**(5-Methyl-2-oxo-1,3-dioxolen-4-yl)methyl *trans*-4-(Aminomethyl)cyclohexanecarboxylate Hydrochloride (10).** Compound **35** (5.2 g, 0.014 mol) was dissolved in ethyl acetate (15 mL) and cooled to 10 °C. A 3.8 M solution of anhydrous HCl in ethyl acetate (15 mL) was added and the mixture stirred at 0 °C for 30 min and then at room temperature for 2 h. The white precipitate formed was filtered off, washed with cold ethyl acetate, and recrystallized from isopropyl alcohol; yield 3.0 g (70%); mp 176 °C.

**Stability in Vitro.** For HPLC determinations a miniPump (Milton Roy Co.) was used at a flow rate of 1.0 mL/min. A variable-wavelength detector LC-55 (Perkin-Elmer) was operated at 210 nm.

The degradation of the potential prodrug in a phosphate buffer of pH 7.5 ($\mu$ = 0.1) and in a NaCl/HCl buffer of pH 1.2 ($\mu$ = 0.1) was monitored by reversed-phase HPLC. The initial concentration of all the potential prodrugs was 1 mg/mL, corresponding to 2–4.5 mM. The solutions were stored in a water bath at 37 ± 0.5 °C. At different time intervals samples were withdrawn, and 100 $\mu$L was injected on a HPLC column. The HPLC column was a Chromegabond MC-18 (ES Industries) 250 mm × 4.6 mm i.d. 10-$\mu$m particles. The mobile phase consisted of 55%, v/v, of methyl alcohol in phosphate buffer ($\mu$ = 0.1). The apparent pH of this mixture was adjusted to 3.0. For compounds **9** and **10**, 0.1 M $NaClO_4$ was added. For **14** and **18**, the content of methyl alcohol was 25%, and for **16** and **17**, 32.5%, v/v.

The degradation of the potential prodrug in human heparinized plasma was also monitored by reversed-phase HPLC. To 1000 $\mu$L of plasma in a water bath at 37 ± 0.5 °C was added 100 $\mu$L of an aqueous solution of 23 mM of potential prodrug. A 20-$\mu$L portion of the sample containing an initial concentration of 2.3 mM of potential prodrug in 90% plasma was directly injected on the precolumn Perisorb RP8 50 mm × 4.6 mm i.d. 30–40 $\mu$m particles followed by a column Nucleosil $C_8$ 150 mm × 4.6 mm i.d. 5 $\mu$m particles. It was assumed that the enzymatic activity was stopped immediately at the injection onto the column. The mobile phase was methyl alcohol in phosphate buffer of apparent pH 3.0. The v/v content of methyl alcohol was for **3** 25%, for **7** 30%, for **1** 35%, for **6** 40%, and for **14** and **16** 25% including 0.2 M $NaClO_4$. The release of tranexamic acid from compound **14** was monitored by GC. To 10 mL of heparinized human plasma was added 11.3 mg of **14**, giving an initial concentration of 2.8 mM. This solution was stored in a water bath at 37 ± 0.5 °C. A sample of 5 $\mu$L was withdrawn and analyzed by GC[21] at the following time intervals: 0.5, 3, 6, 9, 15, 30, and 60 min. The amount of tranexamic acid released per mole of **14** was 9.5, 28, 58, 76, 88, 95, and 100% of theoretical.

**Pharmacology.** Male rats, Sprague–Dawley, weighing about 200 g, were obtained from ALAB, Sollentuna, Sweden. After overnight fasting, 2.5 mL of distilled water was given 5 min prior to administration of the potential prodrugs. These were dissolved in distilled water immediately before administration and given by gavage (1 or 0.1 mmol/kg) in a volume of 2 mL/kg. During the experiment the rats were kept in ordinary metabolism cages with free access to food and water. The urine was collected for three consecutive 24-h intervals. At the end of each period the cages were rinsed with 20 mL of distilled water. The collected urines and rinsing waters were kept frozen until they were analyzed by gas chromatography.[21]

**Acknowledgment.** We thank members of the analytical chemistry staff for excellent analytical services.

**Registry No.** 1, 100165-48-8; **2**, 100165-49-9; **3**, 87589-30-8; **4**, 100165-50-2; **5**, 100165-51-3; **6**, 87589-22-8; **7**, 87589-32-0; **8**, 100165-52-4; **9**, 100165-53-5; **10**, 100165-54-6; 11, 87589-52-4; 11 (Z, BOC), 100165-59-1; **12**, 27724-96-5; **13**, 19878-18-3; **14**, 87638-56-0; bis(Z-14), 100165-58-0; **15**, 87589-39-7; **16**, 87589-43-3; **17**, 87589-46-6; **18**, 87589-45-5; **19**, 100227-65-4; **20**, 100165-55-7; **21**, 27687-12-3; **21** (q salt), 87635-73-2; **22**, 15177-68-1; **23**, 27687-14-5; **24**, 33233-67-9; **24** (q salt), 87611-44-7; **25**, 50893-36-2; **26**, 87589-40-0; **27**, 87589-42-2; **28**, 100227-66-5; **29**, 100227-67-6; **30**, 66297-46-9; **31**, 100165-56-8; **32**, 37830-90-3; **33**, 80715-22-6; **35**, 100165-57-9; tranexamic acid, 1197-18-8; 4-(aminomethyl)-benzoic acid, 56-91-7; tetrabutylammonium hydrogen sulfate, 32503-27-8; paraldehyde, 123-63-7; 1,1-dichloro-*N*,*N*'-dimethylacetamide, 5468-76-8; pivalamide, 754-10-9; acetoin, 513-86-0; tetrabutylammonium bromide, 1643-19-2; methylene bis[4-(aminoethyl)benzoate] dihydrochloride, 100165-60-4; methylene *trans*-4-[[[(benzyloxy)carbonyl]amino]methyl]cyclohexane-carboxylate 4-(aminomethyl)benzoate hydrochloride, 87589-51-3.

(21) Vessman, J.; Strömberg, S. *Anal. Chem.* **1977**, *49*, 369.

# A Common Structural Model for Central Nervous System Drugs and Their Receptors

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On the basis of the hypothesis that there is a common structural basis for central nervous system (CNS) drug action consisting primarily of an aromatic group and a nitrogen atom, a four-point model for a common pharmacophore is defined with use of five semirigid CNS-active drug molecules: morphine, strychnine, LSD, apomorphine, and mianserin. Two of the points of the model represent possible hydrophobic interactions between the aromatic group and the receptor, while the other two represent hydrogen bonding between the nitrogen atom and the receptor. The model is then extended by the inclusion of nine additional CNS-active drug molecules: phenobarbitone, clonidine, diazepam, bicuculline, diphenylhydantoin, amphetamine, imipramine, chlorpromazine, and procyclidine, each being chosen as a key representative of a different CNS-active drug class or neurotransmitter system. Consideration of all phenyl group and nitrogen atom combinations, as well as all feasible conformations, shows that all nine molecules closely fit the common model in low-energy conformations. It is proposed that the model may eventually be used to design CNS-active drugs by mapping the relative locations of secondary binding sites. It can also be used to predict whether a given structure is likely to show CNS activity: a search over 1000 entries in the Merck Index shows a high probability of CNS activity in compounds fitting the common structural model.

In the area of central nervous system (CNS) active drugs, many studies have resulted in proposals of receptor requirements for separate CNS classes. Although these requirements vary in detail, it has become clear than an aromatic group and a nitrogen atom are common features of the majority of CNS-active drugs. Specific topographical arrangements of these groups have therefore been proposed as basic requirements for analgesic, hallucino-

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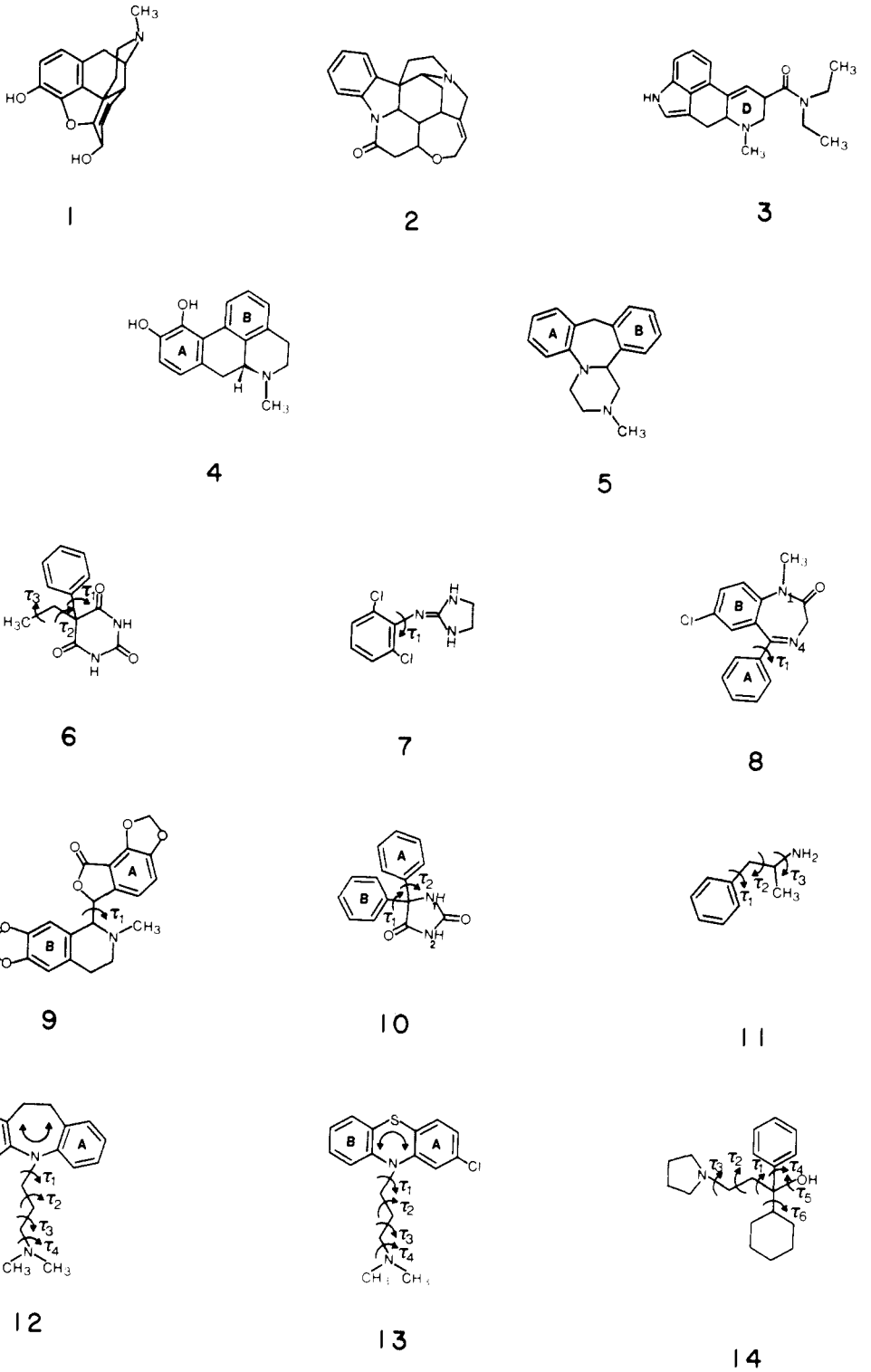
**Chart I**[a]




[a] Structures of the 14 CNS-active drugs used as a basis for this study: morphine (1), strychnine (2), LSD (3), apomorphine (4), mianserin (5), phenobarbitone (6), clonidine (7), diazepam (8), bicuculline (9), diphenylhydantoin (10), amphetamine (11), imipramine (12), chlorpromazine (13), procyclidine (14). Torsion angles used throughout this paper are defined by clockwise rotation about the angle indicated with use of the convention of Klyne and Prelog.[3]

genic, anticonvulsant, stimulant, antidepressant, and antipsychotic activities.[1,2]

The seemingly fundamental role of an aromatic ring and nitrogen atom *within* each of these drugs classes led us recently to examine the differences in topographical arrangements of these groups *between* different CNS drug classes. Using computer graphics, we established[1] that there was in fact a remarkable similarity in the topographical arrangement of these groups in the crystal structures of the following eight drugs, each of which is representative of the specified CNS drug class: morphine (1, analgesic), LSD (3, hallucinogen), phenobarbitone (6, hypnotic), diazepam (8, anxiolytic), diphenylhydantoin (10,

(1) Andrews, P. R.; Lloyd, E. J. *J. Pharm. Pharmacol.* **1983**, *35*, 516.
(2) Andrews, P. R.; Lloyd, E. J. *Med. Res. Rev.* **1982**, *2*, 355.
(3) Klyne, W.; Prelog, V. *Experientia* **1960**, *16*, 521.

anticonvulsant), amphetamine (11, stimulant), imipramine (12, antidepressant), and chlorpromazine (13, antipsychotic) (Chart I).

On the basis of this and other observations, we advanced the following working hypotheses:[1]

1. There is a common structural basis for the activity of many different CNS-active drug classes.

2. The aromatic ring and nitrogen moieties are the primary binding groups whose topographical arrangement is fundamental to the activity of these drug classes.

3. It is the nature and placement of secondary binding groups that determines different classes of CNS drug activity.

Clearly, if these hypotheses could be verified, then they would provide the basis for an extremely useful common pharmacophore to use in drug design. However, while the existence of common structural features in the eight compounds above demonstrates that such a common pharmacophore could exist, it does not necessarily define the most probable common structure. We have therefore carried out a further study of CNS-active drug classes that incorporates several extensions aimed at precisely defining a model for the common structural basis referred to in the first two of our hypotheses.

First, we have expanded the number of CNS drug classes considered to include bicuculline (9, GABA antagonist), strychnine (2, glycine antagonist), procyclidine (14, anticholinergic), and clonidine (7, $\alpha$-adrenergic (Chart I). The first three compounds are important because they each act at receptors for which the natural neurotransmitter lacks an aromatic ring. They may thus indicate the location of residual aromatic binding sites on these receptors that are not utilized by the neurotransmitters themselves.

Secondly, we recognize that the conformation observed in the solid state of a given drug need not be the biologically active form. We have therefore extended our study to include all possible conformations of the drugs in question. Furthermore, in order to restrict the conformational space of the more flexible molecules such as amphetamine (11), imipramine (12), and chlorpromazine (13), we have included some additional semirigid structures [mianserin (5), apomorphine (4), and strychnine (2), Chart I] that are known to have well-characterized activity within their class.

Thirdly, it is clear that in some cases alternative combinations of the aromatic group and nitrogen atom may lead to different superimpositions of these molecules, and hence to different models. To allow for this we have now included all possible pairings of aromatic groups and nitrogen atoms.

Finally, it must be realized that it is not only the common topographical location of the aromatic group and nitrogen atom that is important but also the location of the receptor groups with which they interact. Since the geometry of these interactions restricts the number of possible orientations of a drug molecule at its receptor, we have developed our model using a combined drug–receptor entity derived from the geometries observed crystallographically for similar interactions in biopolymers. Thus we have assumed that the aromatic group interacts via a planar hydrophobic ($\pi$–$\pi$) bond with an aromatic group of the receptor protein located approximately 3.5 Å away and that the nitrogen atom forms a hydrogen bond, 2.8 Å long, with an electronegative atom of the receptor.

## Method

1. Classical potential energy calculations were performed by pairwise summation of the van der Waals interactions between nonbonded atoms. The parameterization, which was developed by Giglio[4] on the basis of hydrocarbon and amide structures, has been used in our laboratory to study a number of systems of biological interest.[5] The calculations were carried out at fixed values of all bond lengths and bond angles, ignoring electrostatic charges. It was shown that these approximations have no effect on the qualitative nature of the results but have the great advantage of allowing very rapid determination of all alternative biologically active conformations. We stress, however, that relaxation of nontorsional degrees of freedom reduces both the energy differences and the rotational barriers between alternative conformations. The quantitative energy differences, therefore, should not be used, for example, to calculate relative conformer populations.

For each molecule, the conformational variables were considered up to three at a time, and the potential energy surfaces were calculated at rotation intervals of 10° for each variable, with refinements at 5° intervals where necessary. In molecules with more than three consecutive conformational variables [e.g., imipramine (12)], the interactions between variables were determined by considering overlapping groups of torsion angles. The lowest energy conformation located by this exhaustive search procedure was used as the global minimum conformation for calculation of the relative energies of all alternative molecular conformations.

Molecular comparisons and superimpositions were performed by using the Victorian College of Pharmacy Ltd. molecular modelling system MORPHEUS,[2] which minimizes the sum of the squares of the distances between corresponding atoms in the two or more molecules being compared, with the fit between molecules being expressed as the root mean square (RMS) of the distances between matched points. The resultant energies and distances were then plotted as two-dimensional surfaces against variable torsion angles.

2. The crystal structures of the following 14 CNS-active drugs were used as a basis for this study: (5*R*,6*S*,9*R*,13*S*,14*R*)-(−)-morphine,[6] strychnine,[7,8] (5*R*,8*R*)-(+)-LSD,[9] (*R*)-(−)-apomorphine,[10,11] (*S*)-(+)-mianserin,[12] phenobarbitone,[13] clonidine,[14] diazepam,[15] (1*S*,9*R*)-(+)-bicuculline,[16] diphenylhydantoin,[17] (*S*)-(+)-amphetamine,[18] imipramine,[19] chlorpromazine,[20] and (*R*)-(−)-procyclidine.[21]


(4) Giglio, E. *Nature (London)* **1969**, *222*, 339.
(5) Andrews, P. R.; Carson, J. M.; Caselli, A.; Spark, M. J.; Woods, R. *J. Med. Chem.* **1985**, *28*, 393 and references therein.
(6) Gylbert, L. *Acta Crystallogr., Sect. B* **1973**, *B29*, 1630.
(7) Peerdeman, A. F. *Acta Crystallogr.* **1956**, *9*, 824.
(8) Robertson, J. H.; Beevers, C. A. *Acta Crystallogr.* **1951**, *4*, 270.
(9) Baker, R. W.; Chothia, C.; Pauling, P. *Mol. Pharmacol.* **1973**, *9*, 23.
(10) Giesecke, J. *Acta Crystallogr., Sect. B* **1977**, *B33*, 302.
(11) Giesecke, J. *Acta Crystallogr., Sect. B* **1973**, *B29*, 1785.
(12) Van Ry, C.; Feil, D. *Tetrahedron* **1973**, *29*, 1891.
(13) Williams, P. P. *Acta Crystallogr., Sect. B* **1973**, *B29*, 1572.
(14) Byne, G.; Mostad, A.; Romming, C. *Acta Chem. Scand., Ser. B* **1976**, *B30*, 843.
(15) Camerman, A.; Camerman, N. *J. Am. Chem. Soc.* **1972**, *94*, 268.
(16) Gorinsky, C.; Moss, D. S. *J. Cryst. Mol. Struct.* **1973**, *3*, 299.
(17) Camerman, A.; Camerman, N. *Acta Crystallogr., Sect. B* **1971**, *B27*, 2205.
(18) Bergin, R.; Carlstrom, D. *Acta Crystallogr., Sect. B* **1971**, *B27*, 2146.
(19) Post, M. L.; Kennard, O.; Horn, A. S. *Acta Crystallogr., Sect. B* **1975**, *B31*, 1008.
(20) McDowell, J. J. H. *Acta Crystallogr., Sect. B* **1969**, *B25*, 2175.
(21) Camerman, N.; Camerman, A. *Mol. Pharmacol.* **1971**, *7*, 406.

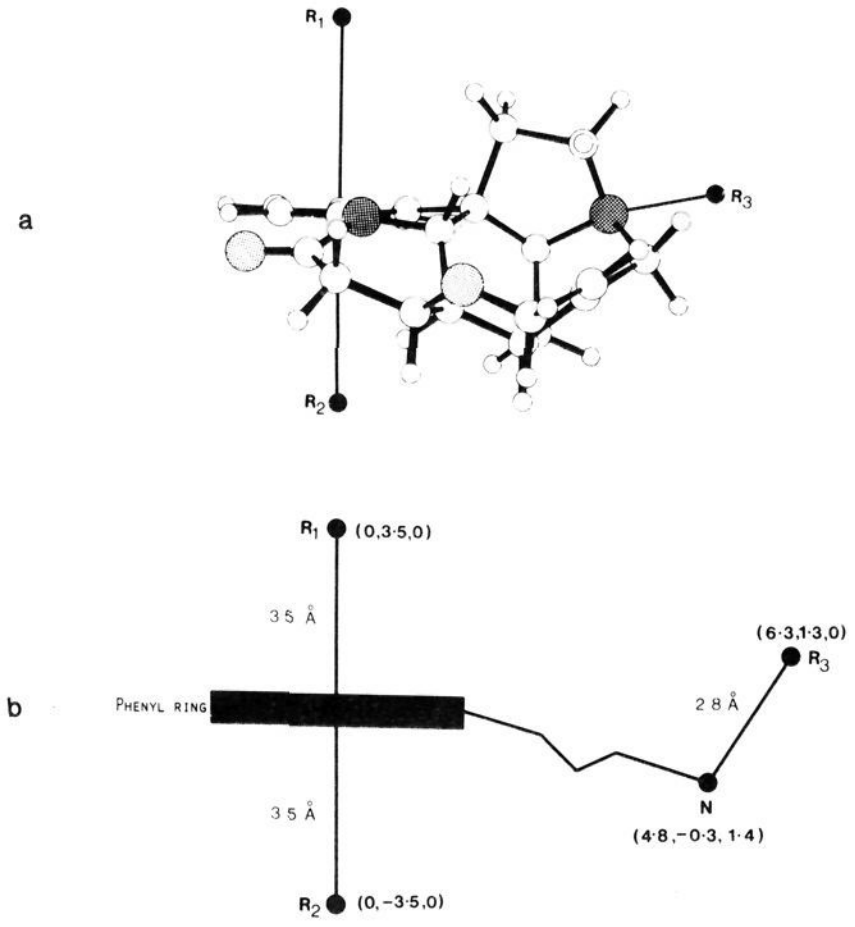



**Figure 1.** (a) Perspective drawing of strychnine (**2**) showing the construction of the hydrophobic receptor points R1 and R2 onto the phenyl ring and of the hydrogen bond receptor point R3 onto the relevant nitrogen. (b) Dimensions of the common model viewed from a point perpendicular to the XOY plane, showing the coordinates of the four points (N, R1, R2, and R3) of the common model, determined from analysis of the semirigid molecules **1**–**5**. For comparison with other models, the angles $R_1$–O–N and O–N–$R_3$ are 93° and 111°, and the dihedral angle $R_1$–O–N–$R_3$ is −47°. The distance between the center of the phenyl ring and the nitrogen atom is 5.0 Å.

3. For all possible combinations of the aromatic group (usually a phenyl ring) and nitrogen atom in these fourteen molecules, three receptor points, $R_1$, $R_2$, and $R_3$, were built onto the solid-state structures. The points $R_1$ and $R_2$, representing hydrophobic bonding, are placed 3.5 Å above and below the center of a phenyl ring as origin. This vertical axis totally defines the position and orientation of the phenyl ring (without specifying its point of attachment) as well as the position and orientation of possible receptor groups above and/or below the plane of the ring. $R_3$, representing hydrogen bonding, is located tetrahedrally 2.8 Å from a nitrogen atom. Although the key nitrogen atoms in this series of drugs vary from basic [e.g., amphetamine (**11**)] to weakly acidic [e.g., phenobarbitone (**6**)], all may participate in some form of hydrogen bonding—either as acceptors or donors—with the same conjugate group, e.g., an amine, attached to the receptor protein. The similarity in respect of these hydrogen bond interactions thus permits the use of a common geometry when modelling their drug–receptor topography. This process is illustrated, using strychnine as an example, in Figure 1a. These extended drug–receptor structures were then used in the analyses described below.

4. Among the 14 molecules, morphine, strychnine, LSD, apomorphine, and mianserin are relatively rigid, and it may be assumed that one of the relatively few extended drug–receptor structures accessible to each of these molecules approximates their biologically active interactions. Mianserin (**5**), for example, has two possible phenyl rings and one key nitrogen that could form a hydrogen bond to the receptor point $R_3$ in two ways through nitrogen inversion of the attached methyl group. (The alternative azepine nitrogen was rejected because the nitrogen–phenyl distance was too small.) Thus mianserin could interact at a receptor in any one of four ways. The five semirigid molecules were therefore used to determine the coordinates of the common model by taking the various possible conformations of these molecules that arise through nitrogen inversions and the mobility of partially restricted or saturated rings, and orientating them so that the receptor points, $R_1$, $R_2$ and $R_3$, lay in the XOY plane, with $R_2$–$R_1$ being the Y′OY axis, the center of the phenyl ring being the origin, and the nitrogen Z coordinate being positive. Analysis of this set of structures then led to the identification of a single arrangement of the $R_1$–$R_2$ and N–$R_3$ vectors that was common to all five semirigid molecules.

**Table I.** Semirigid Molecules Fitted to the Common Model

| | conformer | energy[a] | distance[b] |
|---|---|---|---|
| morphine (**1**) | axial $R_3$ | 0.0 | 0.30 |
| | equatorial $R_3$ | 2.1 | 0.42 |
| strychnine (**2**) | | 0.0 | 0.43 |
| LSD (**3**) | flap-up, axial $R_3$ | 0.0 | 0.41 |
| | flap-down, equatorial $R_3$ | 60.6 | 0.45 |
| apomorphine (**4**) | axial $R_3$ | 0.0 | 0.62 |
| mianserin (**5**) | axial $R_3$ | 0.0 | 0.33 |

[a] Energy above the global minimum for each molecule in kilocalories/mole. [b] Best fit distance, measured as the root mean square (RMS) in angstroms.

5. Two sets of calculations were then performed on all conformations of the nine remaining flexible extended drug–receptor structures. The first calculations gave the energy in kilocalorie/mole of the molecule, while the second calculations gave a measure of best fit (RMS) between the four points $R_1$, $R_2$, $R_3$, and nitrogen of the molecule under consideration and the corresponding points of the common model. Wherever alternative phenyl rings and drug orientations were possible, complete calculations on each were performed. For example, for chlorpromazine (**13**), which has two available phenyl rings, A and B, each having two orientations, the total number of conformations considered for both energy and distance calculations obtained by rotation of each of its four variable torsion angles through 36 steps of 10° was $2^2 \times 36^4$, i.e., ca. $6.7 \times 10^6$. Comparison of the energy data with that obtained by superimposition on the common model led to the selection of those ranges of conformations that combined both low energy (within 5.0 kcal $mol^{-1}$ of the global minimum, i.e., the thermally accessible conformations) and an acceptable fit (RMS < 1.0 Å) to the common drug–receptor geometry. In fact, the average RMS value obtained in the subsequent analysis was 0.57 Å, which corresponds to a deviation between fitted points in a given conformer of 16–25% of the hydrophobic and hydrogen bond lengths used (3.5 and 2.8 Å, respectively). For a benzene ring this corresponds to a 9° tilt of one ring relative to another.

## Results and Discussion

**1. Definition of the Common Drug–Receptor Model.** There were 13 conformations of the five semirigid molecules to consider, which led to 13 pairs of $R_2$–$R_1$ and N–$R_3$ vectors (Figure 2a), from which the least similar vectors were readily eliminated (Figure 2b) by inspection. The remaining seven vectors, consisting of one from each of strychnine, apomorphine, and mianserin, and two from LSD and morphine, were reduced to five, as follows, on the basis of relative energies and receptor occupancy.

The LSD alternatives arise through partial mobility of its D ring in which the methylene "flap" may be up or down. Inversion of the *N*-methyl substituent in this ring therefore generates four conformers, two of which were eliminated from consideration because of their dissimilarity with the other N–$R_3$ vectors. From the energy-fit data

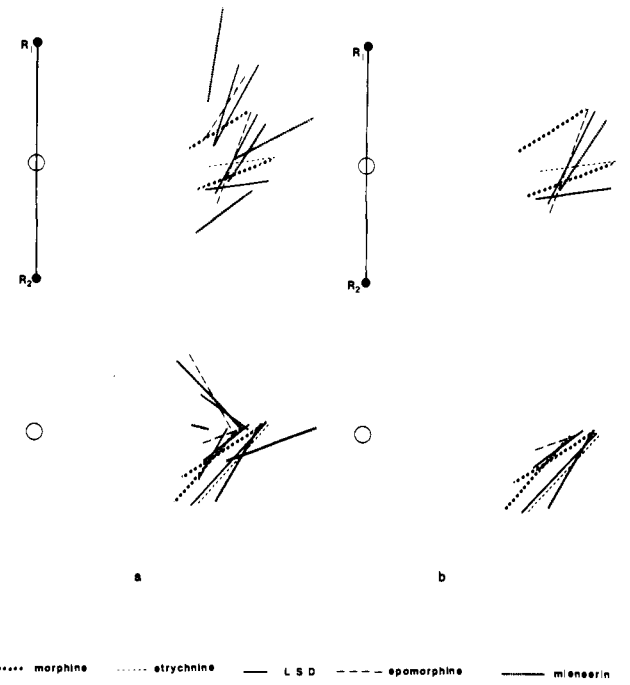



**Figure 2.** (a) The 13 hydrogen bond vectors of the semirigid molecules 1–5 that were considered in defining the coordinates of N and R3 of the common model. (b) The seven hydrogen-bond vectors that remain after eliminating the least similar vectors from those shown in Figure 2a. The upper part of (a) and (b) is the view of the vectors seen from a point perpendicular to the XOY plane, while the lower part shows each group of vectors viewed from above the XOZ plane. The origin is indicated by a circle.

(Table I) determined after energy optimization of the diethylamide side chain of LSD, it is clear that the much higher energy LSD conformer (flap down, equatorial $R_3$) should be excluded despite its good fit.

The energy difference for the morphine conformers is only 2.1 kcal $mol^{-1}$ and both fit the common model comparatively well (Table I). These conformers only differ in having axial and equatorial receptor points $R_3$ (i.e., they are invertomers), but superimposition of each onto the common model was possible by inverting one molecule through ca. 180° with respect to the other. Since neither the energy nor the fit data appear to discriminate sufficiently between them, we chose the morphine equatorial-$R_3$ isomer because computer graphic superimpositions show that it causes no increase in the space required to accommodate the union of these five semirigid molecules. We note, however, that the additional space requirements of the axial isomer are also minimal.

Perspective views of both morphine isomers, together with the conformers of the other semirigid molecules used to determine the common model, are shown in Figure 3. The coordinates of the receptor points of the five chosen structures were then averaged to give the coordinates of the common drug–receptor model: $R_1$ (0.0, 3.5, 0.0), $R_2$ (0.0, −3.5, 0.0), $R_3$ (6.30, 1.30, 0.0), and N (4.80, −0.30, 1.40) (Figure 1b).

An important outcome of these considerations is that since morphine, LSD, mianserin, apomorphine, and strychnine are chiral and enantiospecific in their CNS drug action, then the drug–receptor model defined by them also maps out receptor volume whose chirality is determined by the orientation of the N–$R_3$ vector relative to the $R_1$–$R_2$ vector in the common model and whose shape is complementary to that formed by the superimposition of these five molecules on each other. It is axiomatic that the space occupied by a receptor is forbidden to the binding groups

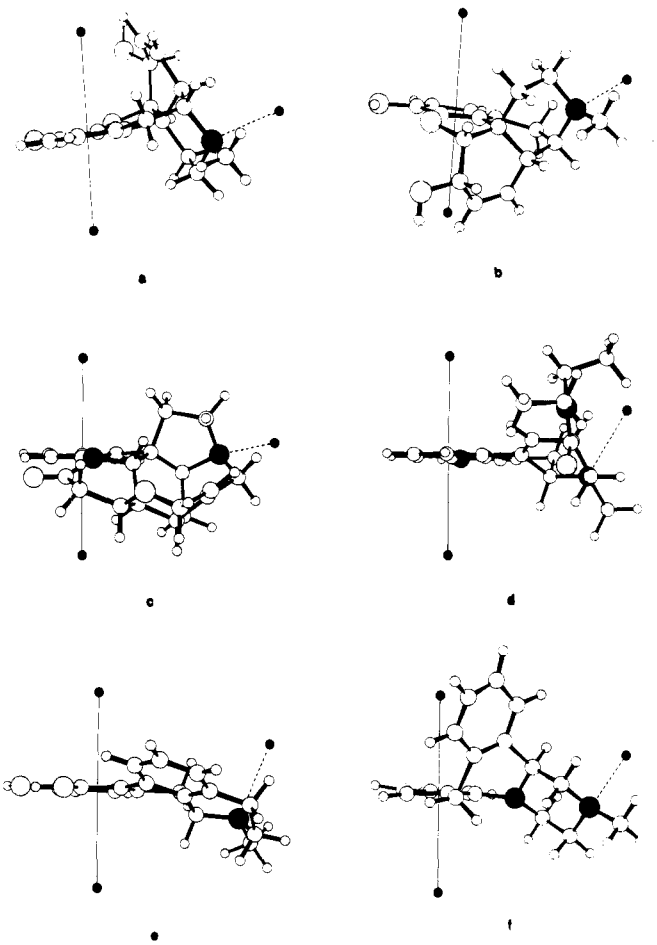



**Figure 3.** Perspective drawings of the semirigid molecules 1–5 determined as having lowest energy, most similar hydrogen bond vectors, and least overlap with receptor essential volume after orientating the four points N, R1, R2, and R3 of each molecule to the average of the coordinates of these points for this set of molecules: (a) morphine, axial hydrogen bond, N–R3; (b) morphine, equatorial hydrogen bond, N–R3; (c) strychnine; (d) LSD; (e) apomorphine; (f) mianserin. In this and subsequent figures R1, R2, and R3 are represented by (●), and nitrogen and oxygen are indicated by dark and light shadings, respectively.

and skeleta of its substrate molecules. Therefore, the receptor essential volume defined in this way by these semirigid molecules provides an additional criterion by which to reduce the number of possible conformations of the more flexible molecules. We shall use this criterion as a general method for choosing between otherwise equally acceptable conformations throughout the remainder of this paper.

**2. Superimposition of the Flexible Molecules onto the Common Model. (1) Flexible Molecules Having One Variable Torsion Angle.** The energy–distance plots for three of the single torsion angle molecules, viz., phenobarbitone (**6**), clonidine (**7**), and bicuculline (**9**), show that each can adopt only one conformation that allows low energy and best fit to the common model. By way of example, the plot for phenobarbitone is shown in Figure 4. These results are not surprising, since the structures of these molecules allow very little flexibility in the rings containing the pertinent nitrogen: phenobarbitone, whose ethyl side chain was first optimized into an extended conformation away from the phenyl group, has a six-membered cyclic amide structure that is essentially flat; clonidine contains a resonance-stabilized guanidine structure, a part of which is incorporated within an imidazolidine ring; and bicuculline has restricted flexibility

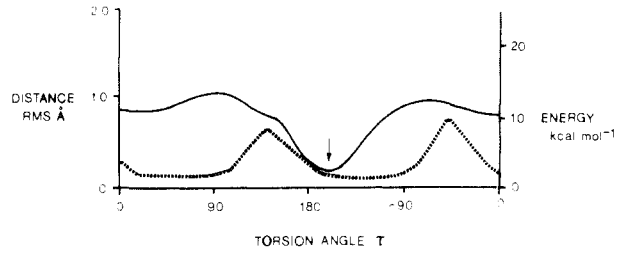



**Figure 4.** Plot of potential energy (--) and distance (–) between receptor points vs. the major torsion angle, for phenobarbitone (**6**). The combination of lowest energy and best fit of the four points of the common model to the corresponding points of phenobarbitone occurs at $\tau = -160°$ (arrowed).

Table II. Conformations of Flexible Molecules Having One Variable Torsion Angle, Fitted to the Common Model with Lowest Energy and Best Fit[a]

| | torsion angle | energy[b] | distance[c] |
|---|---|---|---|
| phenobarbitone (**6**) | −160 | 0.0 | 0.3 |
| clonidine (**7**) | 70 | 0.7 | 0.4 |
| diazepam[d] (**8**): ring A–$N_1$ | | | |
| *S* isomer | −100 | 0.1 | 1.0 |
| *R* isomer | 100 | 0.0 | 0.8 |
| trigonal form | −90 | 0.1 | 0.6 |
| diazepam[d] (**8**): ring B–$N_4$ | | | |
| *S* isomer | −90 | 0.0 | 1.0 |
| *R* isomer | −90 | 0.0 | 0.9 |
| trigonal form | −90 | 0.0 | 0.9 |
| bicuculline (**9**) | −100 | 0.4 | 0.7 |

[a] The relevant torsion angles are shown in Chart I. [b] Energy above the global minimum in kilocalories/mole. [c] Best fit distance, measured as the root mean square (RMS) in angstroms. [d] Chirality is defined by using the convention of Klyne and Prelog.[3]

due to the presence of an isoquinoline structure.

In the remaining single torsion angle molecule diazepam (**8**), there are two possible phenyl–nitrogen combinations (ring A–$N_1$ and ring B–$N_4$, Chart I) and in each case the nitrogen atom is part of a flexible seven-membered ring that has been shown to undergo rapid inversion.[22] These nitrogens could conceivably adopt tetrahedral geometry on interaction with the receptor and hence would show chirality. Consequently, there are eight possible conformers to be examined, each of which may be fitted to the common model in two ways by rigid body rotation of the molecule through 180°. Examination of these 16 possibilities on the basis of low energy and best fit reduced these to the four shown in Table II. A similar analysis, in which it was assumed that the nitrogen atoms had trigonal geometry, led to two additional conformations (Table II; for the ring A–$N_1$ case, the CNS-active metabolite desmethyldiazepam[23,24] was used). To further distinguish between all these isomers requires comparison with rigid analogues or chiral molecules having activity within the same CNS class. A recent study[25] that compared the three-dimensional structures of diazepam with the enantiomers of a 3-methyl-1,4-benzodiazepine and of a rigid anthramycin-type benzodiazepine supports the ring conformation of diazepam shown in Figure 5d,e. The orientation shown in this figure is consistent with both of the phenyl–nitrogen combinations matching the common model with low energy, best fit, and minimal overlap with receptor essential volume.

Table III. Conformations of Diphenylhydantoin Having Lowest Energy and Best Fit to the Common Model[a]

| phenyl ring | torsion angle ranges $\tau_1$ | torsion angle ranges $\tau_2$ | best value of $\tau_1$ and $\tau_2$ | energy[b] dist[c] |
|---|---|---|---|---|
| A ring | −30 to +20 | 80 to 130 | conformer *1* (0, 110) | 2.0, 0.4 |
| | 90 to −160 | 90 to 160 | conformer *2* (110, 160) | 0.0, 1.0 |
| B ring | 70 | 180 to −160 | conformer *3* (70, 180) | 3.0, 1.0 |
| | 70 to 150 | 90 to −160 | conformer *4* (110, 180) | 0.0, 0.7 |
| | −30 to +20 | 80 to 130 | conformer *5* (0, 100) | 1.0, 1.0 |

[a] Energy above the global minimum in kilocalorie/mole. [b] Best fit distance, measured as the root mean square (RMS) in angstroms.

Data for all four of these flexible molecules (**6**–**9**) are summarized in Table II, and perspective views of the best-fit conformers are shown in Figure 5.

**(2) Flexible Molecules Having Two or More Variable Torsion Angles.** Diphenylhydantoin (**10**), amphetamine (**11**), imipramine (**12**), chlorpromazine (**13**), and procyclidine (**14**) have two or more torsion angles to consider, and it is not possible to show all the energy and distance maps required to span their conformational space, even using limited step sizes for their torsion angles. Therefore, only the salient points of the analysis for each of these molecules will be given.

**Diphenylhydantoin (10).** Analysis of the energy and distance maps for the two possible phenyl–nitrogen combinations showed that there were five conformations corresponding to low energy and best fit (Table III). With use of computer graphics it was further shown that conformations *3* and *5* could be eliminated because of overlap with receptor essential volume. Of the remaining three conformations, *1* and *4* are mirror image conformers that fit the model with opposite placements of both their hydantoin and their secondary phenyl rings, while *2* and *4* show opposite orientations of their hydantoin rings. Better stereoisomeric activity data for related compounds will be needed to discriminate between these alternatives. A perspective view of conformer *2* is shown in Figure 6.

**Amphetamine (11).** The flexible side chain of (*S*)-(+)-amphetamine has three torsion angles to vary due to the inclusion of the N–$R_3$ interaction. Examination of the energy maps produced after sequentially varying these angles showed a large number of low-energy conformations that were readily interconvertible but with a preference for $\tau_1 = \pm 90$, $\tau_2 = 180$, and $\tau_3 = \pm 60$ or 180. These correspond essentially to a side chain directed away from the plane of the phenyl ring and in an extended conformation. The many low-energy conformations were reduced to 15 on applying the criterion of optimal fit to the common model, but only one of these, $\tau_1 = 110$, $\tau_2 = 180$, $\tau_3 = -60$ (RMS = 0.5), the energy distance maps for which are shown in Figure 7, showed no overlap with receptor essential volume. The resultant conformation shown in perspective view in Figure 6 is consistent with that of a known active rigid analogue of amphetamine.[2]

**Imipramine (12).** Imipramine shows two broad areas of conformational flexibility: those of the tricyclic nucleus and the (dimethylamino)propyl side chain. For the tricyclic nucleus, it has been shown by using X-ray crystallography that the two phenyl rings are topographically nonequivalent due to the twisting and skewing effects of

(22) Hamor, T. A.; Martin, I. L. "Progress in Medicinal Chemistry"; Ellis, G. P., West, G. B., Eds.; Elsevier: Amsterdam, 1983; pp 157–223.
(23) Fulton, A.; Maguire, K. P.; Norman, T. R.; Worm, J. M. E. "Psychotropic Drugs: Plasma Concentration and Clinical Response"; Burrows, G. D., Norman, T. R., Eds.; Marcel Dekker: New York, 1975; pp 376–379.
(24) Braestrup, C.; Squires, R. F. *Eur. J. Pharmacol.* **1978**, *48*, 263.
(25) Blount, J. F.; Fryer, R. I.; Gilman, N. W.; Todaro, L. J. *Mol. Pharmacol.* **1983**, *24*, 425.

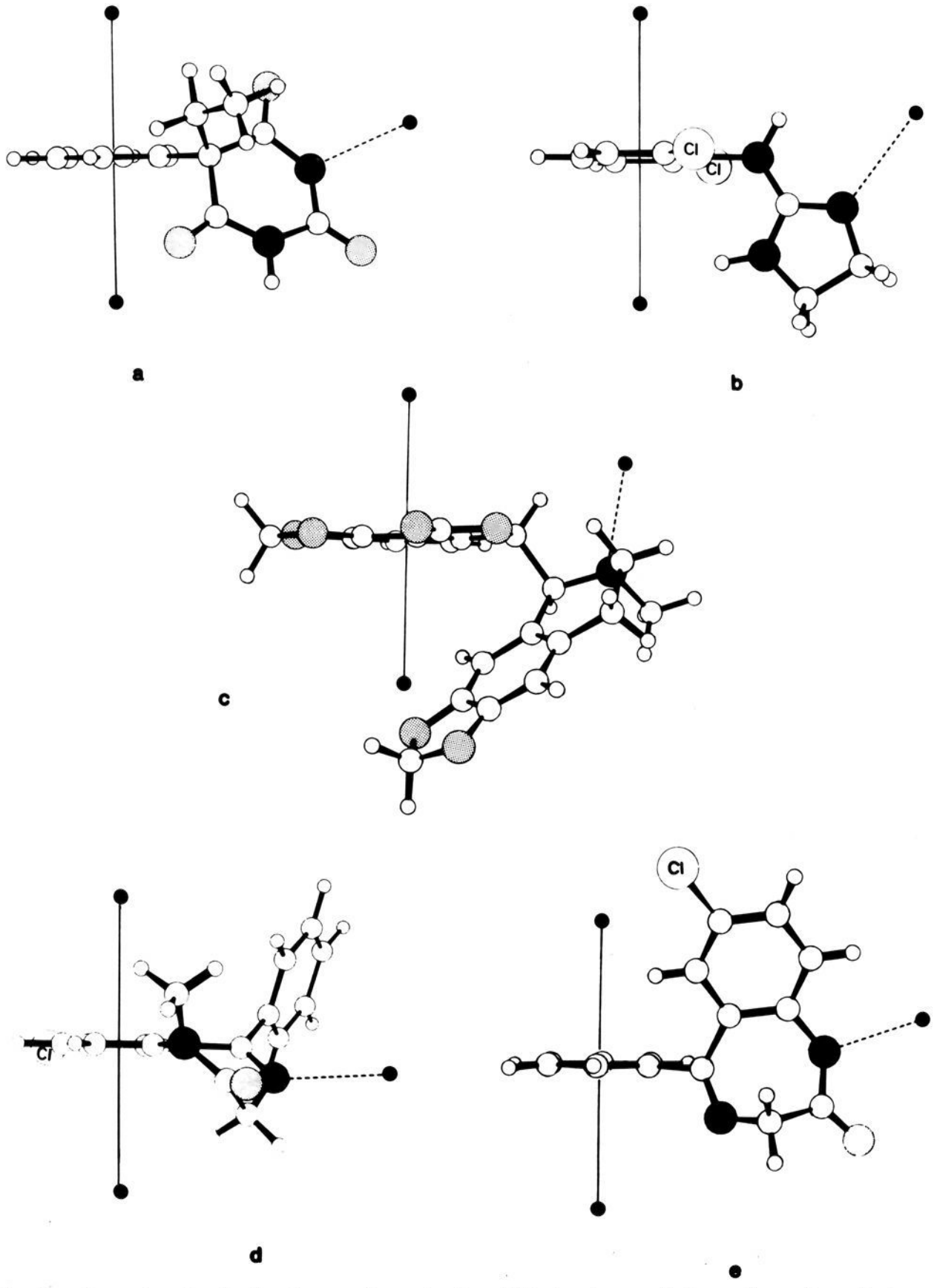



**Figure 5.** Perspective drawings of molecules having one important variable torsion angle in conformations that combine lowest energy and best fit to the common model: (a) phenobarbitone, (b) clonidine, (c) bicuculline, (d) diazepam, ring B–$N_4$, (e) diazepam, ring A–$N_1$.

the ethano bridge.[19] The tricycle is folded along an axis through the azepine nitrogen and one of the ethano bridge carbons, so that one phenyl ring, denoted arbitrarily as the B ring, is coplanar with the three nonaromatic atoms of the central ring, while the second phenyl (ring A) lies in a different plane containing the fold line. Rapid inversion of the tricyclic nucleus also allows a set of dynamic conformers to exist in solution,[26] but the two major forms that result are superimposable on each other. For these reasons, it was necessary to carry out energy-distance calculations for the two phenyl rings, A and B, each orientated in two different ways.

Regarding the flexible side chain, a comprehensive survey of the potential energy of imipramine has shown that it may adopt two different global minimum-energy conformations at either $\tau_1 = 50$ or $\tau_1 = 140°$.[26] Energy-distance calculations were therefore carried out for each of these values in combination with the four phenyl ring possibilities, while varying $\tau_2$, $\tau_3$, and $\tau_4$ sequentially.

This resulted in 21 conformations showing low energy and best fit to the common model, with just three of these showing no overlap with receptor essential volume. The best of these ($\tau_1 = 50$, $\tau_2 = 60$, $\tau_3 = 180$, and $\tau_4 = 30$, RMS = 0.8), shown in perspective form in Figure 6, closely matches (*S*)-(+)-mianserin in all essential features.

**Chlorpromazine (13).** A preliminary survey of the potential energy of chlorpromazine obtained by varying the four torsion angles of the flexible side chain showed two principal equienergy global minima at $\tau_1 = 60$ or 150°. This torsion angle was therefore fixed in turn at each of these values, and energy-distance calculations were carried out sequentially on the remaining three torsion angles for all combinations of phenyl rings and hydrophobic vector orientation. Furthermore, since it has been shown that chlorpromazine exists in the solid state as enantiomorphs

(26) Munro, S. L. A. M. Pharm Thesis, Victorian College of Pharmacy Ltd., 1985.

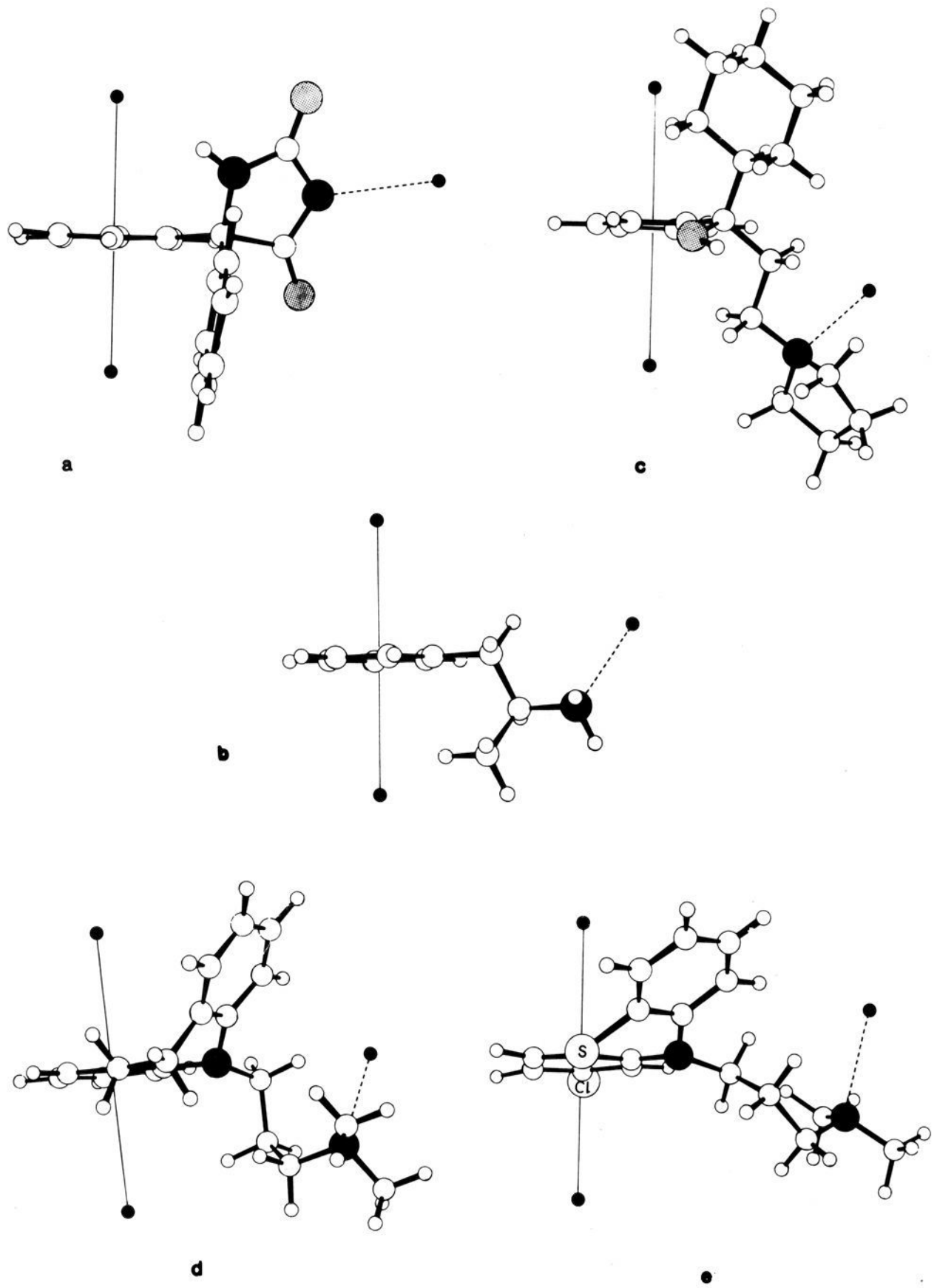



**Figure 6.** Perspective drawings of flexible molecules having more than one variable torsion angle in conformations that combine low energy, a good fit to the common model, and no overlap with receptor essential volume: (a) diphenylhydantoin, (b) amphetamine, (c) procyclidine, (d) imipramine, (e) chlorpromazine.

with respect to the tricyclic nucleus[20] and that this system undergoes rapid inversion in solution,[27] then the possibility exists that either or both of these forms may be biologically active. The above energy-distance calculations were therefore repeated with use of the enantiomeric tricyclic nucleus but with $\tau_1 = -60$ and $-150$. As a result, 62 conformations were found to satisfy the criteria of low energy and best fit to the common model, but only 10 showed no overlap with receptor essential volume. The best of these, involving the A ring as the primary aromatic binding site in which $\tau_1 = -150$, $\tau_2 = 150$, $\tau_3 = 70$, and $\tau_4 = -30$ (RMS = 0.6), is shown in Figure 6. These results establish that either the substituted (ring A) or unsubstituted (ring B) phenyl group could act as a primary binding site and that a variety of $\tau_2$, $\tau_3$, and $\tau_4$ values allow the side chain to insinuate the hydrogen bond vector into a common alignment with that of the model.

**Procyclidine (14).** Although procyclidine has six torsion angles to vary, the values of these that define the conformation of the phenyl, cyclohexyl, and hydroxyl group at the chiral carbon are considerably restricted by steric interactions. These angles were initially set equal to the values found in the crystal structure, while the remaining three that define the conformation of the pyrrolidinylethyl side chain were varied sequentially for all orientations of the phenyl group, to obtain the lowest energy and best fit to the common model, viz., $\tau_1 = -50$, $\tau_2 = 170$, $\tau_3 = -40$, $\tau_4 = -160$, $\tau_5 = 160$, and $\tau_6 = 180$ (RMS = 0.9) (Figure 6).

## Conclusions

The best conformers for all 14 drugs are shown superimposed on each other in Figure 8, which shows not only the common placement of the aromatic rings and the ni-

(27) Soltz, B. A.; Corey, J. Y.; Larsen, D. W. *J. Phys. Chem.* **1979**, *83*, 2162.

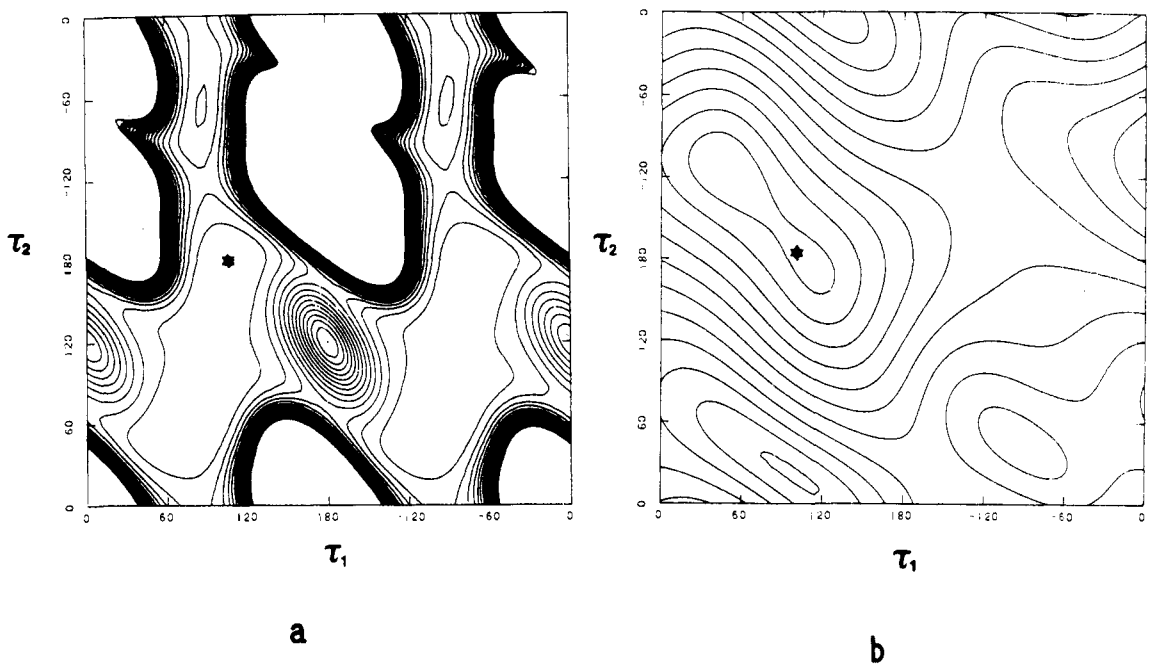



**Figure 7.** Plots of (a) potential energy and (b) distance between receptor points vs. torsion angles $\tau_1$ and $\tau_2$ for (*S*)-(+)-amphetamine (11), with $\tau_3$ fixed at −60°. The combination of lowest energy and best fit of the four points of the common model to the corresponding points of (*S*)-(+)-amphetamine occurs at $\tau_1 = 110°$ and $\tau_2 = 180°$, shown as an asterisk.

**Table IV.** Topological Characteristics and Biological Activities of Compounds Listed in the Merck Index

| classification | total no. | nitrogen | number[a] containing phenyl | nitrogen and phenyl | nitrogen phenyl and topology |
|---|---|---|---|---|---|
| in Merck Index | 876 | 406 (46) | 375 (43) | 245 (28) | 147 (17) |
| biologically active (not CNS) | 319 | 174 (55) | 152 (48) | 97 (30) | 37 (12) |
| CNS active | 104 | 99 (95) | 88 (85) | 87 (84) | 85 (82) |

[a] Figures in brackets are percentages of each class containing the selected topological characteristic (N, phenyl, etc.).

trogen in this diverse group of CNS-active drugs but also the virtually identical position of the corresponding receptor points throughout the series. This supports our initial hypothesis that there is a common structural basis, comprising an aromatic ring and a nitrogen atom in a specific topographical arrangement, for the activity of many *different* CNS drug classes.

Although we have attempted to avoid any bias in this study by selecting only compounds that are generally regarded as key representatives of their pharmacological classes, it could be argued that these observations are a coincidental outcome of our initial selection of the data base. Therefore, since it is not possible to apply the full topographical analysis described above to a significantly larger series of compounds, we have devised a simple topological test of the proposed model and applied it to 1000 randomly selected compounds. The results, given in the Appendix, indicate that Figure 8 is indeed generally applicable to CNS-active drugs.

What are the implications of this common model and the general properties of CNS receptor sites that it maps out?

In its broadest sense for drug design, our common model of the primary binding groups, made up of the aromatic ring and nitrogen atom, provides a framework against which new drugs may be tested for potential CNS activity. This forms the basis for a novel CNS drug development program currently in progress in our laboratory.

In a specific sense, the topographical location of secondary or accessory binding sites relative to the primary sites could be used to categorize drugs as belonging to individual CNS classes. A corollary of this aspect is the ability to define precisely which secondary binding sites among a set of drugs determine their common attribute as distinct from those sites that determine side effects through binding at alternative neurotransmitter receptors. Clearly this information will be necessary before the model can be used as a basis for the design of drugs with specific CNS activities, and we are currently in the process of mapping the locations of these sites. Receptor modelling studies already available within individual drug classes[2] will be invaluable in this regard.

## Appendix

**Testing the Model.** A simple and direct means of testing our proposals would be to apply the full topographical analysis described in the paper to a larger data base of CNS-active *and* -inactive compounds. Unfortunately, the time required (ca. 1 month per compound in our hands) makes such an undertaking impossible. We therefore decided to choose a much larger data base and to apply the following simple topological tests to the proposed model: what percentage of *all* CNS-active drugs in the data base contain a phenyl ring and a nitrogen atom separated by a two to five atom chain? What percentage of CNS-*inactive* drugs exhibit the same topology?

To apply these tests we need an unbiased selection of known compounds together with data on their structure and activity. We therefore selected every tenth entry (those ending in zero) from the Merck Index.[28] Since the

(28) Windholz, M., Ed.; "The Merck Index, An Encyclopedia of Chemicals, Drugs and Biologicals", 10th ed.; Merck and Co.: Rayway, NJ, 1983.

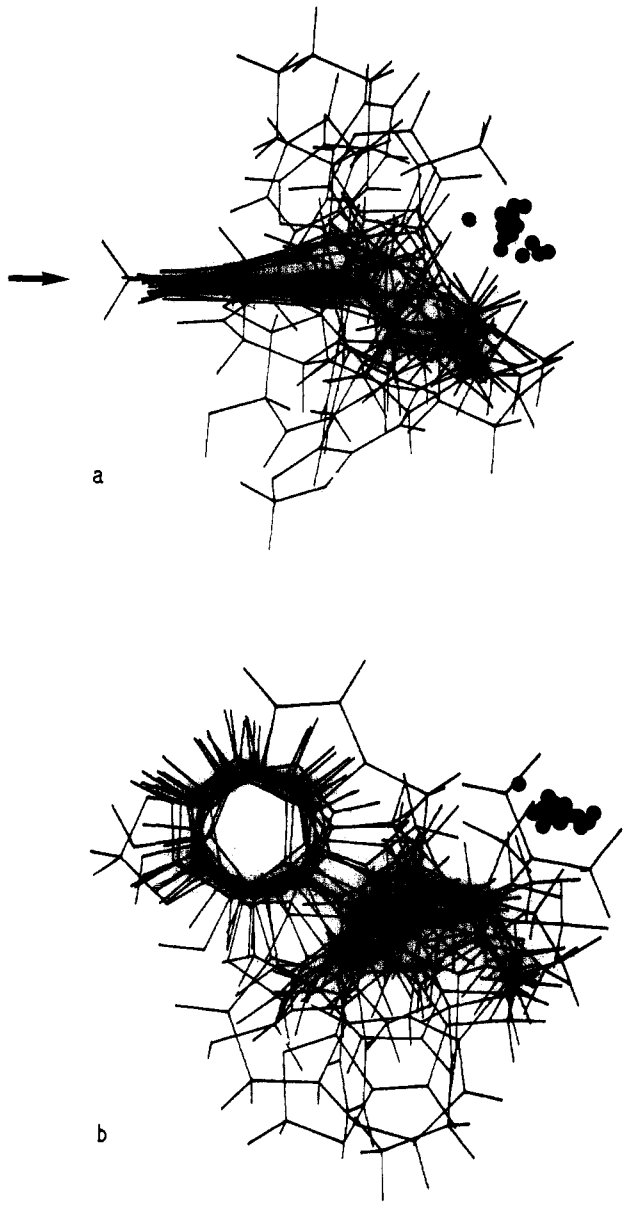



**Figure 8.** (a) Superimposition of all 14 molecules in their lowest energy, best-fit conformations to the common model. The orientations are the same as in Figures 3, 5, and 6, but with 3a and 5d excluded. Line drawings have been used for clarity. (b) Figure 8a viewed from above the phenyl rings (arrowed). The locations of the receptor point R3 for each molecule are indicated (●).

edition used contains precisely 10 000 entries, there were 1000 entries in our initial data base. Of these, 124 were excluded because the identity of the active component was uncertain. In most cases these were mixtures (e.g., 6730: granulated opium) or high-molecular-weight structures (larger than pentapeptides). The remaining 876 entries were classified according to the presence or absence of (i) a phenyl ring (free or fused); (ii) a nitrogen atom (amine, amide, or imine other than heteroaromatic); (iii) a two to five atom chain connecting the phenyl group and nitrogen atom by the shortest path; (iv) biological activity: compounds having a well-defined *Therapeutic Category* or other biological *Use* at the end of the Merck entry were classified as biologically active; (v) CNS activity: recognized CNS categories (e.g., narcotic analgesic, antidepressant) and those recognized as generally having significant CNS effects (e.g., cholinergic, histaminergic) were automatically included. Compounds in therapeutic categories that may or may not involve CNS activity (e.g., antitussives, antihypertensives) were checked individually.[29,30] The results of this classification are given in Table IV and lead to the following conclusions:

(i) The presence of a phenyl ring and a nitrogen atom with the defined topology is a common characteristic of CNS-active drugs. Eighty-two percent of CNS-active compounds contain this grouping compared to only 12% of compounds with other classes of biological activity. Furthermore, the 19 compounds classified as CNS active but lacking the proposed topology[31] are almost all compounds generally regarded as structurally nonspecific drugs (e.g., sedatives, hypnotics, etc.).

(ii) The presence of the phenyl ring and nitrogen atom with the appropriate topology also appears to be a useful predictor of CNS activity, and perhaps toxicity. Of the 147 compounds containing this grouping, 85 (58%) are specifically classified as CNS active in the Merck Index, and many of the remaining 62 entries are clearly CNS active (e.g., 5880, 5-methoxytryptamine) or have established CNS side effects (e.g., 6950, penicillin G calcium). These data thus support the conclusions drawn from our more detailed topographical study on the smaller data base.

**Registry No.** 1, 57-27-2; 2, 57-24-9; 3, 50-37-3; 4, 58-00-4; 5, 24219-97-4; 6, 50-06-6; 7, 4205-90-7; 8, 439-14-5; 9, 485-49-4; 10, 57-41-0; 11, 300-62-9; 12, 50-49-7; 13, 50-53-3; 14, 77-37-2.

(29) Reynolds, J. E. F., Ed. "Martindale, The Extra Pharmacopoeia", 28th ed.; The Pharmaceutical Press: London, 1982.
(30) Gilman, A. G.; Goodman, L. S.; Gilman, A., Eds. "Goodman and Gilman's The Pharmacological Basis of Therapeutics", 6th ed.; Macmillan: New York, 1980.
(31) The 19 compounds were aceglutamide, acetal, acetylcholine bromide, aclatonium napadisilate, alloxidone, atropine sulfate, barbital, butethal, hopantenic acid, glutamic acid, meparfynol, meprobamate, methyprylon, nialamide, nitrous oxide, paramethadione, phenaglycodol, sulphonmethane and taglutimide.