. [e] DPTI = 4-(3′,4′-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline.

cally evoked acetylcholine (ACh) release as a model for D_2 receptor activation.

Chemistry

N-protected 5-keto-1,2,2a,3,4,5-hexahydrobenz[*c*,*d*]-indoles and their 4-keto derivatives, e.g. **5** (Scheme II), represent convenient and readily accessible intermediates for the synthesis of compounds containing the ergoline skeleton.[22] Conversion to the pentacyclic indolo[4,3-*ab*]phenanthridine ring system was efficiently accomplished in two steps by using the Ninomiya enamide photocyclization,[23] which was first described with a *N*-benzoylenamine of β-tetralone leading exclusively to a trans-fused product.[24] Thus racemic **5** was treated with methylamine under acidic conditions to yield the corresponding crude enamine, which, without further purification, was benzoylated with benzoyl chloride to afford enamide **6**. Upon irradiation in acetone, **6** underwent facile, stereospecific cyclization to the photoproduct **7**, the only compound isolated. Assignment of the relative stereochemistry at the C/D ring junction was based on ^{1}H NMR data. The large coupling constant of 10 Hz between H-C(12b) and H-C(6a) strongly suggested the presence of a trans ring fusion. In addition, a diaxial relationship between H-C(5a) and H-C(6a) was indicated by the quartet of H-C(6_{ax}) with a large coupling constant of 12 Hz reflecting two diaxial and one geminal coupling.

Treatment of **7** with lithium aluminum hydride reduced the amide bond in ring D and cleaved the *N*-benzoyl protecting group to yield **8**, which was then oxidized with manganese dioxide to give the target compound **9b**, the structure of which was confirmed by ^{1}H NMR. A coupling constant of 9.5 Hz between H-C(12b) and H-C(6a) again indicated a trans ring junction. This stereochemistry was further confirmed by an NOE between H-C(6a) and H-C(8_{ax}), which, based on inspection of Dreiding models, should only be possible in the trans-fused but not in the cis-fused series. Demethylation of **9b** was achieved by treatment with cyanogen bromide followed by reduction with zinc in acetic acid[25] to give **9a**, which was alkylated with alkyl halides to afford **9c–e**.

Results and Discussion

There were two major concerns regarding our structure hypothesis. The first dealt with the large size and rigidity of the pentacyclic ring system, which could already be critical for a receptor interaction. The second concerned the spatial orientation of the phenyl group, essential for D_1 selectivity, which can freely rotate in SKF 38393 as well as in DPTI (as part of the tetrahydroisoquinoline nucleus) allowing a series of possible conformations. Of these conformations an almost coplanar arrangement of the aromatic rings, like that of the benzergolines, would energetically seem rather unlikely. On the contrary, an orthogonal conformation of the aryl rings was suggested for the interaction with the D_1 receptor,[14] based on the X-ray data of the biologically active enantiomers of SKF 38939[19] and 3′,4′-dihydroxynomifensine.[14]

The biological results obtained with the benzergolines (Table I) proved these concerns to be unjustified. The N-unsubstituted compound **9a** showed D_1 receptor stimulating effects in the adenylate cyclase assay with a potency in the range of that of apomorphine and the two selective D_1 agonists SKF 38393 and DPTI and an efficacy similar to that of DPTI and superior to that of the partial agonists apomorphine and SKF 38393. However, in contrast to apomorphine, **9a** was found to be inactive in the ACh release assay reflecting D_2 activity and can thus be considered as a novel, highly potent and selective D_1 agonist. A comparison of the effects of the N-methylated compound **9b** (racemic) with those of the enantiomerically pure 6-methylergoline (**2**; X = H, R = Me) reveals that the additional phenyl ring has not only induced D_1 selectivity but has also increased the potency 10-fold at the D_1 site, while the efficacy has more than doubled. This

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parallels similar activity and selectivity changes in the benzazepine and DPTI series already discussed and demonstrates that the additional phenyl group exerts a D_1 affinity enhancing, D_2 receptor discriminating role. In addition, it gives further support to the existence of a D_1 receptor specific accessory aryl binding site.

We assume that the indole partial structure in the benzergolines substitutes for the catechol group of the selective D_1 agonists. The inactivity of both the corresponding indoline derivative 8 as well as of benzergolines methylated at the indole nitrogen[26] suggests that the acidic indole proton and the π-electron system of the indole nucleus are responsible for the observed bioisosterism.

The influence of N-alkyl substitution on dopaminergic activity represents an important indicator for the mode of receptor interaction.[8,9,27,10] With respect to D_1 agonist activity, two different patterns have been observed (DA-sensitive adenylate cyclase data). A decrease in potency and efficacy with increasing size of the N-substituent has been found with SKF 38393 and its derivatives,[11] with compounds of the DPTI series,[15] and with β-rotameric aminotetralins.[8] In contrast, an increase in efficacy following a similar structural variation has been observed in the α-rotameric aminotetralin series (potency increase),[8] in the octahydrobenz[g]quinoline series (potency decrease),[10] between apomorphine and *N*-*n*-propylnorapomorphine (potency decrease),[28] between bromocriptine (D_1 antagonist) and 6-ethylnorbromocriptine[30] (D_1 agonist), and between 6-methylergoline and 6-*n*-propylergoline (similar potency).[29] We have investigated corresponding SAR in the benzergoline series. The results show that following an increase in the size of the N(7)-substituent, the efficacy is maintained; equal maximal effects were found for the *N*-methyl and the *N*-*n*-propyl derivatives, whereas the NH and the *N*-ethyl compounds exerted slightly higher efficacy. However, further extension of the *N*-alkyl group to *n*-butyl resulted in a complete loss of activity. The potency, on the other hand, showed a steady decrease with increasing size of the N-substituent. This SAR is clearly different from that found with the benzazepine and DPTI derivatives and resembles more the pattern observed in the apomorphine and octahydrobenz[g]quinoline series, suggesting that an efficient receptor interaction is maintained up to *N*-*n*-propyl substitution. DA agonists N-alkylated with ethyl or *n*-propyl groups usually show high D_2 affinities. However, in the benzergoline series, even such N-substitution did not provoke any D_2 activity, as assessed by the ACh release model. These findings establish that with these compounds a new prototype of a selective D_1 agonist has been identified. Conceptionally derived from the ergolines, the benzergolines represent the first structural class of potent and selective D_1 agonists lacking a catechol group. In contrast to their catechol-type forerunners, they should thus meet the prerequisites for an efficient CNS penetration.

What are the implications of these results? The benzergolines, due to their rigidity and size, are excellent tools to obtain further information concerning the dimensions of the DA receptor sites. Their highly effective interaction at the D_1 site points to ample space available at this receptor subtype. On the other hand, most probably due to the bulk of the additional phenyl ring, they are no longer tolerated by the D_2 receptor. The D_1 selectivity thus appears to result, at least partially, from differences in "docking space". Other implications concern the D_1 agonist pharmacophore. As already discussed, previous data pointed to an almost orthogonal orientation of the crucial phenyl group of D_1 agonists with respect to the plane of the catechol ring. However, high activities were found with the relatively flat benzergolines having almost coplanar aromatic rings. This clearly demands a revision of the postulate[14] that an orthogonal conformation is favored for D_1 receptor stimulation. One might speculate that due to the flexibility of the protein structure of the receptor, several conformations are tolerated within certain limits. Another pharmacophore concept has likewise become obsolete by the new results. With the benzergolines it has clearly been demonstrated that high D_1 agonist activity does not require a catechol structure.

Our structure hypothesis relied on our DA receptor model,[10] and although successful, its validity should not be considered established at this stage. A definitive orientation of the benzergolines in this model and possible implications with respect to the D_1 receptor specific aryl binding site must await data concerning enantioselectivity and absolute configuration of the novel structures. Such investigations are currently underway in our laboratories.

Table II. Physical Properties of New Compounds

no.	mp, °C	recryst solv	formula	analysis
6	134–136	CH_2Cl_2/Et_2O	$C_{26}H_{22}N_2O_2$	C, H, N
7	292–295	CH_2Cl_2/MeOH	$C_{26}H_{22}N_2O_2$	C, H, N
8	147–150	EtOAc	$C_{19}H_{20}N_2$	C, H, N
9a	301–303	MeOH	$C_{16}H_{16}N_2$·HCl	C, H, N
9b	213–215	CH_2Cl_2/toluene	$C_{19}H_{16}N_2$	C, H, N
9c	227–229	MeOH/Et_2O	$C_{20}H_{20}N_2$·$C_4H_4O_4$	C, H, N
9d	224–225	CH_2Cl_2/MeOH	$C_{21}H_{22}N_2$·$^1/_2C_4H_4O_4$·CH_3OH	C, H, N
9e	155–157	EtOH	$C_{22}H_{24}H_2$	C, H, N

Experimental Section

Chemistry. Melting points were determined on a Büchi SMP-20 instrument and are not corrected. ^1H NMR spectra were measured on a Bruker Spectrospin 360 MHz (WH-360) instrument or 90 MHz (HX-90) spectrometer using Me_4Si as an internal standard. IR and mass spectra were also taken of the new compounds and were consistent with the proposed structures. Elemental analyses were within 0.4% of theoretical values. All reactions were followed by TLC carried out on Merck F254 silica plates. Solutions were dried over Na_2SO_4 and concentrated with a Büchi rotary evaporator at low pressure (water aspirator). Yields of crude products are given only if pure according to TLC and NMR. Physical properties of all new compounds are given in Table II.

1,*N*-Dibenzoyl-4-(methylamino)-1,2,2a,3-tetrahydrobenz[*cd*]indole (6). 1-Benzoyl-1,2,2a,3,4,5-hexahydro-4-oxobenz[cd]indole[31] (**5**; 30 g, 108 mmol) was suspended in 1200 mL of Et_2O together with 1.5 g of the acidic Montmorillonit catalyst K10 (FLUKA). Methylamine was passed into the stirred suspension at room temperature; any escaping methylamine was recondensed with a dry ice cooler. During the course of the reaction, dissolution and reprecipitation took place. When the reaction was complete according to TLC (usually 2 h), excess methylamine was removed

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(29) As compared to (−)-6-methylergoline (**2**; X = H, R = Me), a pD_2 of 5.4 (50 % maximal stimulation) was found for (−)-6-*n*-propylergoline (**2**; X = H, R = *n*-propyl) in the adenylate cyclase D_1 model (D_2 effects in the ACh release model, pD_2 = 8.4 (85% maximal inhibition)).

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by bubbling nitrogen through the reaction solution and the resultant crude enamine was filtered off. This solid was dissolved in 600 mL of CH_2Cl_2 and filtered, and the filtrate was cooled to 0 °C and mixed with triethylamine (14.4 g, 108 mmol). To this stirred solution, benzoyl chloride (12.6 mL, 108 mmol) was added dropwise. After the addition, stirring was continued for a further 14 h at room temperature. The reaction mixture was then washed with 2 N HCl, followed by 2 N ammonia solution. The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to yield the crude title compound as a yellow oil (40.2 g, 97%) which was further processed in this form. For analytical reasons, a sample was crystallized from MeOH/Et_2O; mp 134–136 °C.

(5a*S,6a*R**,12b*R**)-4-Benzoyl-4,5,5a,6,6a,7,8,12b-octahydro-8-oxo-7-methylindolo[4,3-*ab*]phenanthridine (7).** The crude compound **6** (40 g, 101 mmol) was dissolved in 2 L of acetone and irradiated with a high-pressure quartz lamp (250 W). A solid deposit was produced which was filtered off after 4 h. Irradiation was continued until TLC revealed no more starting material (usually after an additional 4–5 h). The solution was concentrated and the crystalline solid was filtered off, combined with the deposit, dissolved in CH_2Cl_2/methanol (1:1), boiled with active carbon, filtered, and concentrated until crystallization started. After 14 h at 4 °C, the product was filtered off, washed, and dried to yield the title compound (24 g, 60%); mp 292–295 °C; NMR (DMSO-d_6, 150 °C) δ 7.96–7.13 (12 H, m, aromatic), 4.40 (1 H, dd, H-C(5')), 4.37 (1 H, d, J = 10 Hz, H-C(12b)), 3.83, (1 H, m, H-C(6a)), 3.72 (1 H, t, J = 11 Hz, H-C(5")), 3.46 (1 H, m, H-C(5a)), 3.12 (3 H, s, N-CH_3), 2.63 (1 H, m, H-C(6_{equ})), 1.72 (1 H, q, J = 12 Hz, H-C(6_{ax})).

(5a*S,6a*R**,12*R**)-4,5,5a,6,6a,7,8,12b-Octahydro-7-methylindolo[4,3-*ab*]phenanthridine (8).** A suspension of **7** (17.1 g, 43 mmol) in 150 mL of THF was slowly added to a slurry of $LiAlH_4$ (8.5 g, 224 mmol) in 500 mL of Et_2O at ambient temperature under a N_2 atmosphere. The reaction mixture was refluxed for 2 h, cautiously decomposed by addition of 7 N KOH, treated with $MgSO_4$ and Celite, and filtered. The filter cake was suspended in a 2 N ammonia solution and reextracted with EtOAc. The combined organic phases were dried and filtered, and after standing overnight, the crystalline title compound was filtered off, washed, and dried (4.7 g). The mother liquor was reextracted with 1 N tartaric acid, the aqueous layer was neutralized with concentrated aqueous ammonia solution, reextracted with CH_2Cl_2/EtOAc, and evaporated. Crystallization of the residue from EtOAc gave additional title compound (4.8 g, total yield 80%); mp 147–150 °C.

***trans*-4,6,6a,7,8,12b-Hexahydro-7-methylindolo[4,3-*ab*]phenanthridine (9b).** Compound **8** (2 g, 7.2 mmol) was dissolved in 250 mL of CH_2Cl_2, and activated MnO_2 (Merck) (20 g, ~230 mmol) was suspended in portions in the stirred solution. Stirring at room temperature was continued until no more starting material could be detected on TLC (usually 2–5 h). The reaction mixture was then filtered over Celite and concentrated, and the resultant oil was crystallized from CH_2Cl_2/toluene to yield the title compound (1.2 g, 61%): mp 213–215 °C; NMR (DMSO-d_6) δ 10.76 (1 H, s, N-H), 7.67–6.95 (8 H, m, aromatic), 4.40 (1 H, d, J = 9.5 Hz, H-C(12b)), 3.74 (1 H, d, H-C(8_{equ})), 3.55 (1 H, d, H-C(8_{ax})), 3.26 (1 H, dd, H-C(6_{equ})), 2.87 (1 H, t, J = 13 Hz, H-C(6_{ax})), 2.67 (1 H, m, H-C(6a)), 2.40 (3 H, s, N-CH_3).

***trans*-4,6,6a,7,8,12b-Hexahydroindolo[4,3-*ab*]phenanthridine (9a).** BrCN (38.6 g, 365 mmol) was dissolved in 400 mL of $CHCl_3$, and **9b** (20 g, 73 mmol) was added to the stirred solution, followed by K_2CO_3 (10 g, 73 mmol). The resultant suspension was stirred overnight at room temperature and filtered, and the filtrate was evaporated. The residue was dissolved in 400 mL of concentrated AcOH by warming, and 55 mL of water followed by zinc powder (47.7 g, 730 mmol) was added. The resulting reaction mixture was stirred for 18 h at 90 °C and filtered over Celite, and the Celite was washed with CH_2Cl_2/MeOH. The combined filtrates were evaporated and the residue was taken up in CH_2Cl_2/MeOH = 9:1 and extracted with 1 N Na_2CO_3 solution. The combined organic phases were washed with brine and evaporated, and the residue was chromatographed on silica gel using CH_2Cl_2/MeOH = 95:5 (CH_2Cl_2 10% saturated with NH_3) to yield the solid title compound (11.4 g, 60%). Its hydrochloride was crystallized from MeOH; mp 301–303 °C.

***trans*-7-Ethyl-4,6,6a,7,8,12b-hexahydroindolo[4,3-*ab*]phenanthridine (9c).** To a stirred suspension of **9a** (2.5 g, 9.6 mmol) and K_2CO_3 (2.5 g, 19.2 mmol) in 80 mL of DMF was added dropwise ethyl iodide (1 mL, 12.4 mmol) dissolved in 10 mL of DMF at room temperature, and stirring continued for 18 h. The K_2CO_3 was filtered off and washed with DMF, and the filtrate was evaporated. The residue was distributed between CH_2Cl_2 and water, and the evaporated organic layer was purified by chromatography on silica gel using CH_2Cl_2/MeOH (98:2, CH_2Cl_2 10% saturated with NH_3) as eluant. The title compound (1.8 g, 65%) was obtained as a solid:hydrogen fumarate (MeOH/Et_2O) mp 227–229 °C.

Compounds **9d** and **9e** were analogously prepared by N-alkylation of **9a**.

Reference Compounds. Apomorphine (1) was obtained from Sandoz. (–)-(5*R*,10*R*)-6-methylergoline (**2**; X = H, R = Me) was prepared from (–)-(5*R*,8*S*,10*R*)-8-amino-6-methylergoline via nitrosation and reductive elimination as described for the racemate by Stoll et al.;[32] ^{1}H NMR spectrum, melting point, and optical rotation were in agreement with the data published for the (–)-enantiomer[33] synthesized by a different route. SKF 38393 (**3**; X, Y = H) was prepared according to the literature procedure.[34] 4-(3',4'-Dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline (DPTI, **4**; Y = H, R = H) was the generous gift of Dr. D. E. Nichols, Purdue University, West Lafayette IN.

Pharmacology. The in vitro assays, DA sensitive adenylate cyclase (bovine retina) and electrically evoked ACh release ACH (rat striatal slices), were performed as previously described.[10]

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