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The Conformation of Neuroleptic Drugs

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A study of the conformation of neuroleptic drugs by X-ray diffraction and simple conformational calculations has revealed some relationships among the relative arrangements of possible pharmacodynamic groups for these substances. A hydrogen bond donor at an appropriate distance from the basic nitrogen common to most neuroleptics often results in an enhancement of activity.

INTRODUCTION

It has been shown by Janssen (1) that all known neuroleptic drugs can be regarded as belonging to one of nine categories of methylethylamine derivatives. The first seven of these categories can be derived from the following basic formula:

A—X = Y—C—C—N—C

where A is benzene or an isosteric aromatic ring; X = C, N, O, or S; and Y = C, N, or O. Also X and Y cannot be heteroatoms at the same time, and the X—Y bond only becomes a double bond when X = Y.

This attempt to correlate the chemical topology with activity has been very fruitful in organizing the large body of data on neuroleptics. However, it has two severe limitations. (a) In some cases the fragment associated with activity can be present in different ways in the same molecule; for example, there are three separate ways of obtaining an A—C—C—C—C—N—C or A—N—C—C—C—N—C fragment in spiperone (Fig. 1). (b) Some molecules which do contain the fragment are inactive.

A second type of relationship has been used mainly for phenothiazine derivatives (2). It attempts to correlate their tendency to form charge-transfer complexes with pharmacological activity. Unfortunately, investigators in this field have never extended the results obtained for the phenothiazine derivatives, which are rather weak and aspecific, to the more potent neuroleptic derivatives (e.g., spiperone).

This report compares the three-dimensional structures of neuroleptics, determined by X-ray diffraction, in order to find some correlation between them. Although no clear-cut conclusion emerges, it is possible to establish a number of structural requirements which enable one to predict, at least for the butyrophenones, the effect of certain substitutions on activity. The data on pharmacological activity in this paper refer to the apomorphine test using subcutaneous injections in dogs. Detailed data for a large number of neuroleptic compounds can be found in the literature (1).

This work was supported by a fellowship from le Fonds National de la Recherche Scientifique.

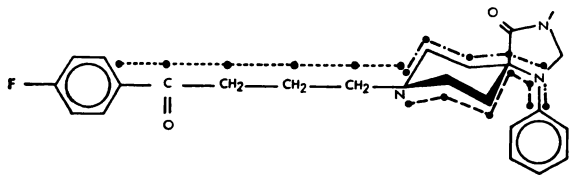
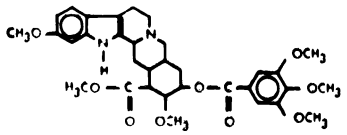
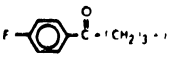
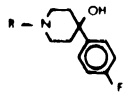
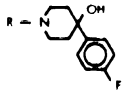
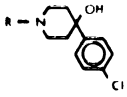
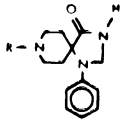
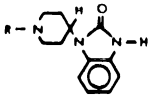
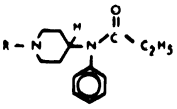
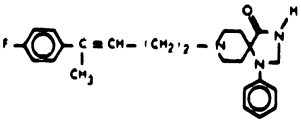
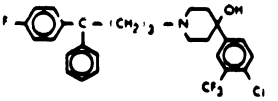


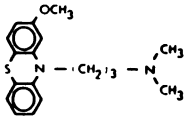
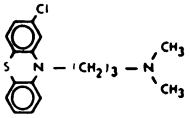
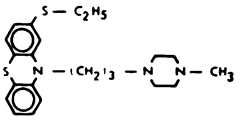
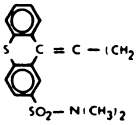
FIG. 1. *Three ways of finding an A—C—C—C—C—N—C or A—N—C—C—C—N—C fragment in spiperone*

TABLE 1

Formulae and references for three-dimensional structures of neuroleptics

Indole derivatives		Reference
Reserpine		3
Butyrophenones and related compounds		
R 1616		4
R 1616 - base		4
Haloperidol		5
Spiperone		6
Benperidol		7
R 4173		8
Spirilene		9
Penfluridol		10

TABLE, 1
(Cont'd.)

Phenothiazine derivatives		Reference
Mopazine (as mopazine maleate)		11
Chlorpromazine		12
Thiethylperazine		13
Thioxanthene derivatives		
Thiothixene		14

RESULTS AND DISCUSSION

The formulae and references corresponding to the known three-dimensional structures of interest are given in Table 1. Although charge-transfer complexes between phenothiazine and *s*-trinitrobenzene and between phenothiazine and 3,5-dinitrobenzoic acid (15, 16) have been published, these structures are not relevant to the neuroleptics. Nor will reserpine be studied in detail, because it produces depletion of brain catecholamines and probably has a mechanism of action which differs from that of most other neuroleptics. The atomic numbering used in this paper refers to the numbering given in the original papers.

The first question which arises in comparing the structures of phenothiazine derivatives and the more potent butyrophenones is whether the side chain of the phenothiazines corresponds to the side chain in butyrophenone or to some fragment in its piperidine ring. The probable conformations for the side chain of butyrophenone derivatives have been calculated using spiperone as a model for a Westheimer approximation (6). The values of ϕ_2 and ϕ_3 as defined in Fig. 2 were raised in 10° steps, while ϕ_1, ϕ_4, and ϕ_5 were fixed at the experimental values found in spiperone. The resulting energy map is shown in Fig. 3.

There are five nearly equal minima, which because of a symmetry plane perpendicular to the mean plane of the piperidine ring correspond to 10 allowed conformations. The shaded regions of the map correspond to unallowed conformations. The same calculation was carried out, assuming a value of $-60°$ for ϕ_1. The extended conformations of the side chain are much more favorable, although the lowest minimum is 5 kcal/mole above the lowest minimum in the first map (Fig. 4). All the known structures of butyrophenones, except R4173, correspond to one of three of the calculated minima of the map shown in Fig. 3.

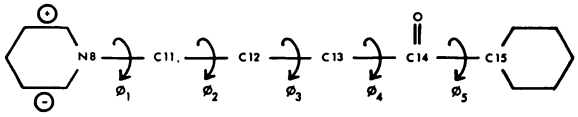


FIG. 2. *Definition of torsion angles used in Westheimer calculation*
A zero value for the torsion angle along the C(12)—C(13) bond in C(11)—C(12)—C(13)—C(14) corresponds to the *cis* conformation. A positive angle corresponds to a clockwise rotation of C(11) when looking down from C(12) to C(13).

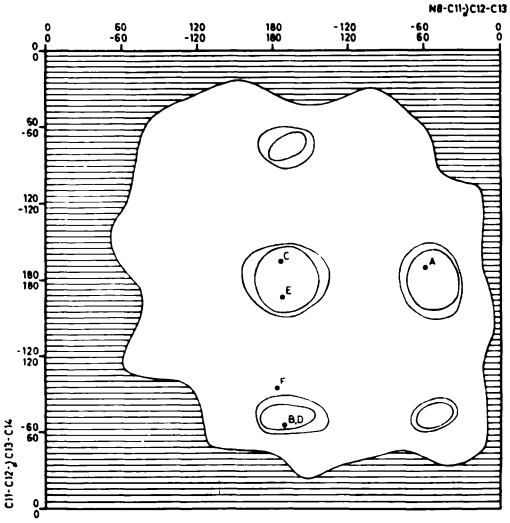


FIG. 3. *Result of conformational energy calculation for spiperone, assuming* $\phi_1 = 180°$
The dots correspond to the conformations found in the crystals: *A*, spiperone; *B*, R1616 base; *C*, R1616; *D*, haloperidol; *E*, benperidol; *F*, R4173. The contours correspond to differences of 1 kcal/mole.

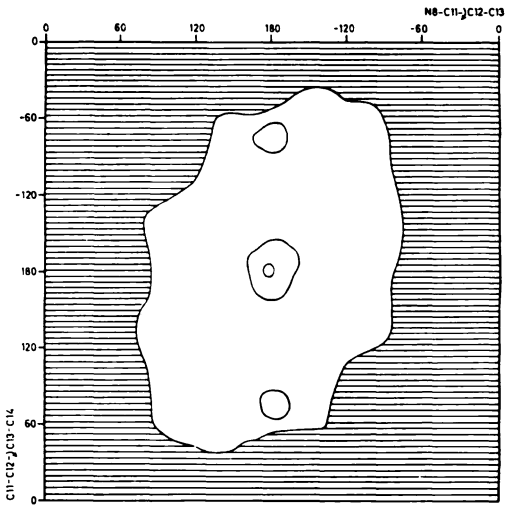


FIG. 4. *Results of conformational energy calculation for spiperone, assuming* $\phi_1 = -60°$
The contours are at intervals of 1 kcal/mole.

R4173 has a conformation only slightly above (≅0.5 kcal/mole) the second contour of the nearest minimum. A similar calculation, using the more sophisticated technique of perturbative configuration interaction using localized orbitals (PCILO), carried out by Coubeils and Pullman (17) for the phenothiazine derivatives, showed that the conformations of chlorpromazine, thiethylperazine, and mopazine in the solid state correspond to the energy minima for the isolated molecule. It should be stressed that all these calculations are strictly valid only for isolated molecules, as strong intermolecular forces exist in the crystal.

R1616 exemplifies the presence of van der Waals forces, hydrogen bonds, and strong ionic interactions in the solid state. In R1616 base only van der Waals forces and hydrogen bonds exist, while in R4173 cohesion of the crystal is due solely to van der Waals forces, since this molecule can form no hydrogen bonds. The good agreement between calculated and observed conformations, regardless of the type of intermolecular interactions in the crystal, indicate that these molecules will tend to maintain an extended conformation in any environment, as shown in Figs. 5 and 6, which are stereoscopic drawings of the unit cells of R1616 and R1616 base, respectively.

Table 2 summarizes the torsion angles of tne side chains of all known structures. The first three groups correspond to the three minima of the energy map in Fig. 3. The side chain of the phenothiazine derivatives has a conformation very similar to that of the

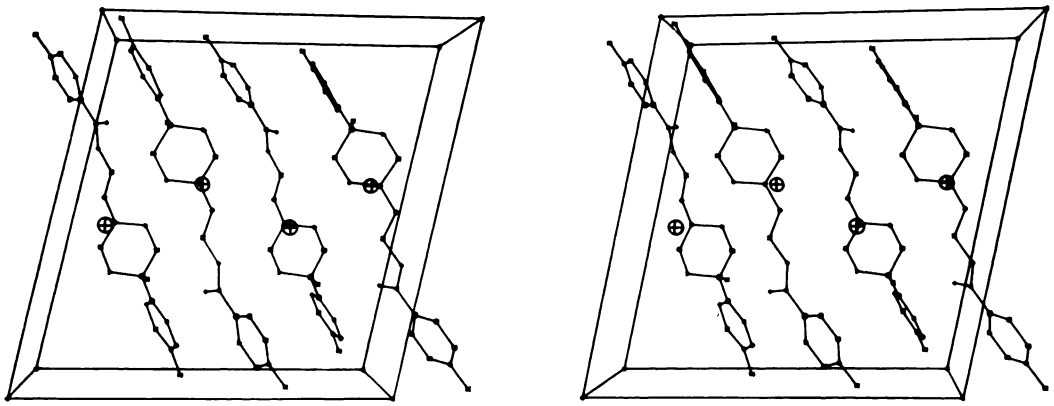


FIG. 5. *Stereoscopic view of contents of one unit cell of R1616*
The large spheres are the chloride ions.

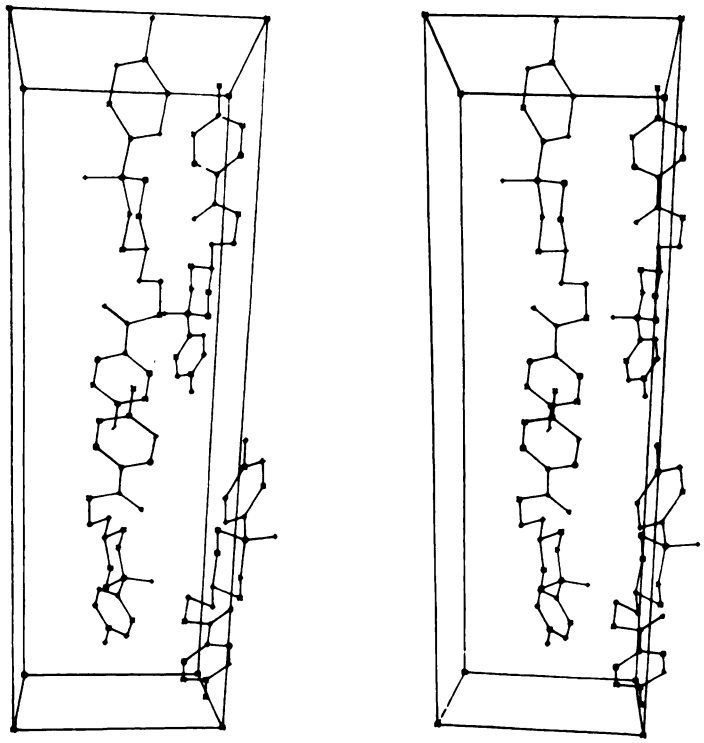


FIG. 6. *Stereoscopic view of contents of one unit cell of R1616 base*

butyrophenones, except for the end of the chain, which is strongly influenced by the presence of the phenothiazine ring. Replacement of the carbonyl group in the side chain of spiperone by a CH_3—C= group, to give spirilene, has no effect on the conformation of the molecule. The side chain of thiothixene has a conformation between those of group II and group III.

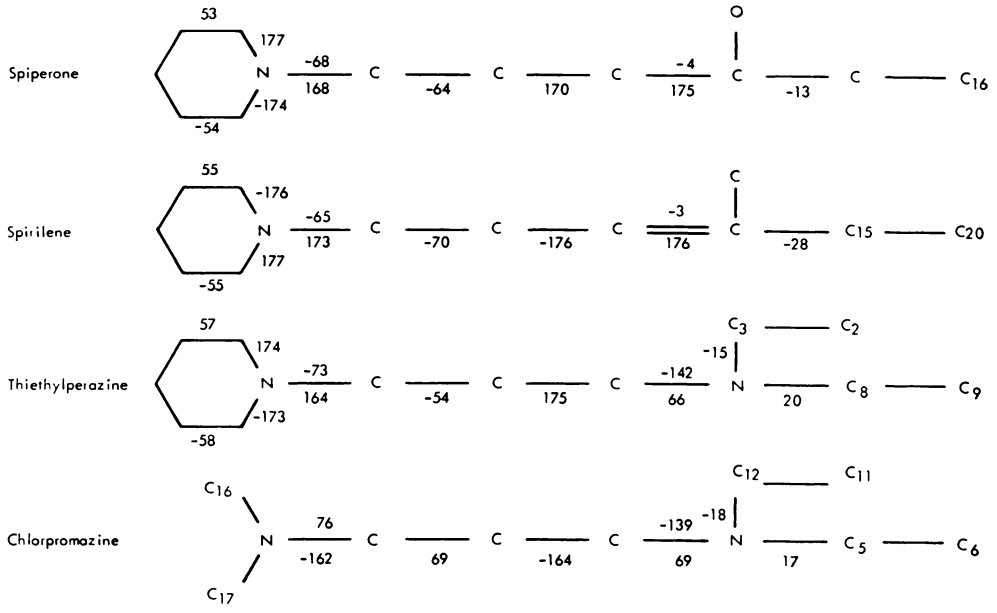
The flexibility of the side chain does not indicate very specific interactions; its main role must be to anchor the molecule in a lipophilic medium. Substitution in this part of the molecule will mainly affect

TABLE 2

Conformation of side chain of neuroleptics

Torsion angles are defined in Fig. 2.

Conformation of the side chain (GROUP I)



Conformation of the side chain (GROUP II)

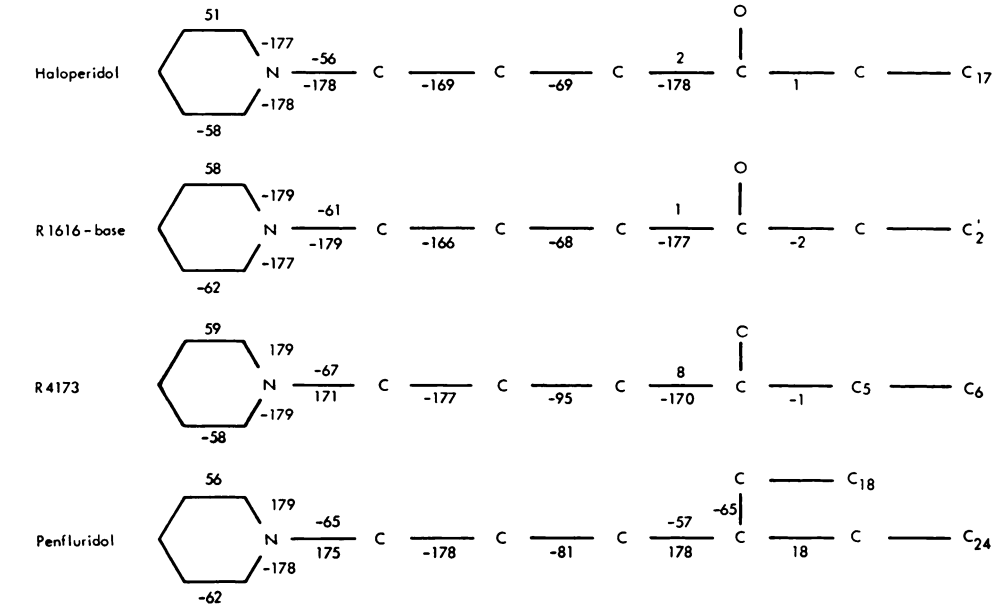
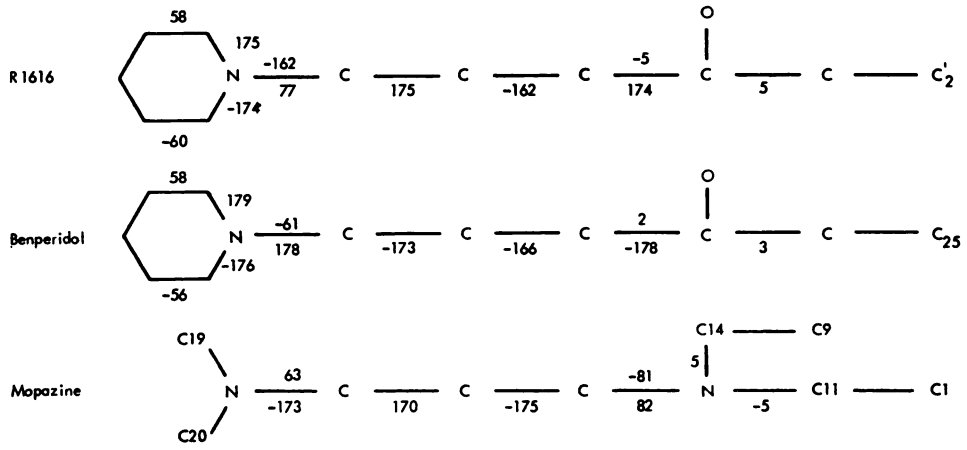
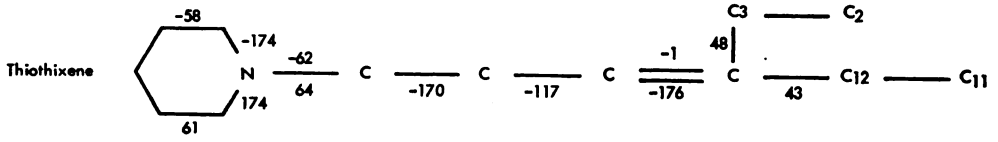


TABLE 2
(Cont'd.)

Conformation of the side chain (GROUP III)



Conformation of the side chain (GROUP IV)



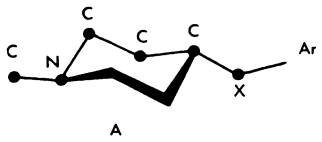
activity through its influence on the partition coefficient between the lipophilic and hydrophilic phases. However, the side chain of phenothiazine derivatives in the solid state perfectly mimics half of the piperidine ring in the chair form, as shown by the comparison of torsion angles in Table 3.

A striking similarity among the most active derivatives is the relative orientation of the piperidine ring and the conjugated group attached to it. In the most potent derivatives (spiperone, benperidol) the mean plane of the conjugated group is nearly perpendicular to the mean plane of the piperidine ring, as shown in the last column of Table 3 and in Table 4. In spiperone this conformation is rigidly fixed. Kaufman (18) has carried out a calculation by the method of complete neglect of differential overlap (CNDO) for chlorpromazine, which shows that if one considers the side chain to be fixed and hence to mimic the piperidine ring, only a small amount of energy is needed to bring the mean plane of the phenothiazine ring perpendicular to the mean plane of the side chain.

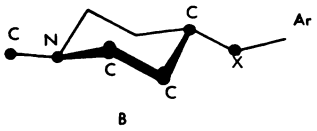
For benperidol there are two possible conformations for the conjugated group. This is shown in Fig. 7, which represents the result of a conformational analysis that takes into

TABLE 3

Comparison of torsion angles in piperidine ring of butyrophenones and related compounds and in side chain of phenothiazine derivatives



A



B

	X	A torsional angles			B torsional angles			angle between the LS mean plane of NCCC and Ar-group	
		C—N—C—C—C—X			C—N—C—C—C—X			A	B
spiperone	N	-174	-55	175	177	54	-173	81°	88°
benperidol	N	-176	-56	177	179	58	-176	88	85
haloperidol	C	-178	-59	175	-177	52	-177	116	63
R1616-base	C	-177	-62	177	-179	58	-177	78	65
R1616	C	-174	-60	176	175	58	-174	82	82
penfluridol	C	-178	-62	177	179	57	-179	127	52
thiethylperazine	N	164	-54	175	-	-	-	46	-
chlorpromazine	N	-	-	-	-162	69	-164	-	68

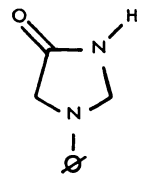
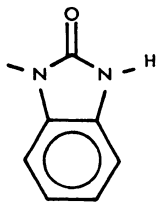
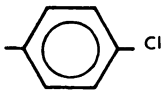
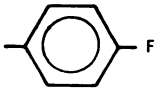
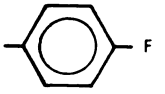
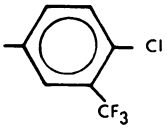
account only van der Waals energy. In both stable conformations the conjugated group is perpendicular to the mean plane of the piperidine ring. Although the lowest energy minimum agrees well with the experimental conformation, the symmetry expected for this curve is not exactly respected, because crystallographic coordinates, which slightly deviate from the ideal symmetry of models, were used. The same situation applies to Fig. 8, which explains the apparent flexibility about the C_7—C_4 bond in haloperidol and related derivatives of 4 hydroxy-4-phenylpiperidines. The conformational energy for haloperidol was calculated on the assumption that the torsion angle (C_8—C_7—O_1—H) was $-170°$.

The value of the torsion angle along the C_7—C_4 bond agrees well with the experimental values for haloperidol, penfluridol, and R1616 base, but not for R1616. Although the difference in energy is small, it is in keeping with a probable torsion angle (C_8—C_7—O_1—H) of $-60°$. Hence the minimum energy torsion angle along the C_7—C_4 bond is expected to be close to 60°, thus bringing the phenyl group perpendicular to the mean plane of the piperidine ring.

Most of the neuroleptics possess a tertiary amino group which can act as a hydrogen bond acceptor, but the highest potency and specificity are obtained when the molecule also contains a hydrogen bond donor. The parameters which characterize this spatial relationship (Fig. 9) are the distance between the acceptor (A) and the donor (B), the angle between the AB vector and the B—H bond (α), the angle between the AB vector and the axis of the lone pair of the acceptor (β), and the torsion angle along the AB vector (ϕ). Assuming that the basic nitrogen always interacts with the same donor, it is evident from the data in Table 5 that the molecules considered cannot form hydrogen bonds with the same acceptor. However, it is obvious that in all the potent butyrophenones and related compounds the intermolecular hydrogen bonds which can be formed by the molecule will be on opposite sides of the mean plane of the piperidine ring. A characteristic feature of spiperone and related compounds is the fact that they

TABLE 4

Angles between least-squares mean plane of piperidine ring and mean plane of conjugated group, and corresponding torsion angles

	conjugated group	angle between LS mean planes	Torsion angle
spiperone		85°	C(10) - C(5) - N(1) - C(21) : 45° C(5) - N(1) - C(21) - C(26) : 32°
benperidol		86°	C(11) - C(10) - N(8) - C(7) : -57° C(10) - N(8) - C(7) - C(6) : - 6°
haloperidol		117°	C(8) - C(7) - C(4) - C(5) : -87°
R1616 - base		117°	C(5)" - C(4)" - C(1)'" - C(6)'" : -89°
R1616		82°	C(5)" - C(4) - C(1)'" - C(6)'" : 56°
penfluridol		128°	C(9) - C(8) - C(4) - C(5) : -88°

preferentially form dimers in the solid state as a result of hydrogen bonding between amide groups. Dimerization can also be expected to occur to a certain extent in benperidol, but is not observed in the solid state.

Since it has been shown that spiperone and pimozide are selectively localized in certain brain regions (19), it is possible that relatively high local concentrations can be reached and that dimerization occurs *in vivo*. This should be taken into account when determining the exact nature of the active species.

The importance of the presence of a hydrogen bond donor in an appropriate orientation is shown by the observation[1] that if the NH group of spiperone is replaced by a CH_2 group the resulting molecule is approximately 100 times less potent than spiperone. In this case dimerization can no longer occur. A number of basic fragments of potent neuroleptics are shown in Fig. 10 It is obvious that they all possess both a hydrogen bond donor and an acceptor. Hydrogen-bonding groups would also explain the great potency of some secondary

[1] P. A. J. Janssen, Personal communication.

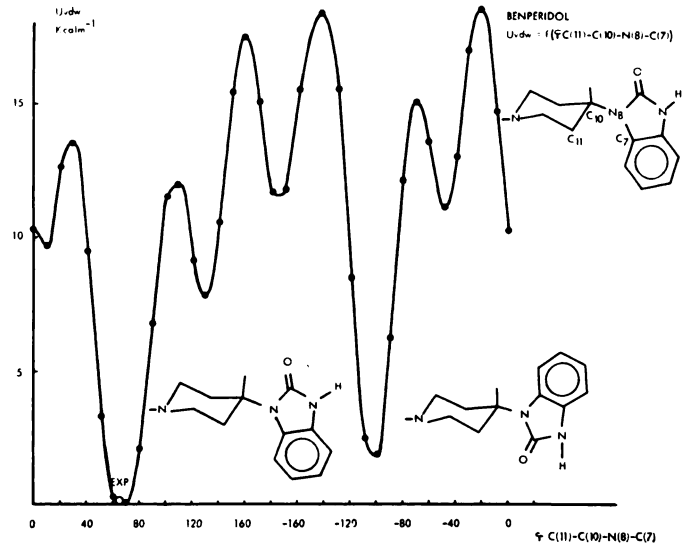


FIG. 7. *Results of conformational energy calculation for benperidol*
The lowest minimum corresponds to the conformation found in the crystal (EXP).

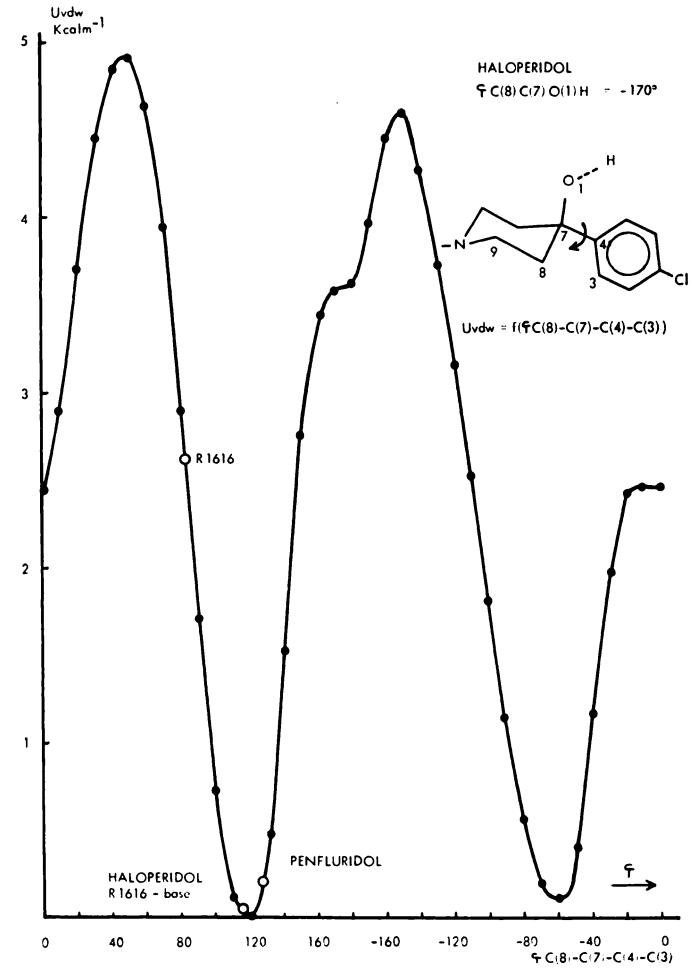


FIG. 8. *Results of conformational energy calculation for haloperidol*
Rotation occurs along the C_7—C_4 bond, assuming that the torsion angle (C_8—C_7—O_1—H) is −170°.

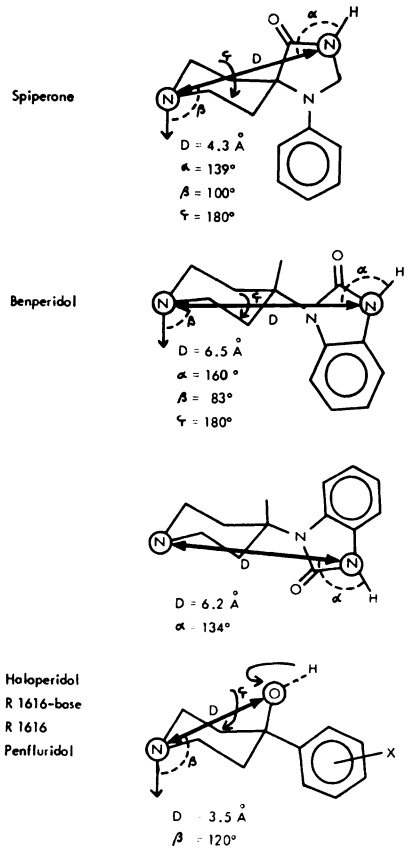


FIG. 9. *Distances (D) between hydrogen bond donor and acceptor in spiperone, benperidol (lowest energy minimum), benperidol (second minimum), and haloperidol*

amines derived from butyrophenones (Fig. 11). The amino group would act as a hydrogen bond donor while the carbonyl group could act as an acceptor.

Although it cannot be decided on the basis of structural data alone whether the phenothiazine derivatives and the other neuroleptics act on the same receptor, analysis of their three-dimensional structures reveals marked similarities which make this hypotheses more plausible. It seems more likely from the present study that the side chain of the phenothiazine derivatives corresponds to the side chain of the butyrophenones.

Once the basic requirements (1) for neuroleptic activity exist in a given molecule, maximal activity can be attained only if a

TABLE 5

Spatial relationship between hydrogen bond donor and acceptor in neuroleptics

Compound	*AB*	α	β	φ
	A			
Reserpine	3.8	113°	131°	30°
Haloperidol	3.5		120°	
Benperidol	6.5	160°	83°	180°
Spiperone	4.3	139°	100°	180°

number of potential pharmacodynamic groups are present in a well-defined relative orientation. Analysis of the structures of the most neuroleptically active butyrophenones and related compounds (i.e., those with no unrelated, non-neuroleptic properties at low dose levels) shows that three main features are undoubtedly associated with their high potency.

1. A tertiary amine or another hydrogen bond acceptor (*A*). In the crystal structures this atom is always involved in a hydrogen bond, except in the case of spiperone and spirilene, which form dimers. This is one of the basic features of all neuroleptics.

2. A planar conjugated group lying in the plane through N and C_4 of the piperidine ring and perpendicular to the mean plane of this ring. The most potent compounds are those in which this spatial orientation is most rigidly fixed (spiperone and benperidol).

3. A hydrogen bond donor (*B*) at a distance between 3.5 and 6.5 A on the side of the mean plane of the piperidine ring opposite to that of the lone pair of the basic nitrogen. The best hydrogen bond donors are NH groups which are part of an amide group.

These features are also potentially present in a large number of neuroleptics for which the three-dimensional structure is not yet known. The phenothiazine derivatives can be considered to possess the first two characteristics, while the potency of some phenothiazines and thioxanthenes can be increased by appropriate substitution with hydroxyl groups (20), as shown in Fig. 12.

These considerations show the importance of groups which can form intermolecular bonds and lay a basis for partially pre-

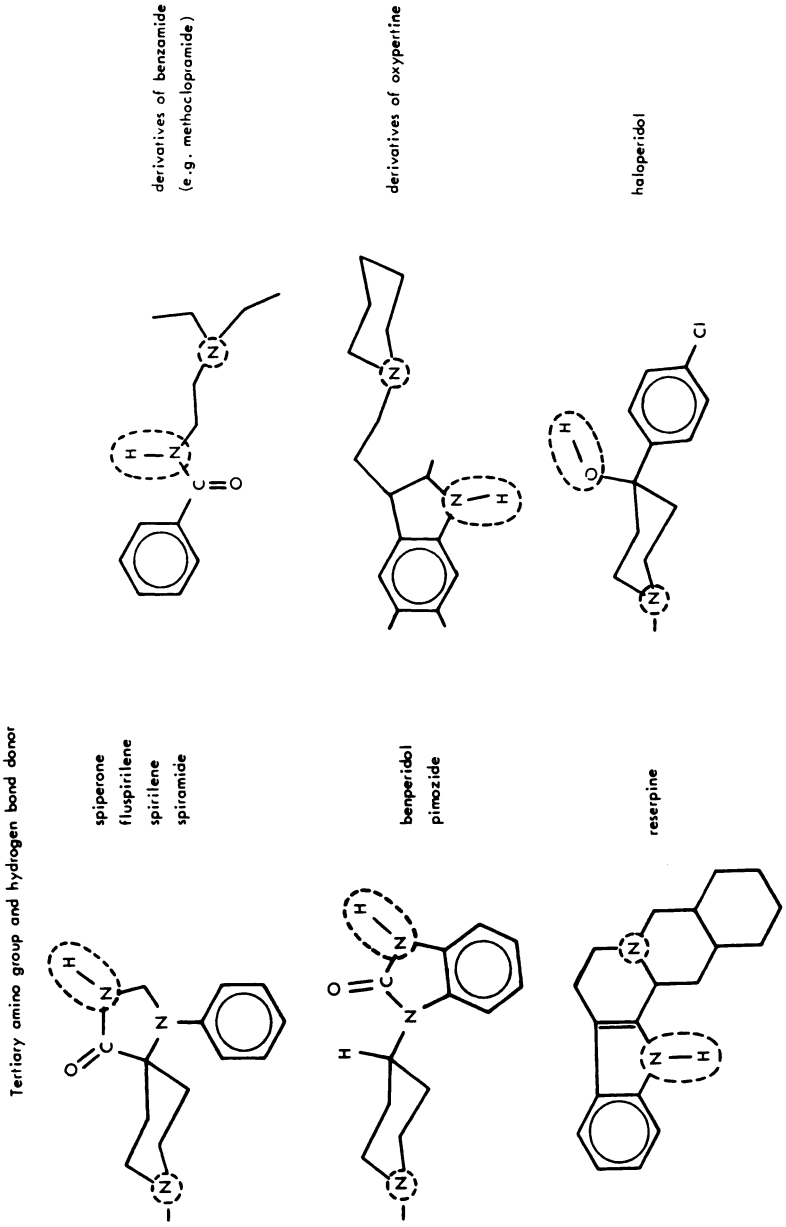


FIG. 10. *Basic fragments of typical neuroleptics, showing hydrogen bond donors and acceptors*

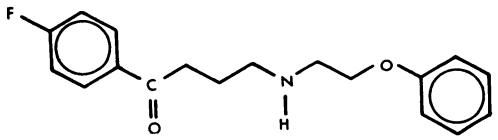


FIG. 11. *Secondary amines derived from butyrophenones*

In this case the amino group can act as a hydrogen bond donor while the carbonyl group could act as an acceptor.

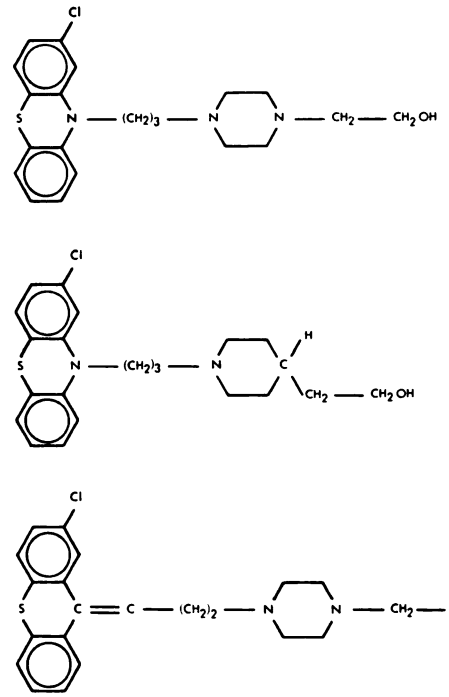


FIG. 12. *Phenothiazine and thioxanthene derivatives substituted with hydrogen bond donors*

Their potencies are 50, 100, and 17 times that of chlorpromazine, respectively (20).

dicting which molecules will have a higher probability of yielding potent derivatives. A good example is provided by R4173. It was predicted that its activity would be very low. This was verified, and the crystal structure was determined. It was observed that the second feature (No. 2 above) was absent, since the phenyl group is perpendicular to the position assumed to be necessary for high potency, and furthermore there is no hydrogen bond donor.

It would be worthwhile to make a more detailed structural study of all categories of neuroleptics in order to establish the relative importance of these structural features and to determine how general they are.

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