Octahydrobenzo[g]quinolines: Potent Dopamine Agonists Which Show the Relationship between Ergolines and Apomorphine

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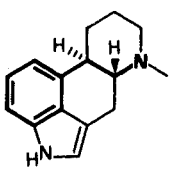
A synthesis of all four diastereoisomeric 3-(*tert*-butoxycarbonyl)-1,6-dimethoxyoctahydrobenzo[*g*]quinolines **13a–d** is presented. The two trans isomers **13b** and **13c** have been converted to tricyclic analogues **20** (CV 205-502) and **26** (205-503) of the potent dopaminomimetic ergolines CQ 32-084 and pergolide, respectively. These two compounds combine the essential moiety of apomorphine with the important 8-substituents of ergolines. Preliminary pharmacological evaluation of **20** and **26** suggests that these novel dopamine agonists combine the specificity of apomorphine with the potency, long duration of action, and good oral activity of the ergolines.

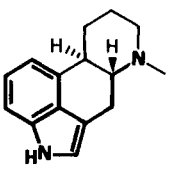
Ergot alkaloids and their synthetic derivatives, with their wide spectrum of pharmacodynamic activity, have found use in the treatment of a variety of pathophysiological disturbances. During the last few years, following the successful use of such compounds as bromocriptine, pergolide, and lisuride for the treatment of hyperprolactinemia, acromegaly, and Parkinsonism, increasing efforts have been concentrated on the synthesis of new derivatives and partial structures with the aim of dissecting out a specifically dopaminomimetic pharmacophore.

The moiety responsible for dopaminomimetic activity of the ergolines had initially been assumed to be a rigid arylethylamine, either a phenylethylamine **1a** or a tryptamine **1b**.[1] Recently the (aminoethyl)indole **1c** was also proposed.[2] These hypotheses led to the synthesis of a variety of partial structures, such as benz[*cd*]indolamines,[3,4] octahydrobenzo[*f*]quinolines,[5] 4-piperidinyl- and 4-tetrahydropyridinylindoles,[6] 4-(2-aminoethyl)indoles,[2,7] and 9-oxaergolines.[8] Some of these compounds were indeed potent dopamine agonists.[9]

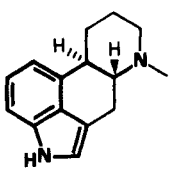
Close comparison of ergolines with the prototypic dopamine agonist apomorphine (**2a**), paying particular regard



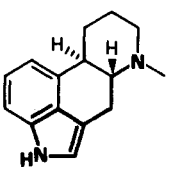
1a



1b

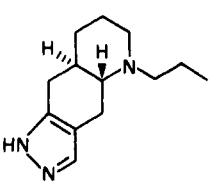


1c

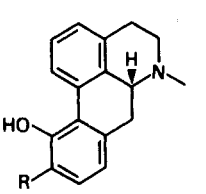


1d

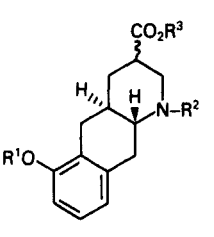
to the absolute configurations of both, led to the proposal[10] that the dopaminomimetic pharmacophore of the ergolines is a rigid pyrrolethylamine **1d**. Strong experimental support for this theory came from the high activity of the corresponding octahydropyrrolo- or pyrazolo[3,4-*g*]-quinolines.[4] Thus the compound LY 141865 has been shown to be a potent and specific D2-agonist[11] despite the lack of a catechol group and an apparent structural dissimilarity to dopamine. The recently reported absolute configuration[12] correlates with that of the natural ergolines or apomorphine.



LY 141865



2a R = OH
2b R = H



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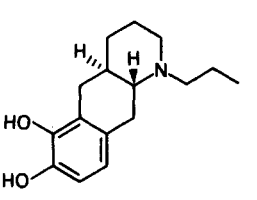

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None of these approaches, however, took note of the knowledge gained from the largely separate fields of er-

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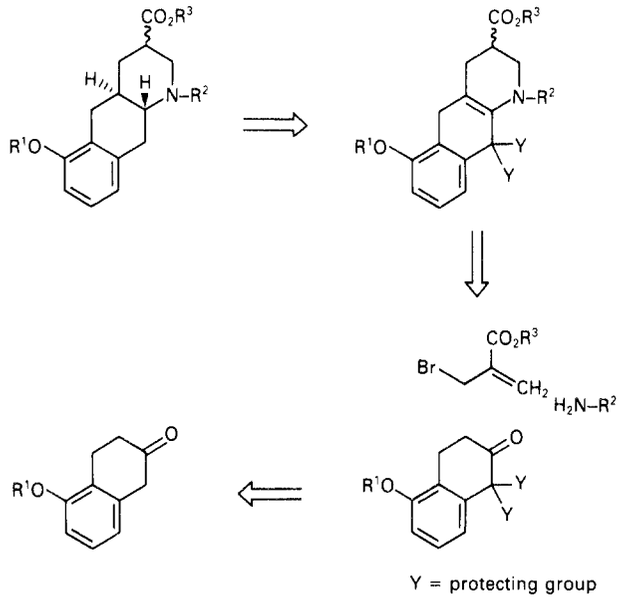
Scheme I



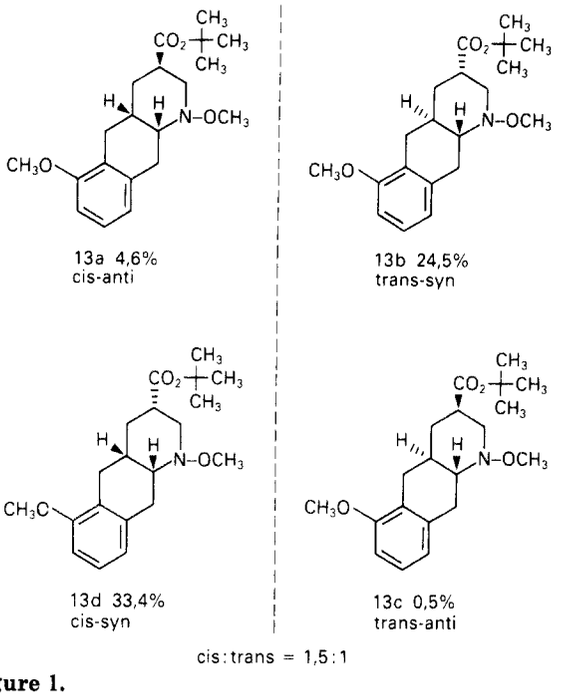


Figure 1.

goline chemistry and that of dopamine analogues. We accordingly selected 3-substituted octahydrobenzo[*g*]-quinolines **3** as a target for synthesis, thus superposing the linear benzo[*g*]quinoline segment of apomorphine on the substituted pyrrolo[3,4-*g*]quinoline moiety of the ergolines. In order to guard against facile attack by catecholamine *O*-methyl transferase (COMT), we chose the monohydroxy compound analogous to 10-deshydroxyapomorphine (**2b**).[13] The carboxy group at position 3 was included to allow easy introduction of various side chains, since substituents at the corresponding 8-position largely determine the overall pharmacodynamic spectrum of ergolines. The importance of the trans ring junction is known from the ergolines,[14,15] and an alkyl group or an easily removable protecting group was chosen as substituent for the nitrogen atom.

During the course of our synthetic efforts, we became aware of the synthesis[16] of the unsubstituted dihydroxy-octahydrobenzo[*g*]quinoline **4**. Despite the potent dopaminomimetic properties of this compound,[16,17] its clear relationship to LY 141865 has, to our knowledge, never been remarked upon!

We report here the synthesis of all four diastereoisomeric 3-(*tert*-butoxycarbonyl)-1,6-dimethoxyoctahydrobenzo-[*g*]quinolines **13a–d** and describe the conversion of the two trans isomers into potent dopamine agonists.

Chemistry

Synthesis of All Four Diastereoisomeric 3-(*tert*-Butoxycarbonyl)-1,6-dimethoxyoctahydrobenzo[*g*]-quinolines 13a–d. Our retrosynthetic analysis of the target structure was strongly influenced by an annelation procedure used in a synthesis of octahydrobenzo[*f*]-quinolines with use of 2-tetralone[18] as starting material. It was our intention to direct the annelation toward C(3) in 5-methoxy-2-tetralone (**6**) by a reversible protection of the more reactive methylene group at C(1). In fact, the approach shown in Scheme I proved to be successful only in a modified form, resulting in a more elaborate synthesis summarized in Scheme II.

Originally Woodward et al. introduced trimethylene- and ethylenedithiotosylates as reagents for protection of reactive methylene groups.[19] Despite their finding that C(1) of 2-tetralone could not be protected by this method due to aromatization,[20] in our hands 5-methoxy-2-tetralone (**6**)[21] was converted in good yield to the corresponding ethylene dithioketal **7a** on reaction in methanol in the presence of sodium acetate. The same reaction conditions allowed the large-scale synthesis of diphenyl dithioketal **7b** with use of the readily available *S*-phenyl benzenethiosulfonate (**5**) prepared by a slightly modified procedure of Trost and Massiot.[22] We were unable to build the third ring in analogy to previously described one-pot reactions,[15,18,23] as originally planned, so a stepwise procedure had to be followed. The lithium enolate of **7b** was generated at low temperature and alkylated with *tert*-butyl 2-(bromomethyl)acrylate (**8**)[24] to yield **9**. Reductive removal of the dithioketal function by aluminum amalgam[25] without concomitant reduction of the acrylate function gave the desired ketone **10**. Reduction of the corresponding oxime ether **11** by sodium cyanoborohydride in methanol generated a mixture of the diastereoisomeric methoxyamines

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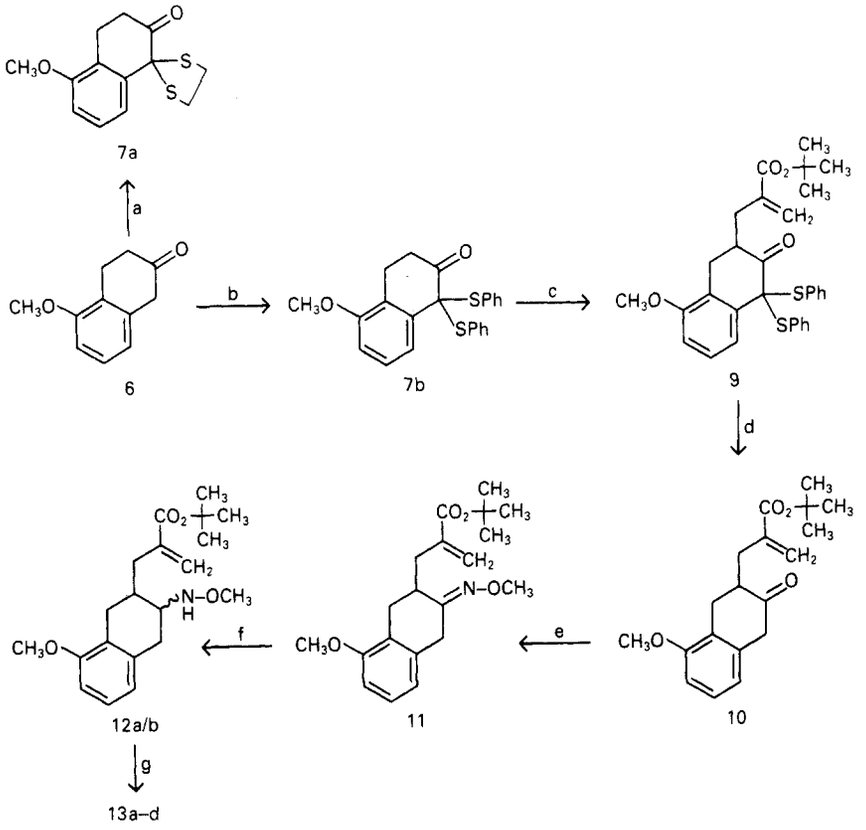
Scheme II[a]



[a] Reagents: (a) $TosSCH_2CH_2STos$-NaOAc-MeOH, (b) 5-NaOAc-MeOH, (c) LDA-Et_2O-THF-HMPT-8, (d) Al(Hg)-THF-H_2O, (e) $H_2NOCH_3 \cdot HCl$-$Na_2HPO_4 \cdot 2H_2O$-MeOH, (f) $NaCNBH_3$-MeOH, (g) room temperature-MeOH.

12a/12b which cyclized at room temperature by intramolecular 1,4-addition of the amino function to the acrylate. A mixture of all four diastereoisomeric octahydrobenzo[*g*]quinolines **13a–d** was the result. As anticipated, no lactam product resulting from 1,2-addition was detected in the IR spectrum. The diastereoisomers **13a–d** were separated by medium-pressure chromatography on silica. Figure 1 shows the relative configuration of all four isomers and the overall chemical yields from oxime ether **11**. The stereochemical assignments were made on the basis of ^1H NMR spectra including the use of double-resonance experiments, as a result of which all protons could be assigned. The chemical shifts and coupling constants of all protons of the piperidine ring are listed in Table I.

The arguments for the stereochemical assignments can be summarized thus: in the trans isomers **13b** and **13c** the signal for HC(10a)—a proton at the ring junction—is a doubled triplet with two large and one small coupling constants. This pattern is only explicable with a trans-diaxial configuration of the junctional protons. To distinguish between the two, use is made of the splitting pattern for HC(3), which shows that this proton is in an axial position in **13c**. Moreover, the well-separated signals for HC(4)ax in **13b** and **13c** are reminiscent of the pattern of the corresponding signals of HC(9)ax of α- and β-dihydrolysergic acid derivatives. Similarly, the splitting pattern of HC(3) is used to distinguish between the two cis-isomers **13a** and **13d**.

According to these assignments, the main products are the cis-3α-isomer **13d** and the trans-3α-isomer **13b**. From the product ratio shown in Figure 1, it follows that oxime ether **11** is reduced predominantly to *cis*-methoxyamine **12a** (ratio cis:trans = 3:2). We were unable to influence the stereochemical outcome of this reduction. On the other hand, the cyclization of *trans*-methoxyamine **12b** is highly stereospecific, giving a product ratio **13b**:**13c** of 50:1. A posteriori we argued that this intramolecular 1,4-addition of the amine to the acrylic function is kinetically controlled. Thus the energetic difference between the transition states is responsible for the product ratio. The transition state on the pathway to **13b** with the newly formed bonds in an *antiperiplanar* relationship as shown in Figure 2 would be of lower energy than that with these bonds in a gauche

Table I. Chemical Shifts and Coupling Constants of All Protons in the Piperidine Ring of Compounds **13a–d**.

	13a (cis-3β)	**13d** (cis-3α)
HC(2)ax	2.47, t, 10 Hz	3.02, dd, 12/10 Hz
HC(2)eq	3.55, dd, 10/3 Hz	3.09, dd, 12/5 Hz
HC(3)	2.95, tt, 12/4 Hz	2.62–2.66, m
HC(4)ax	1.70, td, 13/5 Hz	1.45, t, 12 Hz
HC(4)eq	1.92, d, 13 Hz	1.61, dt, 12/4 Hz
HC(4a)	2.24–2.33, m	2.21–2.31, m
HC(10a)	2.75, br s	nv[a]
	13b (trans-3α)	**13c** (trans-3β)
HC(2)ax	2.62, dd, 10/3 Hz	2.52, t, 11 Hz
HC(2)eq	nv	nv
HC(3)	2.69–2.77, m	2.66, tt, 12/3 Hz
HC(4)ax	1.18, td, 13/5 Hz	1.24, q, 12 Hz
HC(4)eq	2.24, d, 13 Hz	2.11, d, 12 Hz
HC(4a)	1.92–2.08, m	1.65–1.80, m
HC(10a)	2.43, td, 11/5 Hz	2.43, td, 12/4 Hz

[a] Not visible.

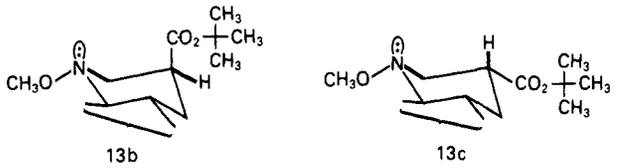
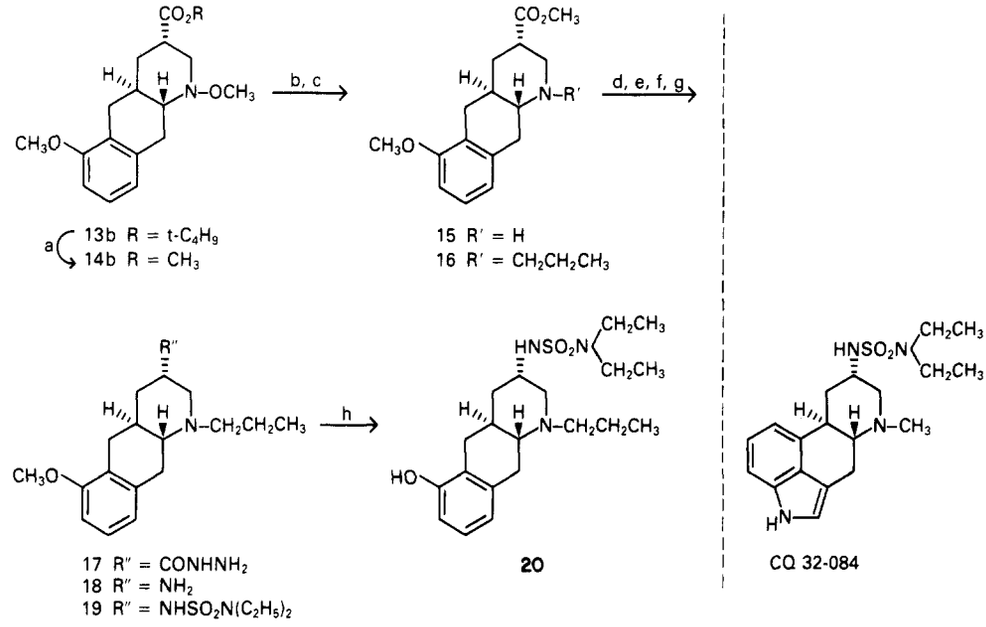


Figure 2.

Scheme III[a]



[a] Reagents: (a) H_2SO_4-MeOH-reflux, (b) Zn-AcOH-H_2O, (c) CH_3CH_2CHO-10% Pd/C-H_2-PrOH, (d) $NH_2NH_2 \cdot H_2O$-MeOH, (e) NOCl-THF, (f) HCl-THF-reflux, (g) Et_2NSO_2Cl-$CHCl_3$, (h) BBr_3-CH_2Cl_2.

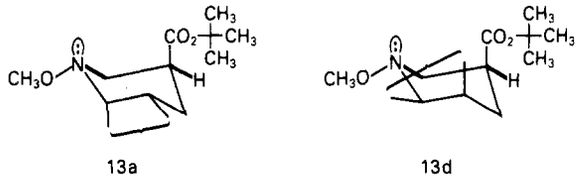


Figure 3.

relationship leading to **13c**. For the more flexible cis-isomers **13a** and **13d**, the product ratio is 1:7. For both cis isomers an *antiperiplanar* relationship of the newly formed bonds is feasible as shown in Figure 3. Close analysis of the conformations shown in Figure 3 reveals that steric hindrance of axial substituents might be more significant in **13a** compared to **13d**. Therefore the product ratio in the cyclization of *cis*-methoxyamine **12a** might reflect the stability of the two products in the conformations generated by a favorable trans addition of NH to the acrylic function. However, this does not imply that **13d** is necessarily thermodynamically more stable than **13a** since, in view of their inherent flexibility, both products can adopt other conformations.

Synthesis of a Tricyclic Analogue of the Ergoline CQ 32-084. (3α)-*trans*-Octahydrobenzo[*g*]quinoline **13b** corresponds to the criteria described for our primary synthetic goal **3** and allows synthesis of a new family of compounds with similarity to derivatives of α-dihydrolysergic acid and apomorphine. For evaluation of the biological activity, we decided to convert **13b** to the tricyclic analogue **20** of the potent dopamine agonist CQ 32-084[26] as illustrated in Scheme III, where the synthesis of **20** is summarized. Compound **13b** was converted to methyl ester **14b**. Treatment with Zn and acetic acid gave the desired secondary amine **15**. Catalytic hydrogenation on Pd/C in the presence of propanal afforded **16**, which was converted to hydrazide **17**. Treatment with a solution of nitrosyl chloride in THF—a method originally developed in peptide chemistry[27]—afforded the corresponding azide, which was converted without isolation in a Curtius rearrangement to yield diamine **18**. Treatment with diethylsulfamoyl chloride afforded sulfamide **19**, which was converted to the final product **20** by ether cleavage with boron tribromide.

Synthesis of a Tricyclic Analogue of Pergolide. Obviously trans-3β-isomer **13c** could serve as starting material for tricyclic analogues of derivatives of β-dihydrolysergic acid. In order to allow the synthesis of the tricyclic analogue **26** of the potent dopamine agonist pergolide,[28] larger amounts of the *trans*-3β-isomer had to be available than those formed in the synthesis described above; cf. Figure 1. This objective was achieved as shown in Scheme IV by epimerization of methyl ester **14b** to **14c**. Reduction of ester **14c** by $LiAlH_4$, conversion of the carbinol **21** to the mesylate ester **22**, and treatment with CH_3SNa afforded sulfide **23**. Reduction with Zn in diluted acetic acid gave the desired secondary amine **24**, which in turn was converted to **25** on reaction with propyl iodide. Ether cleavage using boron tribromide afforded the final product **26**, the desired analogue of pergolide.

Pharmacology

Compounds **20** and **26** were evaluated for dopaminomimetic effects in various animal models in comparison to the corresponding ergolines. The results are summarized in Table II. Both compounds are slightly less active than their ergoline counterparts in inhibiting basal prolactin secretion in male rats after subcutaneous application, whereas **20** is about twice as active by the same route as CQ 32-084 in inhibiting ovum implantation in female rats. Pergolide and **26** are here equiactive. In inhibition of spontaneous lactation in rats after *oral* application, both compounds show considerable gains in comparison to the ergolines: **20** is about 6 times more active than CQ 32-084, while **26** is highly active, yet free of the behavioral side-effects which prevent determination

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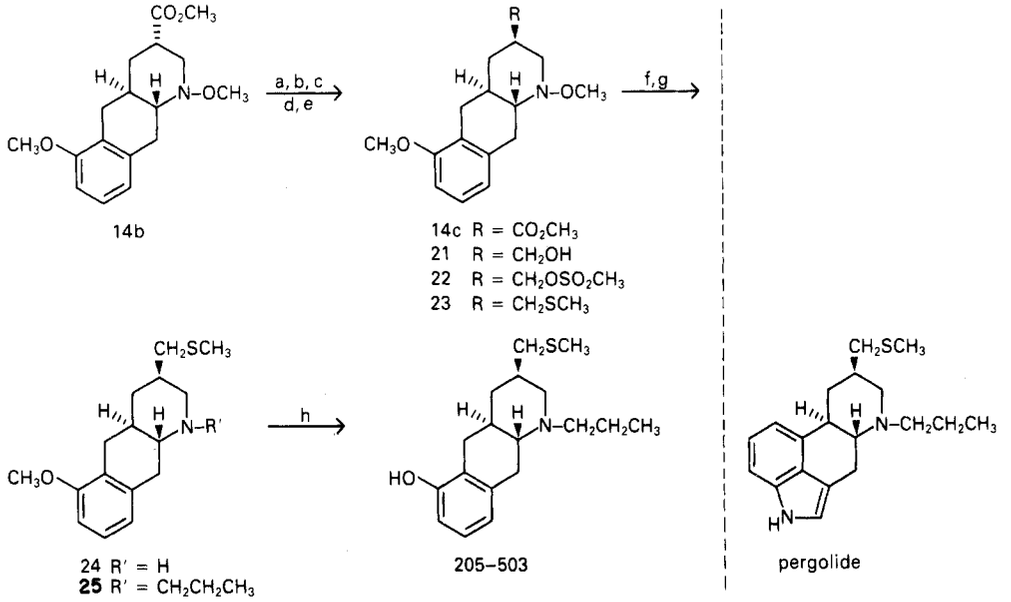
Scheme IV[a]



[a] Reagents: (a) aqueous 1 N NaOH-MeOH, (b) H_2SO_4-MeOH-reflux, (c) $LiAlH_4$-THF, (d) CH_3SO_2Cl-pyridine, (e) $NaSCH_3$-DMF, (f) Zn-AcOH-H_2O; (g) $CH_3CH_2CH_2J$-K_2CO_3-DMF, (h) BBr_3-CH_2Cl_2.

Table II. Biological Activities[a] of **20** and **26** in Comparison to CQ 32-084, Pergolide, and Apomorphine

	in vivo: ID50, μg/kg			in vitro: IC50, nM					
substance	basal prolactin (sc)	ovum implantation (sc)	lactation (po)	SPC[b]	DA[c]	SPFC[d]	5HT[e]	Clon[f]	WB 4101[g]
CQ 32-084	1.4	28 (22–35)	190 (150–267)	25	120	26	>5000	480	3300
20	5	17 (12–22)	30 (24–43)	48	190	5100	4600	5600	7800
pergolide	1.3	21 (17–28)	*h*	145	18	140	385	170	550
26	4	18 (13–24)	58 (43–97)	60	22	720	2000	250	640
apomorphine	>10000[i]	*i*	*i*	1350	15	4500	>10000	430	7750

[a] For details, see Experimental Section. The values in parentheses are 95% confidence intervals. The ID50 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 IC50. In those instances where determinations have been repeated at widely separated time intervals we have found the IC50'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] Due to appearance of stereotyped behavior in the suckling females which prevented the young from feeding normally, it was not possible to obtain an adequate dose–response relationship. [i] Four hours after sc injection, apomorphine has practically no effect on basal secretion of prolactin in male rats. Since the experimental conditions of the other two tests are so chosen that only long-acting (>8 h) compounds show effects, apomorphine was not tested here. The ID50's for inhibition of basal prolactin secretion 30 and 60 min after sc injection are 58 and 81 μg/kg, respectively.

of an ID_{50} for pergolide in this test. Since the interfering stereotyped behaviors produced by pergolide are thought to be serotoninergic in origin, it would follow that **26** is less active at serotonin receptors than the ergoline. In order to investigate this aspect, affinities for various neurotransmitter receptors were determined by means of radioligand binding studies. Affinities to both dopamine binding sites are comparable for the two pairs, whereas **20** and **26** have significantly lower affinity for serotonin binding sites than the corresponding ergolines. At α-adrenoceptors, **20** has very low affinity, while **26** is comparable to pergolide. Results with apomorphine are shown for comparison.

Discussion

Various strategies have been followed in the search for new dopaminomimetic drugs, as has been clearly summarized in a recent review.[29] Interestingly, modifications of apomorphine and of the ergolines have hitherto followed largely separate paths. On the one hand, apomorphine has been extensively modified, including changes in ring size[30] and substitution pattern.[31] Most of these compounds show a marked lack of oral activity, and attempts to circumvent this problem via the synthesis of prodrugs[32] have only rarely met with the hoped-for success. Surprisingly little interest has been shown in compound **4**,[16,17] for reasons which are unclear to us. On the other hand, the good oral activity of ergopeptins such as bromocriptine has prompted successive reductions in molecular complexity, first to low-molecular-weight ergolines and then to various dissections of the lysergic acid moiety itself, in the search for the elusive dopaminomimetic pharmacophore. To this approach belong, e.g., the benz[*cd*]indolamines[3,4] and octahydropyrrolo[3,4-*g*]quinolines.[4] One class of compounds which might be regarded as a combination of these two

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(31) Neumeyer, J. L.; Arana, G. W.; Ram, V. J.; Baldessarini, R. J. in ref 9, pp 11–24.
(32) Campbell, A.; Baldessarini, R. J.; Ram, V. J.; Neumeyer, J. L. *Neuropharmacology* **1982**, *21*, 953.

main approaches is that of the heteroaporphines.[33] We, however, have here for the first time deliberately set out to combine the essential dopaminomimetic pharmacophore of apomorphine with the 8-substituents of ergot derivatives.

The high potency of **20** and **26** is gratifying indeed, but even more so is the good oral activity of these compounds. In this respect, they improve even upon the ergolines, despite having a phenolic hydroxy group, the presence of which might have been expected to predispose the compounds to rapid conjugation and excretion. Preliminary results suggest that modulation of the biological activity is possible by variation of the 3-substituent and that this new class of compound is more specifically dopaminomimetic than the ergolines. It will be of interest to determine the biological activity and absolute configuration of the resolved enantiomers of these compounds. Assuming, however, that the absolute configuration correlates with the natural ergolines, the new compounds provide conclusive evidence that a rigid pyrrolethylamine moiety does indeed represent the dopaminomimetic pharmacophore of the ergolines.

Experimental Section

^{1}H NMR spectra 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 also determined for all new compounds and were consistent with the proposed structures. 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. All reactions were followed by TLC carried out on Merck F254 silica gel plates. Solutions were dried over Na_2SO_4 and concentrated with a Buchi rotary evaporator at low pressure (water aspirator).

***S*-Phenyl benzenethiosulfonate (5)** was prepared according to a simplified procedure of Trost and Massiot.[22] Aqueous hydrogen peroxide (30%, 290 mL, 2.1 equiv) was added carefully in portions to a stirred solution of diphenyl disulfide (300 g, 1.37 mol) in glacial acetic acid (550 mL) at 40–60 °C (not at room temperature as described). Stirring was continued for 48 h, during which time the temperature was kept carefully in the same range. The reaction mixture was concentrated to half the volume and cooled to 10 °C. The precipitated product was recovered by filtration and washed thoroughly with diethyl ether/hexane to yield 315 g (92%) of **5**, mp 44–45 °C. In carrying out this reaction on the scale described, we have found it necessary to work at elevated temperature. In this manner, an uncontrolled exothermic reaction can effectively be avoided.

1,2,3,4-Tetrahydro-5-methoxy-2-oxo-1,1-bis(phenylthio)-naphthalene (7b). A solution of 5-methoxy-2-tetralone (**6**)[21] (70 g, 0.36 mol), **5** (150 g, 0.6 mol), and sodium acetate (120 g, 1.47 mol) in CH_3OH (1.1 L) was stirred at room temperature. Compound **7b** started to precipitate and stirring was continued for 24 h. The reaction mixture was concentrated and cooled to 10 °C and the precipitated product was recovered by filtration to yield 116 g (82%) of pure **7b**: mp 139–141 °C; NMR ($CDCl_3$, 90 MHz) δ 2.67 (s, 4 H), 3.75 (s, 3 H), 6.70 (d, J = 8 Hz, 1 H), 7.0–7.4 (m, 11 H), 7.70 (d, J = 8 Hz, 1 H). Anal. ($C_{23}H_{20}O_2S_2$) C, H, O, S.

***tert*-Butyl 3-[1,2,3,4-Tetrahydro-2-oxo-1,1-bis(phenylthio)-3-naphthyl]-2-methylenepropionate (9).** To a solution of LDA (prepared from 12.6 mL of diisopropylamine and 53 mL 1.6 N *n*-BuLi in hexane) in diethyl ether (240 mL) at −90 °C was added **7b** (23.4 g, 60 mmol) in THF/HMPT (10:1, 275 mL). The temperature of the reaction mixture was carefully kept below −70 °C. Stirring was continued at −70 °C for 1 h. After addition of *tert*-butyl 2-(bromomethyl)acrylate (**8**;[24] 19.8 g, 90 mmol) in THF (50 mL), the temperature was allowed to rise to −20 °C, followed by acidification with excess 2 N HCl and extraction with CH_2Cl_2. The organic layers were dried and evaporated to give a yellow oil, which was crystallized from diethyl ether/hexane at −20 °C. The yield of pure **9** was 21.1 g (66%): mp 120–121 °C (white needles); NMR ($CDCl_3$, 90 MHz) δ 1.45 (s, 9 H), 1.65–2.35 (m, 2 H), 2.65–3.5 (m, 3 H), 3.73 (s, 3 H), 5.55 (d, J = 1 Hz, 1 H), 6.12 (d, J = 2 Hz, 1 H), 6.68 (d, J = 8 Hz, 1 H), 6.9–7.6 (m, 11 H), 7.70 (d, J = 8 Hz, 1 H). Anal. ($C_{31}H_{32}O_4S_2$) C, H, O, S.

***tert*-Butyl 3-(1,2,3,4-Tetrahydro-2-oxo-3-naphthyl)-2-methylenepropionate (10).** Freshly amalgamated aluminum turnings (140 g) were added to a mechanically stirred solution of **9** (100 g, 0.19 mol) in THF/H_2O (9:1, 3 L). After 2 h at 50 °C the reaction mixture was diluted with CH_2Cl_2 and filtered. The filtercake was thoroughly washed with CH_2Cl_2 and the filtrate was concentrated. Water was added, the mixture was extracted with CH_2Cl_2, and the extracts were dried and evaporated. Crystallization from diethyl ether/hexane at −20 °C yielded 42 g (71%) **10**, mp 94–95 °C (pure according to TLC but not odorless). A sample was recrystallized: mp 95–96 °C (odorless): NMR ($CDCl_3$, 90 MHz) δ 1.45 (s, 9 H), 2.1–3.5 (m, 5 H), 3.59 (s, 2 H), 3.82 (s, 3 H), 5.54 (br s, 1 H), 6.17 (d, J = 2 Hz, 1 H), 6.70/6.73 (2 d, J = 8 Hz, 2 H), 7.18 (t, J = 8 Hz, 1 H). Anal. ($C_{19}H_{24}O_4$) C, H, O.

***tert*-Butyl 3-[1,2,3,4-Tetrahydro-2-(methoxyimino)-5-methoxy-3-naphthyl]-2-methylenepropionate (11).** A mixture of **10** (510 g, 1.61 mol), *O*-methylhydroxylamine hydrochloride (272 g, 3.22 mol), and disodium hydrogen phosphate dihydrate (290 g, 1.61 mol) in CH_3OH (10 L) was stirred at room temperature for 4 h. The reaction mixture was concentrated to $^1/_{10}$ at room temperature, diluted with CH_2Cl_2 (4 L), and filtered. The filtrate was extracted with water, and the organic layer was dried and evaporated. Crystallization from hexane yielded 395 g (72%) of oxime ether **11**: mp 72–74 °C; NMR ($CDCl_3$, 90 MHz) δ 1.48 (s, 9 H), 2.1–2.6 (m, 2 H), 2.75–2.9 (m, 3 H), 3.70 (br s, 2 H), 3.76 (s, 3 H), 3.83 (s, 3 H), 5.36 (br s, 1 H), 6.05 (d, J = 2 Hz, 1 H), 6.61/6.65 (2 d, J = 8 Hz, 2 H), 7.04 (t, J = 8 Hz, 1 H). Anal. ($C_{20}H_{27}NO_4$) C, H, N, O.

(±)-3-*tert*-(Butoxycarbonyl)-1,2,3,4,4a,5,10,10a-octahydro-1,6-dimethoxybenzo[*g*]quinolines 13a–d. A mixture of **11** (395 g, 1.14 mol) and sodium cyanoborohydride (400 g, 6.5 mol) in CH_3OH (6 L) was stirred at room temperature for 24 h. The pH was kept carefully in the range of 3–4.5 by addition of 7.5 N HCl in CH_3OH. Then the pH was adjusted to 7 by addition of buffer solution and the reaction mixture was concentrated. The residue was extracted with CH_2Cl_2 to yield after evaporation 400 g brown oil. This material was redissolved in CH_3OH (6 L), potassium dihydrogen phosphate (630 g, 4.6 mol) was added, and the mixture was stirred at room temperature for 72 h followed by 3 h at reflux temperature. After filtration the mixture was concentrated. Water was added followed by extraction with CH_2Cl_2. The organic layers were dried and evaporated. The crude product was subjected to medium-pressure chromatography over silica gel, using CH_2Cl_2/EtOAc (98:2) to elute the four diastereoisomeric octahydrobenzo[*g*]quinolines **13a–d**, all crystallized from hexane. Result (product, yield, R_f (silica, CH_2Cl_2/EtOAc (95:5)), mp): **13a**, 18.2 g (4.6%), 0.55, 100–101 °C; **13b**, 97.0 g (24.5%), 0.52, 104–105 °C; **13c**, 2.1 g (0.5%), 0.50, 115–116 °C; **13d**, 132.2 g (33.4%), 0.40, 83–84 °C.

(±)-(3β,4aβ,10aβ)-3-(*tert*-Butoxycarbonyl)-1,2,3,4,4a,5,10,10a-octahydro-1,6-dimethoxybenzo[*g*]quinoline (13a): NMR ($CDCl_3$, 360 MHz) δ 1.45 (s, 9 H), 1.70 (td, J = 13/5 Hz, 1 H), 1.92 (br d, J = 13 Hz, 1 H), 2.24–2.33 (m, 1 H), 2.47 (t, J = 10 Hz, 1 H), 2.56 (dd, J = 16/12 Hz, 1 H), 2.69 (dd, J = 16/7 Hz, 1 H), 2.75 (br s, 1 H), 2.82 (br d, J = 18 Hz, 1 H), 2.95 (tt, J = 12/4 Hz, 1 H), 3.30 (part of d) and 3.33 (s, together 4 H), 3.55 (dd, J = 10/3 Hz, 1 H), 3.82 (s, 3 H), 6.68 (d, J = 8 Hz, 1 H), 6.75 (d, J = 8 Hz, 1 H), 7.10 (t, J = 8 Hz, 1 H). Anal. ($C_{20}H_{29}NO_4$) C, H, N, O.

(±)-(3α,4aα,10aβ)-3-(*tert*-Butoxycarbonyl)-1,2,3,4,4a,5,10,10a-octahydro-1,6-dimethoxybenzo[*g*]quinoline (13b): NMR ($CDCl_3$, 360 MHz) δ 1.18 (td, J = 13/5 Hz, 1 H), 1.49 (s, 9 H), 1.92–2.08 (m, 1 H), 2.14 (dd, J = 16/12 Hz, 1 H), 2.24 (br d, J = 13 Hz, 1 H), 2.43 (td, J = 11/5 Hz, 1 H), 2.62 (dd, J = 10/3 Hz, 1 H), 2.69–2.77 (m, 2 H), 3.01 (dd, J = 16/5 Hz, 1 H), 3.31 (dd, J = 16/5 Hz, 1 H), 3.58 (s, 3 H), 3.81 (s/m, 4 H), 6.67 (d, J = 8 Hz, 1 H), 6.73 (d, J = 8 Hz, 1 H), 7.10 (t, J = 8 Hz, 1 H). Anal. ($C_{20}H_{29}NO_4$) C, H, N, O.

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(±)-(3β,4aα,10aβ)-3-(*tert*-Butoxycarbonyl)-1,2,3,4,4a,5,-10,10a-octahydro-1,6-dimethoxybenzo[*g*]quinoline (13c): NMR ($CDCl_3$, 360 MHz) δ 1.24 (q, *J* = 12 Hz, 1 H), 1.47 (s, 9 H), 1.65–1.80 (m, 1 H), 2.11 (br d, *J* = 12 Hz, 1 H), 2.22 (dd, *J* = 16/12 Hz, 1 H), 2.43 (td, *J* = 12/4 Hz, 1 H), 2.52 (t, *J* = 11 Hz, 1 H), 2.66 (tt, *J* = 12/3 Hz, 1 H), 2.75 (dd, *J* = 16/11 Hz, 1 H), 3.02 (dd, *J* = 17/5 Hz, 1 H), 3.35 (dd, *J* = 16/5 Hz, 1 H), 3.62 (s/m, 4 H), 3.81 (s, 3 H), 6.67 (d, *J* = 8 Hz, 1 H), 6.76 (d, *J* = 8 Hz, 1 H), 7.11 (t, *J* = 8 Hz, 1 H). Anal. ($C_{20}H_{29}NO_4$) C, H, N, O.

(±)-(3α,4aβ,10aβ)-3-(*tert*-Butoxycarbonyl)-1,2,3,4,4a,5,-10,10a-octahydro-1,6-dimethoxybenzo[*g*]quinoline (13d): NMR (Me_2SO, 150 °C, 360 MHz) δ 1.39 (s, 9 H), 1.45/1.48 (parts of t, *J* = 12 Hz, 1 H), 1.61 (dt, *J* = 12/4 Hz, 1 H), 2.21–2.31 (m, 1 H), 2.57–2.61/2.62–2.66/2.67–2.79 (3 m, together 4 H), 2.90 (dd, *J* = 16/10 Hz, 1 H), 3.02 (dd, *J* = 12/10 Hz, 1 H), 3.09 (dd, *J* = 12/5 Hz, 1 H), 3.42 (s/m, 4 H), 3.75 (s, 3 H), 6.69 (t, *J* = 8 Hz, 2 H), 7.03 (t, *J* = 8 Hz, 1 H). Anal. ($C_{20}H_{29}NO_4$) C, H, N, O.

(±)-(3α,4aα,10aβ)-1,2,3,4,4a,5,10,10a-Octahydro-1,6-dimethoxy-3-(methoxycarbonyl)benzo[*g*]quinoline (14b). Compound **13b** (20 g, 57.6 mol) was stirred overnight in 1 N H_2SO_4/CH_3OH (115 mL) at reflux temperature. After neutralization with 1 N NaOH, the mixture was concentrated and extracted with CH_2Cl_2. The organic layer was dried, evaporated and crystallized from CH_2Cl_2/hexane to yield 16.1 g (92%) pure **14b**: mp 112 °C; NMR ($CDCl_3$, 360 MHz) δ 1.24 (td, *J* = 13/5 Hz, 1 H), 1.90–2.05 (m, 1 H), 2.15 (dd, *J* = 17/12 Hz, 1 H), 2.31 (br d, *J* = 13 Hz, 1 H), 2.45 (td, *J* = 11/5 Hz, 1 H), 2.65 (dd, *J* = 10/3 Hz, 1 H), 2.74 (dd, *J* = 16/11 Hz, 1 H), 2.83 (br s, 1 H), 3.03 (dd, *J* = 17/5 Hz, 1 H), 3.30 (dd, *J* = 16/5 Hz, 1 H), 3.56 (s, 3 H), 3.74 (s, 3 H), 3.81 (s, 3 H), 3.86 (br d, *J* = 11 Hz, 1 H), 6.66 (d, *J* = 8 Hz, 1 H), 6.73 (d, *J* = 8 Hz, 1 H), 7.10 (t, *J* = 8 Hz, 1 H). Anal. ($C_{17}H_{23}NO_4$) C, H, N, O.

(±)-(3β,4aα,10aβ)-1,2,3,4,4a,5,10,10a-Octahydro-1,6-dimethoxy-3-(methoxycarbonyl)benzo[*g*]quinoline (14c). A solution of **14b** (20 g, 65 mmol) in CH_3OH (108 mL) was treated with 10 N NaOH (12 mL) and stirred at 50 °C for 4 h. The mixture was acidified, concentrated, and extracted with CH_2Cl_2/CH_3OH (8:2). The organic layers were dried and evaporated. For reesterification the residue was stirred overnight in CH_3OH/H_2SO_4 (1 N, 250 mL) at reflux temperature to yield a mixture of **14b** and **14c**. To complete the epimerization, this procedure was repeated twice to yield finally 15.6 g (78%) of pure **14c**, crystallized from diethyl ether/hexane: mp 106–108 °C; NMR ($CDCl_3$, 360 MHz) δ 1.29 (q, *J* = 12 Hz, 1 H), 1.67–1.84 (m, 1 H), 2.15 (d, *J* = 13 Hz) and 2.23 (dd, *J* = 16/12 Hz, together 2 H), 2.48 (td, *J* = 12/4 Hz, 1 H), 2.56 (t, *J* = 11 Hz, 1 H), 2.68–2.85 (m, 2 H), 3.02 (dd, *J* = 17/5 Hz, 1 H), 3.35 (dd, *J* = 16/4 Hz, 1 H), 3.61/3.71 (2 s) and 3.68 (br d, *J* = 10 Hz, together 7 H), 3.81 (s, 3 H), 6.68 (d, *J* = 8 Hz, 1 H), 6.75 (d, *J* = 8 Hz, 1 H), 7.11 (t, *J* = 8 Hz, 1 H). Anal. ($C_{17}H_{23}NO_4$) C, H, N, O.

(±)-(3α,4aα,10aβ)-1,2,3,4,4a,5,10,10a-Octahydro-6-methoxy-3-(methoxycarbonyl)benzo[*g*]quinoline (15) Hydrochloride. Zinc dust (59 g) was added to a suspension of **14b** (15 g, 49 mmol) in glacial acetic acid/H_2O (2:1, 300 mL). After stirring overnight at room temperature, the mixture was filtered and the filtercake thoroughly washed with glacial acetic acid. The filtrate was concentrated at 50 °C at reduced pressure. Ice and 10 N NaOH was added to adjust for pH 7 and then the mixture was extracted several times with CH_2Cl_2. The organic layers were extracted with 1 N NaOH, dried, and evaporated to yield a white foam, which was crystallized as hydrochloride from CH_2Cl_2/diethyl ether. **15**: 11.0 g (72%); mp 233–234 °C; NMR (Me_2SO, 360 MHz) δ 1.62 (td, *J* = 13/5 Hz, 1 H), 1.75–1.90 (m, 1 H), 2.16 (dd, *J* = 17/12 Hz, 1 H), 2.28 (br d, *J* = 13 Hz, 1 H), 2.92 (dd, *J* = 17/5 Hz, 1 H), 3.0–3.12 (m, 2 H), 3.12–3.28 (m, 3 H), 3.61 (br d, *J* = 11 Hz, 1 H), 3.70 (s, 3 H), 3.77 (s, 3 H), 6.72 (d, *J* = 8 Hz, 1 H), 6.80 (d, *J* = 8 Hz, 1 H), 7.12 (t, *J* = 8 Hz, 1 H), 8.52 (br s, 1 H), 10.35 (br s, 1 H). Anal. ($C_{16}H_{21}NO_3$·HCl) C, H, N, O, Cl.

(±)-(3α,4aα,10aβ)-1,2,3,4,4a,5,10,10a-Octahydro-6-methoxy-3-(methoxycarbonyl)-1-propylbenzo[*g*]quinoline (16) Hydrogen Oxalate. A solution of **15** (10.2 g, 32.7 mmol) and propionaldehyde (10.2 mL, 0.15 mol) in propanol (200 mL) was hydrogenated over 10% palladium/carbon overnight at room temperature. The mixture was filtered and the filtrate evaporated. The residue was crystallized as hydrogen oxalate salt from acetone. **16**: 9.9 g (74%), mp 192 °C; NMR (Me_2SO, 360 MHz) δ 0.92 (t, *J* = 8 Hz, 3 H), 1.50 (td, *J* = 13/5 Hz, 1 H), 1.55–1.70 (m, 2 H), 1.79–1.96 (m, 1 H), 2.14 (dd, *J* = 17/12 Hz, 1 H), 2.26 (br d, *J* = 13 Hz, 1 H), 2.7–3.0 (m) and 3.02–3.14 (m, together 7 H), 3.24 (br d, *J* = 12 Hz, 1 H), 3.64 (part of d) and 3.66 (s, together 4 H), 3.76 (s, 3 H), 6.73/6.78 (2 d, *J* = 8 Hz, 2 H), 7.12 (t, *J* = 8 Hz, 1 H), 7.5–10.0 (br, 2 H). Anal. ($C_{19}H_{27}NO_3$·$C_2H_2O_4$) C, H, N, O.

(±)-[[(3α,4aα,10aβ)-1,2,3,4,4a,5,10,10a-Octahydro-6-methoxy-1-propyl-3-benzo[*g*]quinolinyl]carbonyl]hydrazide (17). A solution of **16** (10.7 g of free base, 33.6 mmol) in CH_3OH (200 mL) was treated with hydrazine hydrate (65 mL) and stirred at 50 °C for 20 h. The mixture was evaporated to dryness and water was added followed by extraction with CH_2Cl_2. The organic layer was dried and evaporated. The residue was redissolved in CH_3OH and again evaporated to dryness. The residue solidified on standing. For further purification it was pulverized and suspended in hexane (100 mL). The suspension was stirred for 15 min and the product recovered by filtration to yield 8.4 g (80%) **17**, mp 96 °C. A sample was recrystallized from CH_2Cl_2/hexane: mp 99–100 °C; NMR ($CDCl_3$ + D_2O, 360 MHz) δ 0.94 (t, *J* = 8 Hz, 3 H), 1.45 (td, *J* = 13/5 Hz) and 1.49–1.64 (m, together 3 H), 1.67–1.81 (m, 1 H), 2.12 (dd, *J* = 17/12 Hz, 1 H), 2.19 (br d, *J* = 13 Hz, 1 H), 2.26 (dd, *J* = 11/5 Hz, 1 H), 2.34–2.45 (m) and 2.45 (dd, *J* = 13/3 Hz, together 2 H), 2.62–2.74 (m, 2 H), 2.74–2.85 (m, 1 H), 2.89 (dd, *J* = 17/5 Hz, 1 H), 3.12–3.26 (m, 2 H), 3.79 (s, 3 H), 6.66 (d, *J* = 8 Hz, 1 H), 6.72 (d, *J* = 8 Hz, 1 H), 7.10 (t, *J* = 8 Hz, 1 H). Anal. ($C_{18}H_{27}N_3O_2$) C, H, N, O.

(±)-(3α,4aα,10aβ)-3-Amino-1,2,3,4,4a,5,10,10a-octahydro-6-methoxy-1-propylbenzo[*g*]quinoline (18) Dihydrochloride. A solution of **17** (7.2 g, 22.7 mmol) in THF (210 mL) was treated at −30 °C with a solution of nitrosyl chloride (2 N) in THF (11.5 mL, 23 mmol). The mixture was stirred at reflux temperature for 1 h. HCl (4 N, 250 mL) was added and heating continued for 1 h. The mixture was cooled to 4 °C and the precipitated product recovered by filtration to yield 4.1 g (52%) of pure **18** as dihydrochloride. The filtrate was diluted with THF to yield another batch of 0.7 g (9%). Result: 4.8 g (61%) of **18** as dihydrochloride, mp >270 °C dec; NMR (Me_2SO, 360 MHz) δ 0.98 (t, *J* = 8 Hz, 3 H), 1.65–1.76 (m) and 1.81 (td, *J* = 13/4 Hz, together 3 H), 2.19 (dd, *J* = 17/12 Hz) and 2.27 (br d, *J* = 14 Hz, together 2 H), 2.34–2.49 (m, 1 H), 2.92 (dd, *J* = 17/5 Hz, 1 H), 3.04–3.19 (m, 1 H), 3.24 (dd, *J* = 16/12 Hz, 1 H), 3.33–3.61 (m, 4 H + H_2O), 3.72 (part of d) and 3.77 (s, together 4 H), 3.87 (br s, 1 H), 6.78/6.82 (2 d, *J* = 8 Hz, 2 H), 7.16 (t, *J* = 8 Hz, 1 H), 8.95 (br s, 3 H), 10.94 (br s, 1 H). Anal. ($C_{17}H_{26}N_2O$·2HCl) C, H, N, O, Cl.

(±)-*N*,*N*-Diethyl-*N*′-[(3α,4aα,10aβ)-1,2,3,4,4a,5,10,10a-octahydro-6-methoxy-1-propyl-3-benzo[*g*]quinolinyl]sulfamide (19). A solution of **18** (3.6 g, dihydrochloride, 10.4 mmol) and triethylamine (7.3 mL, 52 mmol) in chloroform (120 mL) was treated with diethylsulfamoyl chloride (4.5 mL, 26.2 mmol). The mixture was stirred overnight at 50 °C. Ice and 1 N $NaHCO_3$ (100 mL) was added and stirring continued for 1 h at room temperature. The mixture was extracted with CH_2Cl_2, and the organic layers were dried and evaporated. The residue was subjected to medium-pressure chromatography over silica, using first CH_2Cl_2 and then CH_2Cl_2/CH_3OH (99:1) to elute. The main fraction was crystallized from diethyl ether/hexane to yield 3.7 g (87%) of pure **19**: mp 88–89 °C; NMR ($CDCl_3$, 360 MHz) δ 0.89 (t, *J* = 8 Hz, 3 H), 1.19 (t, *J* = 8 Hz, 6 H), 1.31 (td, *J* = 13/4 Hz, 1 H), 1.37–1.54 (m, 2 H), 1.71–1.85 (m, 1 H), 2.05 (br d, *J* = 13 Hz) and 2.14 (dd, *J* = 17/12 Hz) and 2.23 (td, *J* = 10/5 Hz, together 3 H), 2.42–2.52 (m, 2 H), 2.56–2.74 (m, 2 H), 2.89 (dd, *J* = 17/5 Hz, 1 H), 2.97 (br d, *J* = 12 Hz, 1 H), 3.14 (dd, *J* = 16/5 Hz, 1 H), 3.26 (q, *J* = 8 Hz, 4 H), 3.56 (dm, *J* = 9 Hz, 1 H), 3.80 (s, 3 H), 5.21 (d, *J* = 9 Hz, 1 H), 6.67 (d, *J* = 8 Hz, 1 H), 6.74 (d, *J* = 8 Hz, 1 H), 7.11 (t, *J* = 8 Hz, 1 H). Anal. ($C_{21}H_{35}N_3O_3S$) C, H, N, O, S.

(±)-*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 (20) Hydrochloride. To a solution of **19** (3.1 g, 7.6 mmol) in CH_2Cl_2 (70 mL) was added dropwise at −60 °C a solution of boron tribromide (4.3 mL) in CH_2Cl_2 (30 mL). The mixture was stirred at −10 °C for 4 h. Water (60 mL) was added and the mixture stirred at room temperature for 15 min. Then ice and 10 N NaOH were added, and the basic mixture was extracted with CH_2Cl_2. The organic layers were dried and evaporated. The

residue was redissolved in hot CH_2Cl_2 and precipitated by addition of HCl in diethyl ether. The precipitated product was recovered by filtration and recrystallized from CH_2Cl_2/CH_3OH to yield 2.9 g (89%) of pure **20** as hydrochloride: mp 234–236 °C; NMR (Me_2SO, 360 MHz) δ 0.97 (t, J = 8 Hz, 3 H), 1.10 (t, J = 8 Hz, 6 H), 1.60–1.82 (m, 3 H), 2.00 (br d, J = 14 Hz, 1 H), 2.14 (dd, J = 17/12 Hz, 1 H), 2.20–2.37 (m, 1 H), 2.90 (dd, J = 17/5 Hz, 1 H), 3.0–3.4 (m, 10 H), 3.49 (br d, J = 11 Hz, 1 H), 3.71 (br s, 1 H), 6.61 (d, J = 8 Hz, 1 H), 6.66 (d, J = 8 Hz, 1 H), 6.96 (t, J = 8 Hz, 1 H), 7.85 (d, J = 8 Hz, 1 H), 9.48 (br s, 1 H), 10.5 (br s, 1 H); the signals at 7.85/9.48/10.5 disappear on exchange with D_2O. Anal. ($C_{20}H_{33}N_3O_3S$·HCl) C, H, N, O, S, Cl.

(±)-(3β,4aα,10aβ)-1,2,3,4,4a,5,10,10a-Octahydro-3-(hydroxymethyl)-1,6-dimethoxybenzo[g]quinoline (21). To a suspension of $LiAlH_4$ (1.12 g, 30 mmol) in THF (100 mL) at room temperature was added dropwise a solution of **14c** (6.0 g, 19.7 mmol) in THF (50 mL). After the mixture was stirred at room temperature for 2 h, water (1.2 mL) was added with care, followed by 20% NaOH (1.2 mL) and again water (4 mL). The reaction mixture was stirred for 30 min and filtered. The filtercake was thoroughly washed with CH_2Cl_2 and the filtrate was evaporated to yield 5.1 g (93%) of **21** as a white powder. A sample was recrystallized from diethyl ether: mp 151–152 °C; NMR ($CDCl_3$, 360 MHz) δ 0.87 (q, J = 12 Hz, 1 H), 1.36 (t, J = 4 Hz, 1 H), 1.68–1.82 (m, 1 H), 1.88 (br d, J = 13 Hz, 1 H), 1.94–2.10 (m, 1 H), 2.20 (dd, J = 16/12 Hz) and 2.25 (t, J = 11 Hz, together 2 H), 2.44 (td, J = 12/4 Hz, 1 H), 2.78 (dd, J = 16/11 Hz, 1 H), 3.01 (dd, J = 17/5 Hz, 1 H), 3.36 (dd, J = 16/5 Hz, 1 H), 3.50–3.70 (m) and 3.72 (s, together 6 H), 3.80 (s, 3 H), 6.66 (d, J = 8 Hz, 1 H), 6.76 (d, J = 8 Hz, 1 H), 7.11 (t, J = 8 Hz, 1 H). Anal. ($C_{16}H_{23}NO_3$) C, H, N, O.

(±)-(3β,4aα,10aβ)-1,2,3,4,4a,5,10,10a-Octahydro-3-[(mesyloxy)methyl]-1,6-dimethoxybenzo[g]quinoline (22). An ice-cooled solution of **21** (4.16 g, 15 mmol) in pyridine (60 mL) was treated with mesyl chloride (2.3 mL) and kept overnight at room temperature. $NaHCO_3$ (1 N, 50 mL) was added with care. The reaction mixture was stirred for 30 min and extracted with CH_2Cl_2. The organic layers were dried and evaporated. The residue was crystallized from ethyl acetate to yield 4.6 g (86%) of pure **22**: mp 176–178 °C; NMR ($CDCl_3$, 360 MHz) δ 0.94 (q, J = 12 Hz, 1 H), 1.70–1.84 (m, 1 H), 1.90 (br d, J = 13 Hz, 1 H), 2.20 (dd, J = 16/12 Hz) and 2.2–2.35 (m) and 2.30 (t, J = 11 Hz, together 3 H), 2.45 (td, J = 12/4 Hz, 1 H), 2.78 (dd, J = 16/11 Hz, 1 H), 3.00 ($^1/_2$ dd, J = 5 Hz) and 3.04 (s, together 4 H), 3.36 (dd, J = 16/4 Hz, 1 H), 3.54 (d, J = 10 Hz, 1 H), 3.61 (s, 3 H), 3.81 (s, 3 H), 4.07–4.24 (m, 2 H), 6.67 (d, J = 8 Hz, 1 H), 6.77 (d, J = 8 Hz, 1 H), 7.12 (t, J = 8 Hz, 1 H). Anal. ($C_{17}H_{25}NO_5S$) C, H, N, O, S.

(±)-(3β,4aα,10aβ)-1,2,3,4,4a,5,10,10a-Octahydro-1,6-dimethoxy-3-[(methylthio)methyl]benzo[g]quinoline (23). An ice-cooled solution of methanethiol (5.1 mL) in DMF (25 mL) was treated in portions with a dispersion of sodium hydride in oil (2.0 g, 50% NaH). At 0 °C a suspension of **22** (3.9 g, 11 mmol) in DMF (40 mL) was added. The reaction mixture was stirred at 0 °C for 2 h and evaporated to dryness at high vacuum. Water was added followed by extraction with CH_2Cl_2. The organic layer was dried and evaporated and the residue crystallized from hexane to yield 3.0 g (90%) of **23**. A sample was recrystallized from diethyl ether: mp 93–94 °C; NMR ($CDCl_3$, 360 MHz) δ 0.85 (q, J = 12 Hz, 1 H), 1.65–1.82 (m, 1 H), 1.92–2.09/2.10–2.28 (2 m) and 2.12 (s, together 7 H), 2.35–2.53 (m, 3 H), 2.77 (dd, J = 16/11 Hz, 1 H), 3.02 (dd, J = 17/5 Hz, 1 H), 3.38 (dd, J = 16/4 Hz, 1 H), 3.60 (part of d) and 3.64 (s, together 4 H), 3.80 (s, 3 H), 6.66 (d, J = 8 Hz, 1 H), 6.76 (d, J = 8 Hz, 1 H), 7.11 (t, J = 8 Hz, 1 H). Anal. ($C_{17}H_{25}NO_2S$) C, H, N, O, S.

(±)-(3β,4aα,10aβ)-1,2,3,4,4a,5,10,10a-Octahydro-6-methoxy-3-[(methylthio)methyl]benzo[g]quinoline (24). Compound **23** (2.55 g, 8.3 mmol) and Zn powder (12.3 g) were stirred overnight in acetic acid/water (2:1, 40 mL). The reaction mixture was filtered, the filtercake washed with ethyl acetate, and the filtrate evaporated to dryness. To the residue was added CH_2Cl_2 followed by a second filtration. The filtrate was extracted twice with 1 N $KHCO_3$, dried, and evaporated to yield 2.1 g (91%) of **24** as a white solid. A sample was recrystallized from diethyl ether: mp 106–108 °C; NMR ($CDCl_3$ + D_2O, 360 MHz) δ 0.93 (q, J = 12 Hz, 1 H), 1.44–1.58 (m, 1 H), 1.78–1.91 (m, 1 H), 2.08–2.19 (m) and 2.11 (s, together 5 H), 2.35–2.46 (m, 3 H), 2.53 (td, J = 11/4 Hz) and 2.62 (dd, J = 16/11 Hz, together 2 H), 2.90 (dd, J = 16/5 Hz) and 2.97 (dd, J = 17/5 Hz, together 2 H), 3.27–3.35 (m, 1 H), 3.81 (s, 3 H), 4.0–6.5 (br, 1 H), 6.66/6.74 (2 d, J = 8 Hz, 2 H), 7.11 (t, J = 8 Hz, 1 H). Anal. ($C_{16}H_{23}NOS$) C, H, N, O, S.

(±)-(3β,4aα,10aβ)-1,2,3,4,4a,5,10,10a-Octahydro-6-methoxy-3-[(methylthio)methyl]-1-propylbenzo[g]quinoline (25). Compound **24** (1.47 g, 5.3 mmol) in DMF (15 mL) was treated with propyl iodide (0.7 mL, 7.2 mmol) and K_2CO_3 (1.5 g, 10.9 mmol) and stirred at room temperature for 20 h. The reaction mixture was filtered and the filtrate evaporated to dryness. To the residue was added water followed by extraction with CH_2Cl_2. The organic layers were dried and evaporated to yield 1.5 g (89%) of **25** as a slowly solidifying yellow oil. A sample was recrystallized from hexane: mp 71–72 °C; NMR ($CDCl_3$, 360 MHz) δ 0.80/0.83 (parts of q, J = 12 Hz) and 0.89 (t, J = 8 Hz, together 4 H), 1.45–1.60 (m, 2 H), 1.60–1.75 (m, 1 H), 1.88–2.03 (m, 2 H), 2.03–2.25 (m) and 2.10 (s, together 6 H), 2.34–2.49 (m, 2 H), 2.50–2.70 (m, 2 H), 2.70–2.83 (m, 1 H), 2.97 (dd, J = 17/5 Hz, 1 H), 3.18 (dd, J = 16/5 Hz and d, J = 10 Hz, 2 H), 3.80 (s, 3 H), 6.66 (d, J = 8 Hz, 1 H), 6.74 (d, J = 8 Hz, 1 H), 7.11 (t, J = 8 Hz, 1 H). Anal. ($C_{19}H_{29}NOS$) C, H, N, O, S.

(±)-(3β,4aα,10aβ)-1,2,3,4,4a,5,10,10a-Octahydro-6-hydroxy-3-[(methylthio)methyl]-1-propylbenzo[g]quinoline (26). To a solution of **25** (2.0 g, 6.2 mmol) in CH_2Cl_2 (100 mL) was added dropwise at −30 °C a solution of boron tribromide (3.6 mL, 37.6 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at −10 °C for 5 h. $KHCO_3$ (1 N, 125 mL) was added with care and stirring continued at room temperature for 15 min. Ice and 2 N NaOH were added to adjust for pH 12. The basic mixture was extracted with CH_2Cl_2. The organic layers were dried and evaporated. The residue was redissolved in CH_2Cl_2/CH_3OH (1:1) (100 mL). HCl (7 N) in CH_3OH (10 mL) was added and the solution stirred at reflux temperature for 10 min. After cooling, the reaction mixture was treated with 1 N NaOH to adjust for pH 10. The basic solution was extracted with CH_2Cl_2, and the organic layers were dried and evaporated. The residue was suspended in diethyl ether and filtered to yield 1.28 g (67%) of **26**: mp 173–174 °C; NMR ($CDCl_3$, 360 MHz) δ 0.81/0.85 (parts of q, J = 12 Hz) and 0.90 (t, J = 8 Hz, together 4 H), 1.45–1.62 (m, 2 H), 1.65–1.80 (m, 1 H), 1.90–2.04 (m, 2 H), 2.07–2.28 (m) and 2.10 (s, together 6 H), 2.34–2.47 (m, 2 H), 2.5–2.6/2.6–2.71/2.71–2.83 (3 m, 3 H), 2.90 (dd, J = 17/5 Hz, 1 H), 3.12–3.25 (m, 2 H), 5.14 (br s, 1 H), 6.59 (d, J = 8 Hz, 1 H), 6.72 (d, J = 8 Hz, 1 H), 7.00 (t, J = 8 Hz, 1 H). Anal. ($C_{18}H_{27}NOS$) H, N, O, S; C: calcd, 70.8; found, 69.0.

Inhibition of Prolactin Secretion in Male Rats. Adult male 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 nanograms/milliliter are expressed in terms of the NIH standard rat Prl RP-1, and the dose needed for 50% reduction of serum prolactin level was estimated graphically.

Inhibition of Ovum Implantation. Adult proestrus female rats (Ivanovas strain) were brought together with males of proven fertility. The next morning (day 1) the sperm-positive females were randomly allocated to the different treatment groups (4–10 animals per group). On day 5 a single dose of the drug was injected subcutaneously. The rats were killed on day 12 and the uteri were dissected out and inspected for the presence of fetusses or implantation sites. If none were found, ovum implantation was considered to have been inhibited. The dose required for 50% inhibition was determined by means of probit analysis.

Inhibition of Spontaneous Lactation. A method similar to that described by Auskova et al.[34] was used. Pregnant rats of

(34) Auskova, M.; Rezabek, K.; Zikan, V.; Semonsky, M. *Endocrinol. Exp.* **1974**, *8*, 51.

Ivanovas strain were kept in single cages with 14 h of light, 23 °C, and water and food ad libitum. On the third day postpartum, the number of pups was standardized to eight per female. The litter of each female was weighed daily at 10 a.m. to the nearest gram. Each pup was checked for the presence of milk in its stomach which is apparent as a "milk spot" through the translucent body wall. From day 5 to 8 inclusive the mothers were treated orally with test compound or vehicle (0.5 mL/100 g of body weight). The weight gains of the litters and the presence of milk spots were checked until the 12th day. Suckling mother animals were checked daily for signs of abnormal nursing behavior. Experimental animals which lost more than two pups during this time were excluded from subsequent evaluation. Differences in growth rate between the pups of treated and untreated females were evaluated by means of probit analysis. The ID_{50} is the dose of test compound which given once daily from day 5 to 8 produces a 50% inhibition.

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[35] and [^{3}H]dopamine,[36] both in calf caudate; for serotonin receptors, [^{3}H]spiperone in rat frontal cortex[37] and [^{3}H]serotonin in whole rat brain;[38] and for α-adrenoceptors,[39] [^{3}H]clonidine in rat brain minus cerebellum and [^{3}H]WB4101 in whole rat brain.

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Molecular Interactions of Toxic Chlorinated Dibenzo-*p*-dioxins and Dibenzofurans with Thyroxine Binding Prealbumin

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The interactions of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and related compounds with prealbumin, a model for the nuclear thyroid hormone receptor, have been studied with use of computer graphics and predictions made regarding relative binding affinities for such structures. These modeling predictions were tested by experimentally measuring the binding affinities of dioxin and furan analogues. The results were in general agreement with the modeling predictions and demonstrated that such compounds could be effective competitive binding ligands for thyroxine-specific binding sites in prealbumin. The computer modeling work also demonstrates the importance of lateral chlorine substitution in the binding of these toxic compounds. The prealbumin interaction model should be of use in investigating the structure–toxicity relationships of these classes of toxic compounds. Thus, if prealbumin is a model for the nuclear thyroid hormone receptor, this work would also have major implications bearing on the mechanism of dioxin toxicity and the potential of these compounds to function as potent and persistent thyroxine agonists. A new cooperative receptor mechanism for dioxin toxic action is proposed.

A number of compounds contained in the broad class of halogenated aromatic hydrocarbons including the polychlorinated biphenyls (PCBs), dibenzofurans (PCDFs), and dibenzo-*p*-dioxins (PCDDs) produce a characteristic toxic syndrome.[1] 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and 2,3,7,8-tetrachlorodibenzofuran (TCDF) are two of the most toxic compounds of this type (Chart I, drawn and numbered to correspond with figures and tables). These highly toxic compounds are also inducers of cytochrome P-448 mediated mixed function oxidase enzyme systems. The toxicity and induction response are both thought to involve initial binding of the hydrocarbons to the same cytosolic receptor (Ah receptor), but the subsequent events are not understood.[2]

In previous work[3] from this laboratory, the structure–induction relationship was found to be different from the structure–toxicity relationship. However, both depended,

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