and the pellet resuspended in 14 volumes of Tris-HCl buffer. Aliquots (100 μL) containing approximately 0.3 to 0.4 mg of protein were added to incubation tubes. Total incubation volume was 500 μL and, in addition to tissue and varying amounts of drug compounds, contained the following: Tris-HCl buffer (50 mM, pH 7.7 at 25 °C), $MgCl_2$ (5 mM), ethanol (0.5 to 2%), and [^{3}H]clozapine (2.1 nM, specific activity = 24 Ci/mmol). Tissue samples were incubated both in the presence and absence of 1 μM atropine, a concentration sufficient to block [^{3}H]clozapine binding to muscarinic receptors.[17,30] [^{3}H]Clozapine binding in the presence of 10 μM clozapine was used to define nonspecific binding. Samples (prepared in triplicate) were incubated and filtered as described for [^{3}H]spiroperidol binding except that Tris-HCl buffer for filter washing contained 5 mM $MgCl_2$ and 0.5% ethanol and filters were presoaked in a 100 μM solution of unlabeled clozapine.

Determination of Affinity for Spiroperidol Binding Sites. Utilizing methods described previously,[19] frozen rat caudate nuclei were homogenized in 100 volumes of ice-cold Tris-HCl buffer (50 mM, pH 7.7 at 25 °C). Homogenates were centrifuged (50000*g* for 10 min at 5 °C) and the resulting pellet was resuspended in 100 volumes of Tris-HCl buffer. The tissue suspension was again centrifuged and the pellet resuspended in 150 volumes of Tris-HCl buffer containing the following: Tris-HCl buffer (50 mM, pH 7.7 at 25 °C), NaCl (120 mM), KCl (5 mM), $CaCl_2$ (1 mM), $MgCl_2$ (1 mM), ascorbic acid (0.1%), and pargyline (10 μM). The tissue suspension was warmed to 37 °C for 10 min and then returned to an ice bath. Various drug compounds and [^{3}H]spiroperidol (2.2 nM, specific activity = 35.9 Ci/mmol) were dissolved in 0.1% ascorbic acid. In some cases ethanol was added to aid solubility of the test compounds. The effect of this addition was controlled by adding equal amounts of ethanol to the assays used to determine total and nonspecific binding. Aliquots (1.8 mL) of the tissue suspension were added to incubation tubes together with varying amounts of drug compounds and [^{3}H]spiroperidol for a final volume of 2 mL. Samples (prepared in triplicate) were incubated for 20 min at 37 °C and then filtered over glass fiber filters (Whatman GF/C). Filters were washed with 15 mL of Tris-HCl buffer (50 mM, pH 7.7 at 25 °C), and the radioactivity remaining on the filters was determined by liquid scintillation counting techniques. The amount of [^{3}H]spiroperidol bound in the presence of 10 μM unlabeled spiroperidol is used to define nonspecific binding. Specific binding is defined as the difference between total and nonspecific binding.

Acknowledgment. These studies were supported by the Tennessee Department of Mental Health and Mental Retardation and by a fellowship from Hoffmann-La Roche to P.L.M.

(30) Unpublished observation from this laboratory.

A Dopamine Receptor Model and Its Application in the Design of a New Class of Rigid Pyrrolo[2,3-*g*]isoquinoline Antipsychotics

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A hypothetical model of the interaction of antipsychotic drugs with the dopamine receptor is described. This three-dimensional molecular model has been developed on the basis of plausible intermolecular interactions between pharmacophoric groups of diverse types of antipsychotic drugs and postulated amino acid side chain substituents of the receptor protein. Three essential binding sites (one possibly required for antagonism) and one lipophilic auxiliary binding site are identified. The geometry is defined via the three-dimensional structures of drugs exhibiting receptor activity, including (*R*)-apomorphine, (+)-dexclamol, and molindone (whose crystal structure has been determined). A new conformationally rigid pyrrolo[2,3-*g*]isoquinoline derivative has been designed to conform to the receptor model. The compound (±)-1 (2,6-dimethyl-3-ethyl-4,4a,5,6,7,8,8a,9-octahydro-4a,8a-*trans*-1*H*-pyrrolo[2,3-*g*]isoquinolin-4-one; Ro 22-1319) exhibits potent antipsychotic-like activity. The activity is stereospecific, residing in the (-) enantiomer, predicted and confirmed by X-ray crystal structure analysis of (-)-1·HCl to have the 4a*R*,8a*R* absolute configuration.

The methodology of drug design could be greatly improved if receptors and their mode of interaction with active substances were known in precise molecular detail. Such information could be used, for example, to design conformationally defined structures in which pharmacophoric groups are oriented in the proper spatial arrangement for optimal receptor interaction. Compounds with this three-dimensional complementarity to a receptor should show greater potency, exhibit higher specificity, and have fewer effects at other receptors than conformationally flexible structures. Aspects of this ideal of drug design have been approached in the synthesis of enzyme inhibitors starting from the solid-state structures of enzyme–substrate complexes obtained through X-ray crystallography[1] and in the preparation of intercalating substances on the basis of the Watson–Crick model of DNA and the crystal structures of DNA model fragments.[2]

The molecular features of important pharmacologic receptors, however, are presently unknown beyond their pharmacological and biochemical classification[3] and their

(1) D. A. Matthews, R. A. Alden, J. T. Bolin, S. T. Freer, R. Hamlin, N. Xuong, J. Kraut, M. Poe, M. Williams, and K. Hoogsteen, *Science*, **197**, 452 (1977); K. K. Kannan, I. Vaara, B. Notstrand, S. Lövgren, A. Borell, K. Fridborg, and M. Petef in "Drug Action at the Molecular Level", C. G. K. Roberts, Ed., University Park Press, Baltimore, 1977, p 73; P. J. Goodford, *ibid.*, p. 109; D. W. Cushman, H. S. Cheung, E. F. Sabo, and M. A. Ondetti, *Biochemistry*, **16**, 5484 (1977).

(2) T. K. Chen, R. Fico, and E. S. Canellakis, *J. Med. Chem.*, **21**, 868 (1978); H. M. Sobell, *Annu. Rev. Biophys.*, **5**, 307 (1976).

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description as membrane-bound proteins.[4] For these systems, receptors must be characterized and differentiated not by their own architecture but by what is known about compounds exhibiting receptor activity.

Our own efforts have been directed to the case of dopamine receptors, where considerable process has been made in defining minimal structural requirements for agonist[5] and antagonist[6] activity. For the antagonist neuroleptic drugs, these studies, as well as conformational analyses of the relationship of neuroleptics to dopamine[7] and the synthesis of some semirigid compounds,[8,9] have produced greatly detailed descriptions of the structural characteristics of neuroleptic drugs[6,8,9] and concepts of the shape and geometry of a receptor surface.[9] However, these definitions have been obtained by considering only the molecular features of the drug compounds which are ligands for the protein receptor. Consequently, the existing models for the receptors are abstract and are far removed from our understanding of the chemical structure and dynamics of proteins and their mode of interaction with small molecules.[10] A significant improvement in a receptor model is achieved when the molecular features and properties of the receptor are considered.

In this article, we first detail our development of a hypothetical molecular model of a receptor for antipsychotic drugs in which protein functional groups constitute three-dimensional molecular features of the receptor. We then report the synthesis of a new class of conformationally rigid pyrrolo[2,3-*g*]isoquinoline derivatives designed on the basis of the receptor model. Compounds of this series exhibit a potent antipsychotic-like pharmacological profile with promisingly weak cataleptogenic activity and a lack of autonomic liability. The prototype of the series, (±)-2,6-dimethyl-3-ethyl-4,4a,5,6,7,8,8a,9-octahydro-4a,8a-*trans*-1*H*-pyrrolo[2,3-*g*]isoquinolin-4-one (1, Ro 22-1319), is currently undergoing clinical trails as an antipsychotic drug.

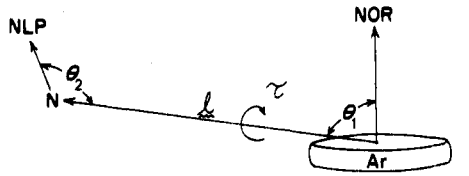
Basis of the Hypothetical Model. Although the actual molecular features of dopamine receptors are unknown, it may be presumed that, within a biochemical class,[3d] the same segments of the receptor protein are responsible for binding all the drug substances having that receptor-mediated activity. This binding is a physicochemical phenomenon which must involve characterizable intermolecular interactions, such as ionic and hydrogen bonding, dipolar effects, π–π interactions such as stacking, and hydrophobic and hydrophilic forces.[10] The drug molecule may be considered to bind by a combination of these forces to the accessible amino acid side chains of the receptor protein.

Dopamine, dopamine agonists such as (*R*)-apomorphine, and neuroleptic drugs all possess a basic nitrogen atom separated by a 5–7-Å chain or framework from an aromatic ring. It is thus reasonable to assume that these two groups are pharmacophores and are bound to complementary functionality on the receptor protein.

The basic amino group can be envisaged to bind to an acidic amino acid residue. Although other groups capable of hydrogen bonding could give a reasonable drug–receptor bond, the amine nitrogen would certainly be protonated in close proximity to an acidic amino acid,[11] so an ammonium–carboxylate bond ($COO^-\cdots H-N^+$) between the protonated amine nitrogen and the carboxylate oxygen along the direction of the hydrogen bond seems most reasonable for the formalism.

The aromatic moiety in our model is considered to form a π–π stacking interaction with an aromatic amino acid residue (e.g., phenylalanine, tyrosine, tryptophan). This face-to-face overlapping of two aromatic rings provides a defined geometrical relationship between the aromatic ring of the drug and the basic nitrogen, as seen in many classes of dopamine agonists and antagonists. The inactivity of compounds having bulky groups which could interfere with stacking and the inactivity of a ring-opened butaclamol analogue[12] (the ring has the correct placement but the wrong orientation) lend support to the stacking model for binding of the aromatic ring. An energy of 5–6 kcal/mol

Table I. Angular Relationships of Pharmacophores in Drugs Acting at Dopamine Receptors[a]



compd	|l|, Å	θ_2, deg	θ_2, deg	τ, deg
(*R*)-apomorphine 1[b]	5.12	99.1	99.4	−9.1
(*R*)-apomorphine 2[b]	5.09	104.1	101.9	7.7
(+)-dexclamol (conformer B)	4.92	101.3	108.6	45.3
pyrroloisoquinoline (−)-1	5.93	88.6	90.6	−19.1
(+)-butaclamol (conformer A)	5.13	84.3	95.5	65.1
molindone hydrochloride	6.06	86.6	88.0	−106.5

[a] |l| = length of vector from midpoint of aromatic ring (Ar) to basic nitrogen (N). θ_1 = angle between normal to aromatic ring (NOR) and vector l. θ_2 = angle between vector l and nitrogen–nitrogen lone-pair (NLP) bond. τ = torsion angle NOR-Ar-N/Ar-N-NLP; + for clockwise rotation viewed from Ar to N. [b] There are two molecules (1, 2) in the unit cell.[14b]

(3) (a) α_1,α_2 receptors: S. Berthelsen and W. A. Pettinger, *Life Sci.*, **21**, 595 (1977); (b) β_1,β_2 receptors: K. P. Minneman and P. B. Molinoff, *Biochem. Pharmacol.*, **29**, 1317 (1980); (c) H-1,H-2 receptors: J. W. Black, W. A. M. Duncan, C. J. Durant, C. R. Ganellin, and E. M. Parsons, *Nature (London)*, **236**, 385 (1972); (d) D-1,D-2 receptors: J. W. Kebabian and D. B. Calne, *ibid.*, **277**, 93 (1979).

(4) B. D. Boyan-Salyers and Y. Clement-Cormier, *Biochim. Biophys. Acta*, **617**, 274 (1980).

(5) J. G. Cannon, C. Suarez-Gutierrez, T. Lee, J. P. Long, B. Costall, D. H. Fortune, and R. J. Naylor, *J. Med. Chem.*, **22**, 341 (1979); N. J. Bach, E. C. Kornfeld, N. D. Jones, M. O. Chaney, D. E. Dorman, J. W. Paschal, J. A. Clemens, and E. B. Smalstig, *J. Med. Chem.*, **23**, 481 (1980); H. L. Komiskey, J. F. Bossart, D. D. Miller, and P. N. Patil, *Proc. Natl. Acad. Sci. U.S.A.* **75**, 2641 (1978).

(6) H. W. Gschwend in "Neuroleptics", S. Fielding and H. Lal, Eds., Futura, New York, 1974, p 1; A. Pletscher and E. Kyburz in "Schizophrenia Today", D. Kemali, G. Bartholini, and D. Richter, Eds., Pergamon, London, 1976, p 183.

(7) A. P. Feinberg and S. H. Synder, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 1899 (1975); J. P. Tollenaere, H. Moereels, and M. H. J. Koch, *Eur. J. Med. Chem. Chim. Ther.*, **12**, 199 (1977).

(8) L. G. Humber, F. T. Bruderlein, and K. Voith, *Mol. Pharmacol.*, 11, 833 (1975); W. C. Randall, P. S. Anderson, E. L. Cresson, C. A. Hunt, T. F. Lyon, K. E. Rittle, D. C. Remy, J. P. Springer, J. M. Hirshfield, K. Hoogsteen, M. Williams, E. A. Risley, and J. A. Totaro, *J. Med. Chem.*, **22**, 1222 (1979).

(9) (a) L. G. Humber, F. T. Bruderlein, A. H. Philipp, M. Götz, and K. Voith, *J. Med. Chem.*, **22**, 761 (1979); (b) A. H. Philipp, L. G. Humber, and K. Voith, *ibid.*, **22**, 768 (1979).

(10) For a recent review, see P. A. Kollman in "Burger's Medicinal Chemistry", 4th ed., Part 1, M. E. Wolff, Ed., Wiley, New York, 1980, p 313.

(11) This conclusion is in contrast to that of Humber,[9b] who ruled out protonation on the basis of the pK_a of butaclamol (5.9) and of homogenized caudate tissue (7.3).

(12) M. J. Kukla, J. L. Bloss, and L. R. Brougham, *J. Med. Chem.*, **22**, 401 (1979).

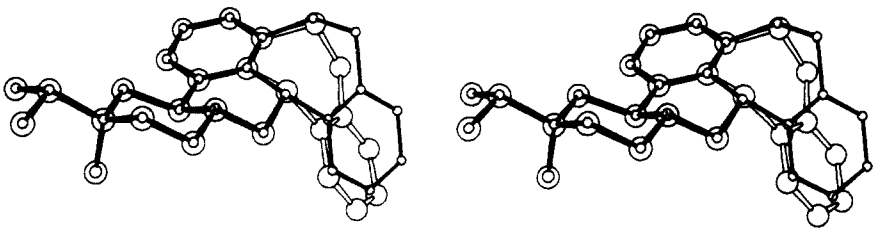


Figure 1. Dexclamol conformer A (solid bonds) from crystal structure[14] superimposed on computer-generated conformer B (open bonds).

has been calculated by Kier for similar stacking interactions in a series of phenylethylamines binding to a tryptophan ring model.[13]

The separation between these two hypothetical receptor features and the geometrical relationship between them can be defined by considering how representative classes of compounds (especially rigid analogues) could bind both features. The angular relationships which are observed in X-ray crystallographic studies[14] indicate that the nitrogen–nitrogen lone pair (or N^+–H) bond in the rigid compounds forms a torsion angle (τ) with the normal to the aromatic ring varying over a small range (ca. 60°, see Table I). This relationship might be expected if the two pharmacophores were interacting with the receptor features from the same face of the molecule. The adaptability of the receptor to accommodate the range of torsion angles exhibited by several rigid compounds can be understood to lie in internal rotations of the protein side chains without altering the peptide backbone.

Illustration of the Hypothetical Model. The X-ray crystal structure of the potent neuroleptic drug (+)-dexclamol[14a] has been used as the starting point for the illustration of the model (the crystal structure of the *tert*-butyl analogue, butaclamol, has higher standard deviations). The biologically relevant conformer B[9] was generated from the crystal structure conformer A (by refection and superposition of appropriate atoms) and is used for further modeling. (See Figure 1 and supplementary material.)

In the model (Figure 2), the carboxylate of the receptor is positioned above the protonated basic nitrogen at a normal linear hydrogen bond distance of 2.9 Å (N to O). The aromatic ring is represented for simplicity as a phenyl positioned above the convex face of the A ring of dexclamol to avoid steric contacts on the concave face at a distance equal to twice the van der Waal's radius (3.6 Å) with the ring planes parallel (Figure 2a).[15]

When compounds with flexible chains between the aromatic ring and basic nitrogen are oriented to bind the carboxylate and to stack with the π system, the coincidence of another group of features among dopamine antagonists becomes apparent (Figure 3). Thus, in all tricyclic and diphenylbutylpiperidine compounds, a second aromatic ring appears at a location which could match that occupied by ring B of dexclamol. In butyrophenones, the presence of a ketone carbonyl instead of this second aromatic moiety is apparent. A carbonyl group at this position is also seen in atypical neuroleptics such as molindone and the benzamides. Since the common characteristic of a carbonyl oxygen and an aromatic ring is their localization of electron density, we speculate that a third molecular feature on the receptor may be another aromatic amino acid residue. This residue could bind ring B of dexclamol or the second aromatic ring of the tricyclics or diphenylbutylpiperidines by a stacking interaction. The carbonyl groups of the other neuroleptics could bind by interaction of the n electrons with the face of the aromatic ring of the receptor.[16]

This third binding site would not be occupied by functionality on dopamine or rigid congeners such as ADTN,[17] and the second aromatic ring of apomorphine would interfere with stacking by presenting its edge rather than its face. These observations offer a tentative molecular rationalization of the mechanism of antagonism by implying that binding this third site by some electronegative group leads to antagonist activity and is unnecessary for agonist activity.

A fourth binding region of low structural specificity can also be identified. It may bind bulky alkyl or aryl groups and a variety of spiropiperidine or benzimidazolone groups seen in the butyrophenone analogues. This site is most probably a lipophilic cavity of large dimension nearest the binding site for the basic nitrogen (dashed lines, Figure 3). This auxiliary site corresponds to the accessory binding site elucidated by Humber, et al.[9] Pyrroloisoquinoline compounds we have prepared indicate that binding this site is unessential for in vivo pharmacological activity, although probably required for strong displacement of [^{3}H]spiroperidol in in vitro receptor binding assays.[18]

Drug Design. Study of this receptor model led to the design of a series of 4a,8a-*trans*-pyrrolo[2,3-*g*]isoquinoline derivatives (e.g., 1) incorporating some functionality conceptually derived from molindone and a conformation and configuration built into a rigid molecular framework to conform to the receptor model (Figure 2b).

The 4a,8a-trans ring fusion of these compounds assures that the aromatic ring, nitrogen lone pair, and carbonyl group are fixed in an orientation to optimize receptor interaction with the first, second, and third essential binding sites, respectively. The torsion angle τ (see Table I) between the normal to the aromatic ring and the nitrogen–nitrogen lone-pair bond in these compounds is −19°. Thus, in terms of conformation, 1 resembles apomorphine (τ = −9.1°) more closely than dexclamol (conformer B) (τ =

(13) T. Dipaolo, L. H. Hall, and L. B. Kier, *J. Theor. Biol.*, 71, 295 (1978).

(14) (a) Dexclamol: P. Bird, F. T. Bruderlein, and L. G. Humber, *Can. J. Chem.*, **54** , 2715 (1976); (b) (*R*)-Apomorphine: J. Giesecke, *Acta Crystallogr., Sect. B*, **29**, 1785 (1973).

(15) For a definition of stacking criteria, see W. K. Olson, *Biopolymers*, **15**, 859 (1976). The 3.6-Å separation represents a minimum; Kier's calculations[13] used a 4.5-Å separation.

(16) Such an interaction has been directly observed in the crystal structure of an imidazo[1,5-*a*][1,4]diazepine associated with a molecule of acetone. In the complex, the actone oxygen is almost directly above the midpoint of the aromatic ring at a distance of 3.57 Å and the carbonyl group is at an angle of 129° (ring midpoint–O-C) (J. F. Blount and A. Walser, unpublished results).

(17) J. G. Cannon, T. Lee, H. D. Goldman, B. Costall, and R. G. Naylor, *J. Med. Chem.*, **20**, 1111 (1977).

(18) Analogues of 1 having lipophilic functional groups targeted for the auxiliary binding site (e.g., the 6-benzyl derivative) are potent in [^{3}H]spiroperidol binding. Details of this study will be published in due course (G. L. Olson, W. D. Horst, and R. A. O'Brien).

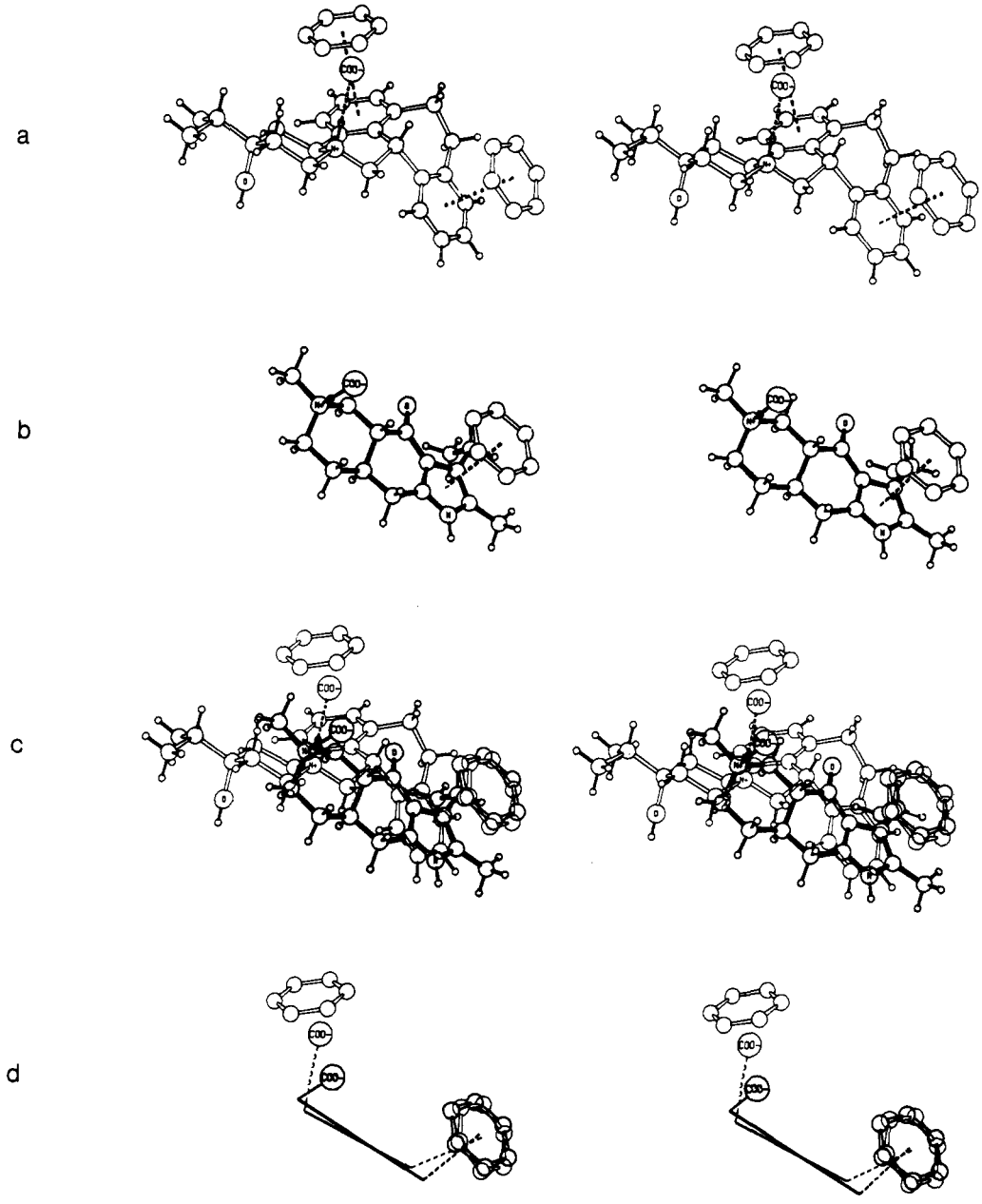


Figure 2. (a) Dexclamol conformer B (open bonds) and idealized receptor groups; (b) pyrroloisoquinoline 1 (solid bonds) and idealized receptor groups; (c) least-squares superposition of a and b; (d) position of receptor features in c indicating range of motion of primary receptor functional groups to bind both drugs optimally.

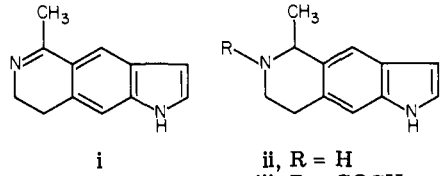
45.3°). If a traditional pattern matching exercise were carried out considering only the aromatic ring centers and the basic nitrogen and its lone pair for these three drugs, one could conclude that they match quite poorly.[19] If the least-squares superposition of dexclamol (conformer B) and the pyrroloisoquinoline (Figure 2c) encompasses not only these points but also the aromatic ring binding site of the receptor, a very reasonable picture of the interaction of these diverse drugs with a dynamic receptor emerges (Figure 2d). The closeness of the receptor features for these seemingly unrelated drug compounds is striking, and can easily be understood in terms of small motions of the functional groups of the receptor protein side chains.

The three-dimensionality of the receptor model enables the prediction of the absolute configuration of the receptor-interactive enantiomer of a chiral antipsychotic. In the pyrroloisoquinoline series, the 4a*R*,8a*R* configuration (as illustrated in the figures) is predicted. Indeed, resolution of (±)-1 with *d*- and *l*-tartaric acids afforded a biologically active (-) enantiomer [(-)-1·HCl, $[\alpha]^{25}_{D}$ -120.8° (*c* 0.81, H_2O)] and an inactive (+) enantiomer [(+)-1·HCl, $[\alpha]^{25}_{D}$ +121.4° (*c* 0.44, H_2O)]. An X-ray crystal structure determination of (-)-1·HCl showed it to have the predicted 4a*R*,8a*R* configuration.

Chemistry. Pyrrolo[2,3-*g*]isoquinoline is a new tricyclic heterocycle,[20] so new approaches had to be developed for the synthesis of the target compound 1. In one route

(19) See Table I: $\Delta\tau$ = 64.3°; $\Delta|l|$ = 1.01 Å.

(20) Compounds i–iii are the only other reported examples of the pyrrolo[2,3-*g*]isoquinoline ring system [S. Naruto and A. Terada, *Chem. Pharm. Bull.*, **23**, 3184 (1975)].



i ii, R = H
iii, R = $COCH_3$

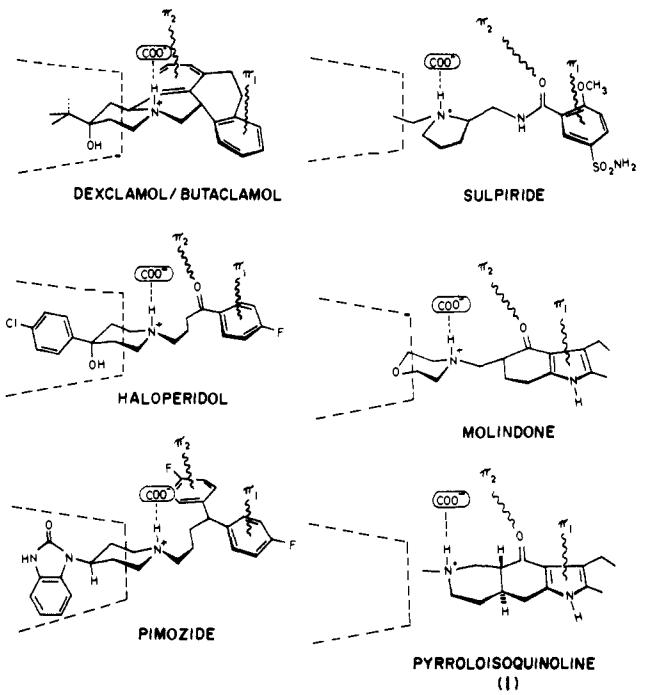
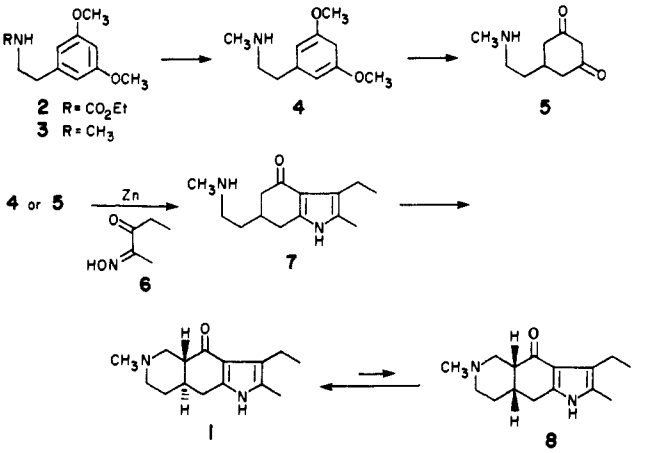


Figure 3. Receptor interactions of diverse antipsychotic drugs: aromatic groups (π_1, π_2), carboxylate group (COO^-), and auxilliary lipophilic binding site (dashed lines).

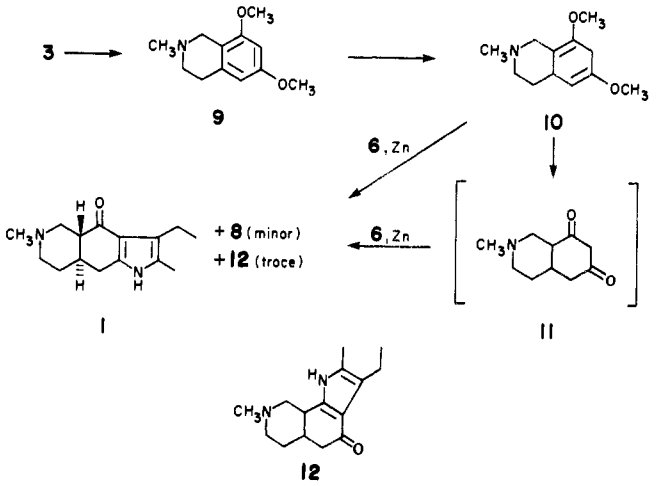
Scheme I



(Scheme I), the pyrrole ring is formed first using the Knorr reaction[21] on a symmetrical 1,3-diketone, followed by closure of the isoquinoline ring by an intramolecular Mannich reaction. In the other route (Scheme II), the pyrrole is synthesized by the Knorr process on a preformed isoquinoline to afford the pyrrolo[2,3-*g*]isoquinoline as the major product, together with a trace of a compound tentatively identified as the pyrrolo[2,3-*h*]isoquinoline isomer.

In the first approach (Scheme I), (3,5-dimethoxyphenyl)ethylamine[22] was converted to the carbamate **2** with ethyl chloroformate. Reduction of crude **2** with sodium dihydrobis(2-methoxyethoxy)aluminate afforded the *N*-methylamine **3** in 83% overall yield. Birch reduction of **3** with lithium in ammonia containing *tert*-butyl alcohol afforded the bis(enol ether) **4** in 75% yield. Hydrolysis of **4** with 6 N HCl in tetrahydrofuran gave diketone **5** in 69% yield after ion-exchange chromatography. Knorr condensation of **5** with 2-isonitroso-3-pentanone[23] (**6**) in

Scheme II



70% acetic acid afforded the dihydroindolone **7** in 52% yield. To avoid isolating the water-soluble, zwitterionic diketone **5**, the Knorr reaction was carried out directly on the bis(enol ether) **4** after a period of heating in the 70% acetic acid solvent to give **7** in 47% overall yield.

Reaction of **7** as its HCl salt with paraformaldehyde in octanol at 175–180 °C afforded the 4a,8a-*trans*-pyrrolo[2,3-*g*]isoquinoline **1** in 40% yield as the major product. The cis isomer **8** was enriched in the mother liquors from the crystallization of **1** and could be isomerized by heating the HCl salt at 190 °C in ethylene glycol (e.g., from a 40:60 mixture to a 75:25 mixture of **1**/**8**). A distinct, broad, one-proton doublet in the NMR spectrum of the major, trans isomer **1** at δ 3.47 ppm, assigned to the equatorial proton at C-5, and a three-proton singlet at δ 2.30 ppm, assigned to the 6-methyl of the cis isomer **8**, served to identify the isomers. The structure of **1** was unequivocally established via the X-ray crystal structure of (–)-**1**·HCl.

In the second route (Scheme II), the tetrahydroisoquinoline **9** was prepared by refluxing **3** with formalin (88% yield). Birch reduction of **9** afforded the crude bis(enol ether) **10**, together with several demethoxylated products. Crude **10** was condensed directly with **6** (Zn, 70% acetic acid) to give **1**, via the diketone **11**, in 29% overall yield after chromatography. NMR of the chromatographed product indicated the presence of ~12% of a slightly more polar compound presumed to be the pyrrolo[2,3-*h*]isoquinoline isomer **12**.

Pharmacology. The activity of the pyrroloisoquinoline (±)-**1** and its enantiomers, as their water-solbule HCl salts, was determined in a rat discrete avoidance procedure. In this, as in similar discrete avoidance procedures,[24] antipsychotic drugs are distinguished from other types of compounds by the larger separation they exhibit between doses which block avoidance responding (ABD) and doses which block escape responding (EBD). The clinical potency of antipsychotic drugs with known therapeutic activity is significantly and highly correlated with their potency in this procedure[25] and with their dopamine antagonist activity.

The pharmacological data shown in Table II indicate that (±)-**1** has antipsychotic-like activity in the avoidance

(21) S. Hauptmann, H. Blume, G. Hartmann, P. Haendel, and P. Franke, *Z. Chem.*, **6**, 107 (1966).
(22) F. Benington, R. D. Morin, L. C. Clark, Jr., and R. P. Fox, *J. Org. Chem.*, **23**, 1979 (1958).
(23) L. Claisen and O. Manasse, *Ber. Dtsch. Chem. Ges.*, **22**, 527 (1889); A. F. Ferris, *J. Org. Chem.*, **24**, 1726 (1959).
(24) L. Cook and A. B. Davidson in "Psychopharmacology: A Generation of Progress", M. A. Lipton, A. DiMascio, and K. F. Killam, Eds., Raven Press, New York, 1978, p 563.
(25) A. B. Davidson, E. Boff, D. A. MacNeil, and L. Cook, *Soc. Neurosci. Abstr.*, in press.

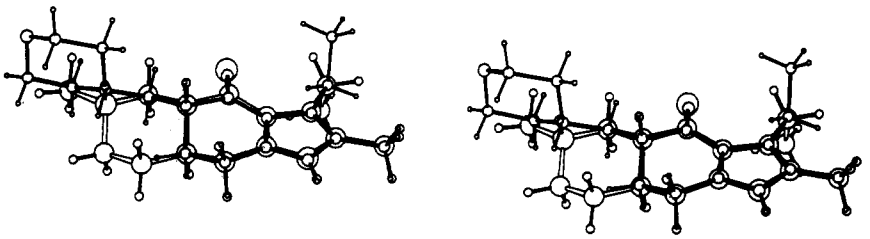


Figure 4. Superposition of solid-state structures of (−)-1·HCl and molindone hydrochloride; pyrrole ring atoms coincident.

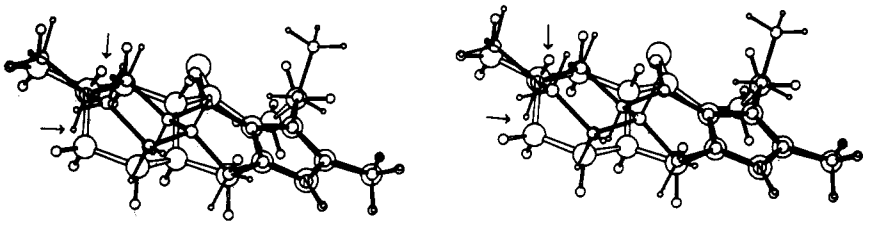


Figure 5. Superposition of (−)-1 and (+)-1 showing coincidence of pharmacophoric atoms but opposite direction of nitrogen lone pairs (arrows); pyrrole ring atoms coincident.

Table II. Activity of Compounds in the Rat Discrete Avoidance Test

compd	avoidance blockade: ABD_{50},[a] mg/kg po	escape blockade: EBD_{20},[b] mg/kg po
(±)-1·HCl	0.72 (0.43-1.26)[c]	9.8
(−)-1·HCl	0.49 (0.18-1.22)	3.6
(+)-1·HCl	>6.0	*d*
haloperidol	0.35 (0.17-0.66)	2.7
molindone	3.6 (0.5-10.5)	17.1

[a] The dose estimated to product a 50% block of avoidance responding. [b] The dose estimated to produce a 20% block of escape responding. [c] Figures in parentheses are 95% confidence limits. [d] Not applicable because of lack of avoidance blockade.

test in the potency range of haloperidol and over five times the potency of molindone. In other aspects of its pharmacology, (±)-1 resembles haloperidol, except that 1 has significantly decreased cataleptogenic liability and weaker autonomic effects.[25] The biological activity is highly stereoselective, with virtually all the activity in the avoidance test residing in the 4a*R*,8a*R* enantiomer (−)-1. Similar stereospecificity is observed in direct measures of dopamine antagonism.[25]

Discussion

These results demonstrate the important contribution of conformation to biological activity. The pyrroloisoquinoline 1 has the same pharmacophoric groups (aromatic ring, carbonyl oxygen, and tertiary amine nitrogen and its lone pair) as molindone, yet 1 is much more potent and specific because these groups are conformationally fixed in 1 by a rigid molecular framework to complement the receptor. Indeed, in the crystalline state (Figure 4), molindone adopts a very different conformation (Table I) from that which would be expected to interact with the receptor. In solution, steric interactions[26] would strongly disfavor a matching conformation of the pharmacophoric groups of molindone and 1 when the lone-pair direction is included.

The role of the nitrogen lone pair as a pharmacophoric group in the interaction of neuroleptic drugs with the dopamine receptor is further supported by the stereospecific biological activity of 1. Because of its relatively flat structure, the positions of the pharmacophoric groups in (+)-1 and (−)-1 excluding the lone pair are very similar. This can be seen in Figure 5, where the pyrrole ring atoms of (+)-1 and (−)-1 have been superimposed, with the result that the basic nitrogen and carbonyl oxygen atoms are practically coincident. The only important difference is the 180° opposition of the lone pairs (arrows, Figure 5). If the nitrogen lone pair were not an essential ligand for the receptor, the two enantiomers could be expected to have similar activity. This effect cannot be clearly demonstrated in other rigid neuroleptics because the pharmacophoric groups are held in a curved backbone, making the enantiomers different in overall shape as well as in the orientation of the nitrogen lone pair.

Summary

The value of a hypothetical model lies in its ability to offer a structural basis for biological results and to guide synthetic efforts. The model detailed here depicts the interaction of antipsychotic drugs with specific molecular fragments of a protein receptor by means of reasonable intermolecular forces. One auxiliary and three essential binding sites (one perhaps required for antagonism) are identified. The geometrical arrangement and range of motion of the binding functional groups are defined by the three-dimensional structures of different classes of drugs exhibiting receptor activity. This molecular model, although not considered to be an actual representation of a dopamine receptor, has proved to have significance in the design, rational modification, and interpretation of structure–activity relationships in a series of novel, highly active pyrrolo[2,3-*g*]isoquinoline compounds. The potency, stereospecificity, and reduction of certain side effects in these compounds may be attributed to their specificity for a complementary dopamine receptor.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were determined in $CDCl_3$ with Me_4Si as internal standard on a Varian T-60, HA-100, or XL-100 spectrometer, and IR spectra were obtained on a Perkin-Elmer 621 or Digilab FTS-14 instrument and were consistent with the assigned structures. Microanalyses were performed by Dr. F. Scheidl of the Chemical Research Department of Hoffmann-La Roche, and results for C, H, N, and

(26) The equatorial hydrogens α to the morpholine nitrogen and at C-6 come into contact if molindone is conformed to have the pharmacophoric groups in the same orientation as 1.

Cl were within ±0.4% of the theoretical values. Products were generally isolated by extraction, and extracts were concentrated after appropriate washing and drying on a rotary evaporator at aspirator pressure and 30–50 °C.

***N*-Methyl-1-(3,5-dimethoxyphenyl)ethylamine (3).** In a 5-L flask was placed (3,5-dimethoxyphenyl)ethylamine hydrochloride[27] (32.6 g, 0.15 mol), water (600 mL), dichloromethane (600 mL), and 1 N NaOH (150 mL). The mixture was mechanically stirred in an ice bath during the dropwise addition over 30 min of a solution of ethyl chloroformate (16.28 g, 0.15 mol) in dichloromethane (60 mL). During the addition, a total of 150 mL of 1 N NaOH was added in 8 portions to keep the pH between 8 and 9. Following the addition, the mixture was stirred in the ice bath for 1 h. The mixture was transferred to a separatory funnel and the organic layer was separated. The aqueous solution was extracted once with dichloromethane (200 mL), and the combined organic solutions were washed with water (100 mL), brine (100 mL), and dried (Na_2SO_4). Evaporation of the solvent afforded the crude carbamate **2** (37.1 g, 98% yield) as a colorless oil.

A solution of the crude **3** (37.1 g, 0.15 mol) in dry THF (100 mL) was added dropwise over 15 min to a mechanically stirred, ice-cooled solution of sodium dihydrobis(2-methoxyethoxy)aluminate (Red-Al, 180 mL, 70% solution in benzene, 0.24 mol). After the addition, the mixture was heated to reflux for 1 h and then cooled in an ice bath. Excess hydride was decomposed by the dropwise addition of 5% NaOH (100 mL). After all the base had been added, the organic layer was separated and the aqueous layer was extracted with ether (100 mL). The combined organic solutions were concentrated to an oil, and the oil was dissolved in ether (300 mL), washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and filtered. To the filtrate was added 5 M HCl in ether (70 mL) to precipitate **3**·HCl. The solid was collected and recrystallized from ethanol (180 mL) and ether (270 mL) to give **3**·HCl as a white, crystalline solid (28.9 g, 83% yield overall from **2**): mp 160–164 °C; IR (KBr) 3385 (NH), 1608, 1598 (aromatic) cm^{-1}; NMR ($CDCl_3$) δ 2.72 (s, 3, NCH_3), 3.18 (s, 4, CH_2CH_2), 3.74 (s, 6, OCH_3), 6.30–6.45 (m, 3, aromatic). Anal. ($C_{11}H_{18}NO_2Cl$) C, H, N, Cl.

***N*-Methyl-1,5-dimethoxycyclohexa-1,4-diene-3-ethylamine (4).** A solution of **3**·HCl (185.2 g, 0.8 mol) in water (1 L) was made alkaline with ammonium hydroxide (160 mL) and extracted with dichloromethane (3 × 1 L). The extracts were washed with brine (1 L), dried, and evaporated to give the free base **3** (156.0 g).

In a 22-L flask equipped with a mechanical stirrer and dry ice condenser was condensed anhydrous ammonia (4 L). To the stirred ammonia was added a solution of **3** (156.0 g, 0.80 mol) in ether (400 mL) and *tert*-butyl alcohol (400 mL, dried by distillation from CaH_2) over 15 min. To the efficiently stirred, refluxing mixture was added Li wire (33.6 g, 4.8 g-atoms, 0.02% Na, Alfa, 3.2-mm wire cut into 50 5-in. pieces) as rapidly as foaming would permit (optimally one 5-in. piece every minute over a 50-min period) [**Caution**: a large condenser with a large vent opening to an efficient hood, frequently replenished with dry ice, is needed to cope with the vigorous refluxing and hydrogen evolution!] After the addition, the blue solution was stirred under reflux for 2 h. Ether (2 L) was added and solid NH_4Cl (280 g) was added in 3- to 4-g portions over 30 min until the blue color dissipated. The condenser was removed and the ammonia was allowed to evaporate overnight through a soda–lime drying tube.

To the residue was added ice–water (2.8 L). The alkaline mixture was transferred to a separatory funnel, rinsing with ether (800 mL), and the layers were separated. The aqueous solution was extracted with dichloromethane (2 × 1.5 L), and the extracts were combined, washed with brine, and dried (Na_2SO_4). Evaporation of the solvents on a rotary evaporator at 40 °C and then at 40 °C (1.0 torr) for 1.5 h to remove *tert*-butyl alcohol afforded the crude **4** as a yellow oil [150.7 g, 91% pure by GC (4 ft × 3 mm 10% XE-60, 175 °C), 96% crude yield]. The crude product was distilled through a 12-in. Goodloe column to give the 120.6 g of pure bis(enol ether) **4** (76.5% yield) as a colorless oil: bp 86–87 °C (0.15 torr); IR (film) 1694, 1660 (enol ether) cm^{-1}; NMR ($CDCl_3$) δ 2.40 (s, 3, CH_3-N), 3.52 (s, 6, OCH_3), 4.56 (br d, 2, vinyl H). Anal. ($C_{11}H_{19}NO_2$) C, H, N.

6-[2-(*N*-Methylamino)ethyl]-2-methyl-3-ethyl-6,7-dihydro-1*H*-4(5*H*)-indolone (7). a. Via 5. To a stirred solution of **4** (5.5 g, 27.9 mmol) in 20 mL of THF was added 10 mL of 6 N HCl in one portion. The warm solution was heated for 15 min at 50 °C and concentrated to give a light yellow oil. The crude oil was dissolved in water (25 mL), and the solution was mixed with 50 g of Dowex 50X8 resin (previously washed with 2 N HCl and deionized water) in a sintered glass funnel. After a few minutes, the aqueous solution was drawn out by suction, and the resin was rinsed with 4 × 50 mL of water and then with eight 35-mL portions of 2 M aqueous pyridine. Fractions 3–8 had a pH between 7.16 and 7.86 and were pooled and concentrated to dryness to give 3.9 g of wet diketone **5**. An analytical sample (380 mg) crystallized from water and had mp 171–174 °C. The remainder was dried over P_2O_5 to afford 2.9 g of light yellow solid **5** (>95% pure by GC on XE-60 at 210 °C; combined yield 69.4%): mp 166–169 °C; IR (KBr) 2720, 2460 (NH_2^+), 1515 (diketone enolate) cm^{-1}; NMR (D_2O) δ 3.16 (s, 3, CH_3N^+), 3.42–3.60 (m, 2, CH_2N^+); MS, *m/e* 169 (M^+). Anal. ($C_9H_{15}NO_2$) C, H, N.

To a solution of diketone **5** (2.80 g, 16.5 mmol) in 70% acetic acid (30 mL) was added isonitroso ketone **6** (2.3 g, 20 mmol), followed by zinc powder (3.2 g, 49 mg-atoms) added in portions over 5 min. The resulting mixture was stirred at reflux for 1 h and cooled slightly. An additional 1.6 g of Zn powder (24.5 mg-atoms) was added, and the mixture was heated at reflux for 1.5 h, cooled to room temperature, and filtered. The filtrate was evaporated, and the residue was dissolved in water (30 mL) and washed with dichloromethane. The aqueous solution was made alkaline with NH_4OH and extracted with dichloromethane. The extracts were washed with brine, dried, and concentrated to give 3.1 g of crude tetrahydroindoline **7**. Crystallization from 2:1 toluene–ethyl acetate gave 1.86 g of **7** in two crops, mp 101–104 °C. An additional 150 mg of **7** was isolated from the dichloromethane washes by chromatography (dry column, silica gel, eluted with organic phase of a mixture prepared by shaking 90 mL of $CHCl_3$, 30 mL of CH_3OH, 10 mL of H_2O, 6 mL of acetic acid): combined yield 52%. Recrystallization from ethyl acetate gave **7** as a white solid, mp 116–120 °C.

b. Direct Process. A solution of bis(enol ether) **4** (60.0 g, 0.305 mol) in 700 mL of 70% aqueous acetic acid was refluxed for 15 min and then removed from the heating bath. Zinc powder (59.5 g, 0.915 g-atom) was added over 10 min with stirring and the mixture was heated to reflux. To the mixture was added a solution of isonitroso ketone **6** (42.1 g, 0.366 mol) in 175 mL of 70% acetic acid over 1 h. The mixture was then heated an additional 2.5 h and cooled to room temperature. After 1 h, the precipitated zinc acetate was removed by filtration, and the filter cake was washed with dichloromethane (500 mL). The filtrate was concentrated on a rotary evaporator at 40–50 °C and then heated at 100 °C (1.0 torr). The residue was dissolved in water (500 mL) and the acidic (pH 4.5) solution was washed with dichloromethane. The aqueous solution was made basic with ammonium hydroxide (165 mL), and brine (500 mL) was added. The solution was extracted with dichloromethane, and the extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent afforded the crude tetrahydroindolone **7** (56.0 g). The crude product was recrystallized from 2:1 toluene/ethyl acetate to give 30.8 g of crystalline **7**, mp 114–120 °C. An additional 2.6 g was recovered from the mother liquor via the oxalate (overall yield 47%).

Further recrystallization from ethyl acetate–chloroform gave analytically pure **7**: mp 117.5–120.5 °C; IR (KBr) 3260 (NH), 1623 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.10 (t, 3, J = 7 Hz, CH_3CH_2), 2.12 (s, 3, CH_3Ar), 2.42 (s, 3, CH_3N), 9.70 (br s, 1, NH); UV (EtOH) λ_{max} 210 nm (ε 11 750), 251 (ε 10 400), 293 (ε 4300). Anal. ($C_{14}H_{22}N_2O$) C, H, N.

2,6-Dimethyl-3-ethyl-4,4a,5,6,7,8,8a,9-octahydro-4a,8a-*trans*-1*H*-pyrrolo[2,3-*g*]isoquinolin-4-one [(±)-1]. To a solution of tetrahydroindolone **7** (17.0 g, 72.5 mmol) in methanol (170 mL) was added 4 M ethereal HCl (20 mL). The solvents were evaporated and the crude solid was dried at 50 °C (1.0 torr) for 2 h to give 19.7 g of crude **7**·HCl. In a 3-L flask equipped with a mechanical stirrer, thermometer, and distillation head were placed 1-octanol (1 L), crude **7**·HCl (19.7 g), and paraformaldehdye (21.8 g, 0.726 mol). The mixture was heated to boiling and the

(27) S. Ahmad, W. B. Whalley, and D. F. Jones, *J. Chem. Soc. C*, 3590 (1971).

water which was liberated was removed by distillation until the octanol solution reached 175–180 °C, whereupon the mixture was refluxed for 1 h. An additional 6.54 g (0.218 mol) of paraformaldehyde was added in three portions over 5 min, water was distilled out as before, and the dark mixture was heated for an additional 1 h. The mixture was cooled and poured into water (1 L). The layers were separated and the octanol solution was extracted with 5% HCl. The combined aqueous solutions were washed with chloroform (2 × 150 mL) and made basic with ammonium hydroxide (120 mL). The mixture was extracted with chloroform (1 × 400 mL, 4 × 200 mL), and the combined extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave the crude pyrroloisoquinoline (12.0 g, 58.5% yield) as a dark tan solid. The crude 1 was crystallized from dichloromethane–methanol–ether to give partially purified 1 (8.20 g, 46% yield), mp 203–226 °C. An analytical sample was recrystallized from dichloromethane–ether: mp 205–206 °C; IR (KBr) 3265 (NH), 1618 (C=O) cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 1.09 (t, 3, J = 7 Hz, CH_3CH_2), 2.12 (s, 3, CH_3Ar), 2.33 (s, 3, CH_3N), 3.47 (br, d, 1, J = 11 Hz, equatorial C_5 H), 9.87 (br, s, 1, NH); UV (2-propanol) λ_{max} 208 nm (ϵ 14500), 250 (10720), 292 (4150); MS m/e 246 (M^+). Anal. ($C_{15}H_{22}N_2O$) C, H, N.

Treatment of the paritally purified 1 (8.20 g) with 4 M ethereal HCl (12 mL) in methanol (80 mL) and evaporation of the solvents gave the crude 1·HCl. Recrystallization from ethanol and decolorization [Darco-G60) gave pure (±)-1·HCl (5.40 g, 26.3% overall yield, dried 18 h at 80 °C (0.05 torr)]. An analytical sample was prepared by further recrystallization and drying: mp 222–228 °C dec. Anal. ($C_{15}H_{23}N_2OCl$) C, H, N, Cl.

From the mother liquors of several similar preparations, material rich in the 4a,8a-cis isomer 8 was obtained: NMR ($CDCl_3$ + Me_2SO-d_6) δ 1.22 (t, 3, J = 7 Hz, CH_3CH_2), 2.15 (s, 3, CH_3Ar), 2.30 (s, 3, CH_3N). A sample of a 60:40 mixture of 8·HCl/1·HCl (4.7 g) was heated in ethylene glycol at reflux for 8 h. The solution was poured into water, made alkaline with ammonium hydroxide, and extracted with chloroform. The chloroform was washed with water, dried (Na_2SO_4), and evaporated. The crude product consisted (NMR) of a 75:25 mixture of 1:8 and on recrystallization from dichloromethane–methanol–ether afforded 2.40 g of the trans isomer 1, mp 205–206 °C.

Resolution of (±)-1. Racemic 1 (1.20 g, 4.87 mmol) was dissolved in methanol and a solution of d(+)-tartaric acid (0.74 g, 4.93 mmol) in methanol was added. The solution was concentrated, and the precipitated tartrate was recrystallized twice from methanol. The free base was liberated with ammonium hydroxide, isolated by dichloromethane extraction, and converted as for the racemic compound to the hydrochloride. After two recrystallizations from ethanol and drying at 80 °C (0.005 torr), there was obtained 0.15 g of pure, white, crystalline (−)-1·HCl: mp 240–245 °C; $[\alpha]^{25}_D$ −120.78° (c 0.81, water). Anal. ($C_{15}H_{22}N_2O$·HCl·0.25H_2O) C, H, N.

The mother liquors from the crystallization of the (+)-tartrate salt were treated with ammonium hydroxide and extracted with dichloromethane to isolate the free base, which was treated as above with l-(−)-tartaric acid in methanol (0.46 g, 3.06 mmol). The precipitated (−)-tartrate was recrystallized twice from methanol and converted as above to the hydrochloride to give 0.10 g of pure (+)-1·HCl: mp 240–244 °C; $[\alpha]^{25}_D$ +121.38° (c 0.44, water). Anal. ($C_{15}H_{22}N_2O$·HCl·0.25H_2O) C, H, N.

Alternate Route. 1,2,3,4-Tetrahydro-6,8-dimethoxy-2-methylisoquinoline (9).[28] A solution of 3·HCl[27] (15.0 g, 64.7 mmol) in 30 mL of water was treated with 35 mL of 2 N NaOH and extracted with dichloromethane. The extracts were concentrated on a rotary evaporator and the residue mixed with aqueous formaldehyde (65 mL, 37% formalin solution). The mixture was heated to reflux for 2 h, made alkaline with 2 N NaOH (15 mL), and extracted with dichloromethane. The combined extracts were wahsed with brine, dried ($MgSO_4$), and concentrated to give crude 9 as a yellow oil (15.5 g). The oil was dissolved in ethanol (100 mL), and ethanolic HCl was added until the solution was acidic to wet pH paper. Ether (75 mL) was added, and the salt was allowed to crystallize to give 10.15 g (64% yield) of 9·HCl. Analytically pure material was prepared by recrystallization from ethanol–ether: mp 199–200 °C; NMR ($CDCl_3$) δ 2.92 (s, 3, NCH_3), 3.76 (s, 6, OCH_3), 6.24–6.34 (m, 2, aromatic). Anal. ($C_{12}H_{17}NO_2$·HCl) C, H, N.

Table III. Crystal Data for (−)-1·HCl and Molindone Hydrochloride

	(−)-1·HCl	molindone hydrochloride
formula	$C_{15}H_{22}N_2O$·HCl·C_3H_8O	$C_{16}H_{24}N_2O_2$·HCl
space group	$P2_12_12_1$	$P2_1/n$
a, Å	7.409 (2)	13.184 (3)
b, Å	11.295 (2)	13.601 (3)
c, Å	23.718 (4)	9.473 (2)
β, deg		106.30 (2)
Z	4	4
d_{calcd}, g cm^{-1}	1.147	1.274
μ (Cu Kα), cm^{-1}	17.9	21.3

1,2,3,4,4a,7-Hexahydro-6,8-dimethoxy-2-methylisoquinoline (10). To a solution of *tert*-butyl alcohol (9.1 g, 123 mmol), ether (50 mL), and ammonia (150 mL) was added 9·HCl (1.0 g, 4.1 mmol). After the mixture was stirred for 2–3 min, lithium wire (0.51 g, 82 mmol) was added to the refluxing mixture over 30 min in short pieces. The blue solution was allowed to reflux for 2.5 h and solid NH_4Cl was added until the color dissipated. Ether (100 mL) was added and the ammonia was allowed to evaporate overnight. Ice–water (100 mL) was added and the organic phase was separated. The aqueous solution was extracted with chloroform, and the combined organic solutions were washed with brine, dried, and concentrated to give crude 10 as a yellow oil (0.58 g, 68% yield). The crude product consisted of a mixture of the desired 10 (45.5%) [GC–MS, 10% OV-101, 100–270 °C; m/e 209 (M^+), 208 (M^+ − H), 194 (M^+ − CH_3)] and three major overreduction products (54.5%) resulting from demethoxylation and reduction of 9. No reaction of 9 with Li in NH_3 was observed in the absence of a proton source or when the blue solution was quenched slowly with ammonium chloride or wet ether. With less acidic alcohols, conversion was lower than with *tert*-butyl alcohol (MeOH, 19%; EtOH, 50%, *t*-BuOH, 93%) but the relative proportion of 10 in the mixture was not significantly different (MeOH, 40% EtOH, 44%; *t*-BuOH, 45.5%).

2,6-Dimethyl-3-ethyl-4,4a,5,6,7,8,8a,9-octahydro-4a,8a-*trans*-1*H*-pyrrolo[2,3-*g*]isoquinolin-4-one (1). From 10. A solution of crude 10 from the Birch reduction [0.58 g, 46% pure (GC), ~1.2 mmol] in 70% acetic acid (10 mL) was heated to 90–100 °C for several minutes to hydrolyze the bis(enol ether) to the diketone 11. To the hot solution was added zinc powder (0.6 g, 9.25 mg-atoms) and the isonitroso ketone 6 (0.7 g, 6.1 mmol). The mixture was heated for 3 h at reflux, cooled, and filtered to remove unreacted zinc and zinc acetate. The filtrate was concentrated to dryness on a rotary evaporator at 50–60 °C. To the residue were added dichloromethane and ammonium hydroxide, and the layers were separated. The aqueous solution was extracted with dichloromethane, and the combined extracts were washed with brine, dried (Na_2SO_4), and concentrated to give crude 1 containing less than 5% of the cis isomer 8. Chromatography on Alumina III eluting with 1% methanol in dichloromethane afforded 1 (0.19 g, 29% overall yield from 9·HCl) as a white solid. A late-eluting fraction (60 mg) from the chromatography was a mixture (ca. 1.5:1) of 1 and a closely related compound tentatively assigned the pyrrolo[2,3-*h*] isomeric structure 12: NMR ($CDCl_3$) δ 2.20 (s, CH_3Ar), 2.33 (s, CH_3N).

Crystal Structure of (−)-1·HCl. The sample was recrystallized from 2-propanol to give hexagonal prisms and was air dried. The crystal data are summarized in Table III. The intensity data were measured on a Hilger-Watts diffractometer (Ni filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). The size of the crystal used for data collection was approximately 0.05 × 0.4 × 0.5 mm; the data were corrected for absorption. Of the 1571 independent relfections of $\theta < 57°$, 1271 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple solution procedure[29] and was refined by full

(28) D. B. Clayson, *J. Chem. Soc.*, 2016 (1949), describes the preparation from cotarnine.

(29) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).

matrix least squares. In the final refinement, anisotropic thermal parameters were used for the heavier atoms, and isotropic temperature factors were used for the hydrogen atoms and the four carbon and oxygen atoms of the 2-propanol molecule. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indexes are $R = 0.086$ and $wR = 0.095$ for the 1271 observed reflections. The final difference map has no peaks greater than ± 0.3 eÅ^{-3}, except for one peak of 0.6 eÅ^{-3} found about 1 Å from two carbon atoms of the 2-propanol molecule.

The absolute configuration was determined by carrying out two refinements, one using the correct value of the imaginary part of the anomalous dispersion correction for chlorine ($\Delta f''$) and the other with the sign of $\Delta f''$ reversed (equivalent to refining the antipode). The weighted discrepancy indexes at the end of the two refinements were 0.0955 and 0.1002 for $\Delta f''$ and $-\Delta f''$, respectively. Thus, according to the test described by Hamilton,[30] the absolute configuration is established at better than the 0.995 confidence level.

Crystal Structure of Molindone Hydrochloride. A sample (Endo Laboratories) was recrystallized from 1:1 methanol–acetonitrile and air dried. The crystal data are summarized in Table III. The intensity data were measured as above. The size of the crystal used for data collection was approximately $0.5 \times 0.10 \times 0.08$ mm; the data were corrected for absorption. Of the 2202 independent reflections for $\theta < 57$, 1811 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved and refined as above. The final discrepancy indexes are $R = 0.042$ and $wR = 0.049$ for the 1811 observed reflections. The final difference map has no peaks greater than ± 0.2 eÅ^{-3}.

Pharmacology. Discrete Avoidance Response in Rats. Male Charles River CD rats were trained and tested in experimental chambers equipped with a response lever, a grid floor for delivery of electric shock (unconditioned stimulus; UCS), and a speaker for presentation of auditory stimuli (conditioned stimulus; CS). Behavioral trials were presented at 2-min intervals during each 1-h session. Each trial consisted of a 15-s CS, continuing for an additional 15 s accompanied by the UCS (1.0 mA, 350 V.A.C. scrambled). The rats could terminate a trial at any time by pressing the response lever. A response during the CS period was considered an avoidance response, while a reponse occurring during the UCS period was an escape response.

Trained rats which maintained a reliable control base line of avoidance behavior of zero to three avoidance failures per session were used to test experimental compounds. One control and one experimental session were alternated during each week. The compounds were adminstered 60 min before the start of each session to a minimum of three rats at each dose level over a range of doses. Rats received vehicle alone during control sessions.

For each dose group, the proportion of trials in which the rats failed to exhibit an avoidance or an escape response was determined, using the ten trial session segment in which the largest such effect occurred. The dose required to produce a 50% block of avoidance responding (ABD_{50}) was computed by regression analysis ($y = a + b \log x$), and 95% confidence limits were computed as described by Tedeschi et al.[31] The lowest dose required to produce a 20% block of escape responding was estimated graphically from a dose–effect curve.

Acknowledgment. We thank members of our Physical Chemistry Department for obtaining the spectral and microanalytical data, Elliot Chiang for checking several synthetic procedures, and Mary Zolcinski for technical assistance with the discrete avoidance test.

Supplementary Material Available: Tables I–VIII list final atomic parameters, final anisotropic thermal parameters, bond lengths, and bond angles for (–)-1·HCl and molindone hydrochloride. Table IX lists atomic coordinates for dexclamol conformer B (7 pages). Ordering information is given on any current masthead page.

(30) W. C. Hamilton, *Acta Crystallogr.*, 18, 506 (1960).

(31) D. H. Tedeschi, P. J. Fowler, W. H. Cromley, J. F. Pauls, R. Z. Eby, and E. J. Fellows, *J. Pharm. Sci.*, **54**, 1046 (1964).

Inhibition of Cholesterol Side-Chain Cleavage. 3.[1] 22-Azacholesterol Analogues Bearing Aryl-Substituted Side Chains

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The potent inhibitory activity of 22-azacholesterol analogue **2a**, in which the (3-methylbutyl)amino side chain had been replaced by the (phenylethyl)amino side chain, on the conversion of cholesterol to pregnenolone prompted the synthesis and enzymatic studies of two series of 22-azacholesterol analogues bearing (arylalkyl)amino and (arylalkyl)amido side chains. The potent inhibitory activity of both the amines (**2**) and the amides (**3**) indicated that a basic nitrogen was not a requirement for inhibitory activity. However, the amide analogue (**4**) in which the positions of the carbonyl and the nitrogen were interchanged was a much poorer inhibitor. The inhibitory activities in the phenylacetamido series were decreased by electron-withdrawing groups on the aromatic ring, while an electron-donating group effected a small increase.

Inhibitors of cholesterol side-chain cleavage (CSCC) are of interest as potential biochemical tools in the elucidation of the mechanism of the CSCC reaction, as well as potential therapeutic agents for the modulation of the excessive production of adrenocortical hormones caused by various disease states.[2] One such inhibitor, aminoglutethimide (α-ethyl-α-*p*-aminophenylglutarimide), has been used in the treatment of such conditions,[3] but its unwanted side effects[4] make it desirable to find more specific in-

(1) Taken in part from the Ph.D. Dissertation of N.G.D., University of Illinois at the Medical Center, Chicago, IL, 1980. For the previous paper in this series, see ref 5.

(2) (a) T. E. Temple and G. W. Liddle, *Annu. Rev. Pharmacol.*, **10**, 199 (1970); (b) P. E. Graves, V. I. Uzgiris, and H. A. Salhanick, *Steroids*, **35**, 543 (1980).

(3) (a) R. Cash, A. J. Brough, M. P. Cohen, and P. S. Satch, *J. Clin. Endocrinol.*, **27**, 1239 (1967); (b) L. M. Fishman, G. W. Liddle, D. P. Island, N. Fleischer, and O. Kuchel, *ibid.*, **27**, 481 (1967); (c) R. I. Misbin, J. Canary, and D. Willard, *J. Clin. Pharmacol.*, **16**, 645 (1976); (d) R. J. Santen, A. Lipton, and J. Kendall, *J. Am. Med. Assoc.*, **230**, 1661 (1974).

(4) D. H. Nelson, in "The Adrenal Cortex: Physiological Function and Disease", Vol. XVIII, L. H. Smith, Jr., Ed., W. B. Saunders, Philadelphia, 1980, pp 54–60.

0022-2623/81/1824-1034$01.25/0