J. Pharm. Pharmac., 1975, 27, 553–563 *Received January* 29, 1975

Dopamine receptor blockade and the neuroleptics, a crystallographic study

ALAN S. HORN, MICHAEL L. POST* AND OLGA KENNARD* **

*MRC Neurochemical Pharmacology Unit, Department of Pharmacology, University of Cambridge, Hills Road, Cambridge U.K. and *University Chemical Laboratory, Lensfield Road, Cambridge, U.K.*

The X-ray structures of 12 drugs of the tricyclic class having varying pharmacological profiles have been examined in detail in an attempt to rationalize the known structure-activity relations of neuroleptic drugs with respect to their ability to block dopamine receptors in the brain. Further evidence is presented in support of the theory that the neuroleptics are able to block dopamine receptors because of a conformational complementarity between certain portions of these drugs and dopamine.

There is a large body of evidence that supports the concept that the neuroleptics probably bring about their clinical effects by a blockade of dopamine receptors in the brain, (Carlsson & Lindqvist, 1963; Nyback & Sedvall, 1968; Horn & Snyder, 1971; Matthysse, 1973; Bunney, Walters & others, 1973; Snyder, 1974). Through the use of the dopamine sensitive adenylate cyclase enzyme system in the rat corpus striatum and in other dopamine rich brain areas it has recently been possible to examine the effects of various dopaminergic agonists and antagonists on a system that is a useful *in vitro* model of the dopamine receptor (Kebabian, Petzold & Greengard, 1972; Horn, Cuello & Miller, 1974; Miller, Horn & others, 1974; Clement-Cormier, Kebabian & others, 1974; Miller, Horn & Iversen, 1974; Karobath & Leitich, 1974). The structure-activity relations for various classes of neuroleptics resulting from studies with this assay system agree well with the findings from a variety of animal tests (Moller-Nielsen, Pedersen & others, 1973; Miller & others, 1974). A molecular mechanism that attempted to explain how chlorpromazine is able to block dopamine receptors has drawn attention to a possible complementarity between certain portions of the X-ray structures of the chlorpromazine molecule and dopamine (Horn & Snyder, 1971). Dopamine is a flexible molecule and its preferred conformation at its receptor site has been the object of recent speculation (Horn & Snyder, 1971; Miller & others, 1974; Sheppard & Burghardt, 1974). The most important conformations to consider are the *trans* form (Fig. 1a) and the two *gauche* conformers (Fig. 1b, c). It is known from X-ray analysis that the *trans* conformation of dopamine is the preferred form in the solid state (Bergin & Carlstrom, 1968) and similar results have been obtained in solution by nmr analysis and *in vacuo* by theoretical calculations (Bustard & Egan, 1971). Apomorphine (Fig. 2) is a well known dopamine agonist that is thought to have a direct action on the dopamine receptor (Andén, Rubenson & others, 1967; Ernst, 1967). It may be considered as an analogue of the fully extended *trans* form of dopamine and as it is a rigid molecule

** External Staff, Medical Research Council.

there is no doubt about its conformation at the receptor, recently its X-ray structure has been reported (Giesecke, 1973). 2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN) (Fig. 3) is another rigid analogue of dopamine that resembles very closely the *trans* form of the latter molecule. This compound has been shown to produce long lasting dopamine-like effects in rats after intraventricular injections (Woodruff, Elkhawad & Pinder, 1974) to mimic dopamine's inhibition of the firing of cells in the caudate nucleus upon iontophoretic application (Woodruff, Elkhawad & others, 1974) and to be as potent as dopamine in the stimulation of the dopamine

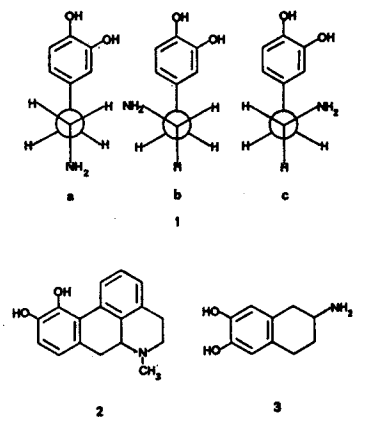

FIG. 1. Newman projections of the *trans* conformation of dopamine (a) and the two *gauche* conformations (b and c).

FIG. 2. Apomorphine.

FIG. 3. 2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN).

sensitive adenylate cyclase system (Miller & others, 1974). Behavioural studies with other dopamine agonists have also supported the suggestion that it is the *trans* form of the amine that is the preferred conformation at the receptor (Costall, Naylor & Pinder, 1974). From the published coordinates for dopamine and apomorphine we calculate the distance of the nitrogen atom from the centre of the catechol ring to be 5·14 Å in dopamine and 5·08 Å and 5·12 Å in apomorphine, there being 2 molecules in the asymmetric unit of the latter compound. It is therefore suggested that the binding site for dopamine's amine group at its receptor is about 5·1 Å distant from the centre of the aromatic ring. In an attempt to obtain information about structural and conformational requirements for effective dopamine antagonism we have examined the X-ray structures of several compounds of the tricyclic class having varying pharmacological profiles. Values for the distances from each aromatic ring to the nitrogen atom(s) in the side chain have been calculated in all cases from published and unpublished X-ray results (Table 1).

A crystallographic and theoretical study of the conformations of the other main class of neuroleptics, the butyrophenones, has been reported by Koch (1974). It is known from a variety of animal tests and clinical data (Zirkle & Kaiser, 1970; Klein & Davis, 1969) that potent neuroleptics of the tricyclic class (the phenothiazines and thioxanthenes) usually have a non-planar tricyclic nucleus that is bridged by a hetero atom and which has a substituent at the 2 position; the amine containing side chain is normally separated from the tricyclic nucleus by a chain of 3-carbon atoms.

Table 1. *Distances of the side chain nitrogen atom(s) from the geometric centres of the benzene rings A and B of the tricyclic system.*

	Distance in Å		
α-Flupenthixol (base)	A–N_1 = 5·82		A–N_2 = 7·75
	B–N_1 = 7·46		B–N_2 = 10·26
β-Flupenthixol (base)	A–N_1 = 6·09		A–N_2 = 8·24
	B–N_1 = 6·45		B–N_2 = 9·30
α-Chlorprothixene (base)	A–N = 6·24		
	B–N = 7·43		
Chlorpromazine (base)	A–N_1 = 5·12		
	B–N_1 = 6·81		
Chlorpromazine (HCl)	A–N_1 = 6·70		
	B–N_1 = 6·18		
Triflupromazine (HCl)	A–N_1 = 6·38	Conformation A	
	B–N_1 = 6·42		
	A–N_1 = 6·28	Conformation B	
	B–N_1 = 7·28		
2-Methoxypromazine (maleate)	A–N_1 = 6·35		
	B–N_1 = 6·64		
Thiethylperazine (base)	A–N_1 = 5·93		A–N_2 = 7·37
	B–N_1 = 6·42		B–N_2 = 9·09
Promethazine (HCl)	A–N_1 = 6·04		
	B–N_1 = 5·36		
Diethazine (HCl)	A–N_1 = 5·26		
	B–N_1 = 6·16		
Isothazine (HCl)	A–N_1 = 6·17		
	B–N_1 = 5·20		
Imipramine (HCl)	A–N_1 = 6·24	Conformation A	
	B–N_1 = 7·21		
	A–N_1 = 6·53	Conformation B	
	B–N_1 = 6·07		

The distances of the side chain nitrogen atom(s) from the geometric centres of the benzene rings were computed in all cases from reported, as well as unpublished, coordinates for the crystal structures.

Studies by Gordon, Cook & others (1963) have indicated that, in general, (with some exceptions) electron withdrawing substituents at the 2-position are usually found in the most potent compounds.

As with dopamine, chlorpromazine has a flexible side chain that can probably exist in several conformations which have only small differences in potential energy. One can therefore try to obtain information about the receptor-preferred overall conformation and critical interatomic distances for a neuroleptic of this class by examining the structures of more rigid analogues such as the thioxanthenes and dibenzo-diazepines and dibenzo-oxazepines. The thioxanthenes are of interest as they display stereoselectivity in blocking dopamine-related effects, the *cis* isomer is active whilst the *trans* isomer is much weaker or almost inactive. This is found both in behavioural tests (Moller-Nielsen & others, 1973); and in *in vitro* studies using the dopamine-sensitive adenylate cyclase system (Miller & others, 1974). With the dibenzo-diazepines and dibenzo-oxazepines (Fig. 4a–c) there is a difference in neuroleptic potency depending on the position of the chlorine atom and the nature of the bridging hetero atom (N or O) (Burki, Ruch & others, 1974). These compounds are of particular interest as they are more or less rigid, apart from rotation about the exocyclic C-N bond and small conformational changes in the piperazine ring and the tricyclic nucleus. The distances of the nitrogen atoms of the piperazine ring from the centres of the benzene rings, however, are more or less constant and the distances found in the crystal and in atomic models will probably correspond very closely to

those occuring at the receptor. At physiological pH the nitrogen atom of the amino side chain of the neuroleptics will be positively charged and this introduces an obvious difficulty in relating the X-ray structures of the free bases to receptor-preferred conformations as protonation may effect the conformation of the side chain. As the dibenzo-diazepines and dibenzo-oxazepines are more or less rigid molecules, however, the conformation of the charged species will probably not differ significantly from that of the free base.

Recently, the dibenzo-diazepine HF-2046 (Fig. 4a) has been shown to be much more potent in inhibiting conditioned-avoidance response, producing catalepsy, acting as an apomorphine antagonist and increasing the turnover of dopamine in the corpus striatum, than its positional isomer clozapine (Fig. 4b) (Burki & others, 1974). The antipsychotic dibenzo-oxazepine, loxapine (Muller & Heimann and Kielholz & others*, unpublished observations) (Fig. 4c) was more potent than either of the above compounds. In *in vitro* (dopamine adenylate cyclase) studies, HF-2046 is a more active antagonist ($Ki = 1{\cdot}8 \times 10^{-8}$ M) than either loxapine ($Ki = 4{\cdot}5 \times 10^{-8}$ M) or clozapine ($Ki = 1{\cdot}7 \times 10^{-7}$ M) (Iversen, Horn & Miller, 1974). The X-ray structures of all three of the above compounds have been briefly reported but full crystallographic details have not yet been published (Petcher & Weber, 1973).

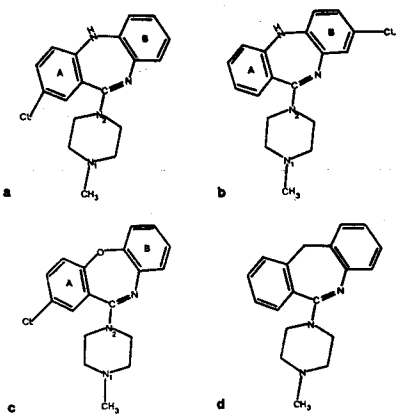

FIG. 4. Structural formulae for (a) HF-2046, (b) clozapine, (c) loxapine and (d) perlapine.

The blockade of dopamine receptors by the neuroleptics is thought to be competitive (van Rossum, 1967; York, 1972; Clement-Cormier & others, 1974) and for simplicity this will be taken to mean occupation of the same site as the natural agonist, although other interpretations are possible. If it is assumed, therefore, as previously suggested (Horn & Snyder, 1971), that the antagonism is a result of a certain complementarity between a portion of the antagonist and dopamine, then it can be seen that, in the present case comparing the figure of 5·14 Å for dopamine with the two distances A–N_1 and B–N_1 in HF-2046 using standard molecular models, the A ring of HF-2046 could overlay the portion of the receptor normally occupied by dopamine's aromatic ring, and the nitrogen atom N_1 could occupy the binding site of dopamine's amine nitrogen, the difference in the two distances A–N_1—dopamine being less than 1 Å whilst the other distance B–N_1—dopamine results in a difference slightly greater than 2·5 Å. That there is a small difference in the A–N_1—dopamine distance rather than an exact "lock and key" fit would tend to indicate

* Unpublished material made available by Lederle Laboratories, Pearl River, New York.

either that this difference was still compatible with effective binding or that the antagonist brings about a conformational change on binding to the receptor.

Although little is known about what constitutes effective and ineffective interatomic distances in agonists and antagonists it seems more reasonable to consider that the closer the resemblance the more effective will be the antagonism. Clozapine differs from HF-2046 only in the position of the chlorine atom, the distances A–N_1 and B–N_1 are thus virtually the same as those in HF-2046 (Petcher & Weber, 1973). Thus the greater neuroleptic potency of HF-2046 in comparison with clozapine should be explicable solely in terms of the position of the chorine atom. It is known that the position of this substituent is critical; if it is substituted in positions 3, 4, 6, 7 or 8 no catalepsy is found (Burki & others, 1974). It has also been shown that replacement of the bridging hetero atom (N or O) by carbon and removal of the halogen atom in the 2 position yields the compound perlapine (Fig. 4d) which has only weak neuroleptic activity and is not active clinically as an antipsychotic (Stille, Sayers & others, 1973). It is also only a weak inhibitor of the dopamine-sensitive adenylate cyclase system, having a Ki of $4{\cdot}80 \times 10^{-7}$ M (Iversen & others, 1974).

A similar effect by halogens is also found in the phenothiazines and thioxanthenes (Zirkle & Kaiser, 1970; Petersen & Moller-Nielsen, 1964). Because of this positional specificity it is unlikely that this is a lipid solubility effect by halogen, in fact this has been ruled out for the phenothiazines (Green, 1967). It is also unlikely that the chlorine atom is directly affecting the conformation of the piperazine ring.

There are several other possibilities, namely that it is having some effect on the receptor i.e. increasing the binding or bringing about a favourable conformational change, or it may interact with the hetero atom through a resonance effect (Gordon & others, 1963), or its presence alone may affect the conformation of the tricyclic nucleus as has been suggested for some other similar systems (Aizenshtat, Klein & others, 1972). With the phenothiazines, theoretical studies (Coubeils & Pullman, 1972) have indicated that the conformation of the side chain is dependent on the folding of the tricyclic system along the S–N axis, thus the 2-substituent might have an indirect effect on the conformation of the side chain. It seems most likely, however, that its potency enhancing action is *via* a direct receptor effect as even if it is affecting the dihedral angle of the ring system there appears to be no direct correlation between this angle and neuroleptic potency (Table 2). A tricyclic nucleus that is not planar, however, is apparently a requirement for neuroleptic activity as derivatives of the planar aromatic ring systems, acridine and anthracene, are very weak or inactive; this is even true of compounds which have a 3-carbon side chain amine function together with a $-CF_3$ or –Cl group at the 2 position (Zirkle & Kaiser, 1970).

As a result of theoretical calculations and model building it has been suggested (Feinberg & Snyder, 1975) that in certain neuroleptics the 2-substituent is exerting a direct Van der Waals force of attraction on the amino group of the side chain. We feel this is unlikely, however, as in the crystal structures, where it is likely that the conditions for such an effect would be very favourable, the distances involved are too great for this to occur (Table 3). Even if it did occur it is unlikely that such a weak force of attraction between these two functions would be sufficient to determine the overall conformation of the molecule especially in aqueous solutions. The above proposals also do not account for the potency-enhancing effect of the halogen atom in the dibenzo-diazepines and dibenzo-oxazepines; as the side chain amine is part of a fairly rigid ring system its conformation cannot be influenced by the halogen

Table 2. *Dihedral angle and inhibition of dopamine sensitive adenylate cyclase by various tricylic drugs.*

	Ki (M) dopamine adenylate cyclase	Dihedral angle
α-Flupenthixol	$1{\cdot}0 \times 10^{-9}$	151° (base)
α-Chlorprothixene	$3{\cdot}7 \times 10^{-8}$	141° (base)
Triflupromazine	$4{\cdot}4 \times 10^{-8}$	134°, 141° (HCl)
Chlorpromazine	$4{\cdot}8 \times 10^{-8}$	139° (base)
Thiothixene	$1{\cdot}7 \times 10^{-7}$ (cis-trans?)	141° (base, cis)*
Thiethylperazine	$\sim 7 \times 10^{-7}$	139° (base)
Imipramine	3×10^{-6}	130°, 123° (HCl)
Isothazine, ethoproperazine	$4{\cdot}1 \times 10^{-6}$	137° (HCl)
Promethazine	$>5 \times 10^{-6}$	140° (HBr) 141° (HCl)
β-Flupenthixol	$>5 \times 10^{-6}$	143° (base)
Diethazine	$1{\cdot}1 \times 10^{-5}$	138° (HCl)
2-Methoxypromazine	—	157° (maleate)

* Schaefer (1967)

The Ki is the inhibition constant which was calculated from the relationship Ki = IC50/(1+S/Km) where the IC50 is the concentration of drug required to produce a 50% inhibition of the dopamine-stimulated increase in adenylate cyclase activity in homogenates of the rat brain corpus striatum, S is the concentration of dopamine added and the Km is concentration required for half-maximal activation of the enzyme. The dihedral angle is the angle between the planes of the two outer aromatic rings of the tricyclic nucleus. Both sets of values are quoted from references contained in the text.

substituent. Early theoretical studies on the phenothiazines had suggested a possible link between the ring systems, electron donating ability and pharmacological effects (Karreman, Isenberg & Szent-Gyorgyi, 1959; Bodea & Silberg, 1968; Malrieu, 1967). It has been shown, however, that this is unlikely and that the phenothiazines do not display exceptional electron donor ability (Bloor, Gilson & others, 1970). As will be shown by a consideration of other neuroleptics the distance of the other N atom of the piperazine ring from either benzene ring in HF-2046 and clozapine is probably not compatible with effective antagonism. In loxapine (Fig. 4c) the distances A–N_1 and B–N_1, are closely similar to those in HF-2046 and thus again suitable for a blockade of the dopamine receptor.

Table 3. *Interatomic distances of the 2-substituent from the side chain nitrogen atom(s).*

	Atoms	Å
Chlorpromazine (base)	Cl . . . N_1	4·81
,, (HCl)	Cl . . . N_1	8·23
α-Chlorprothixene (base)	Cl . . . N	6·64
Triflupromazine (HCl)	F_3C . . . N_1 (A)	6·78
	F_3C . . . N_1 (B)	6·54
Thiethylperazine (base)	S . . . N_1	6·60
	S . . . N_2	7·04
α-Flupenthixol (base)	F_3C . . . N_1	5·46
	F_3C . . . N_2	6·41
β-Flupenthixol (base)	F_3C . . . N_1	7·00
	F_3C . . . N_2	8·34

The distances of the 2-substituent from the nitrogen atom(s) in the side chain were computed in all cases from reported, as well as unpublished, coordinates for the crystal structures.

The thioxanthenes are less rigid than the dibenzo-diazepines but they have less conformational freedom than the phenothiazines. α-Flupenthixol (Fig. 5a) is known to be a very potent neuroleptic (Moller-Nielsen & others, 1973) and is the most active antagonist yet tested on the dopamine-sensitive adenylate cyclase system having a Ki = $1{\cdot}0 \times 10^{-9}$ M whereas the β-isomer is very weak in blocking dopamine related effects in animals and has a Ki in the above *in vitro* system of 5×10^{-6} M (Miller & others, 1974). A mixture of the α and β forms is in clinical use as an antipsychotic agent (Klein & Davis, 1969; Gottfries, 1971). It is of interest, therefore, that in the free base of α-flupenthixol the distance A–N_1 is 5·82 Å and B–N_1 is 7·46 Å (Table 1) which corresponds closely to the distances found in models of HF-2046 and loxapine. The distances A–N_2 and B–N_2 are 7·75 and 10·26 Å, respectively.

The crystal structure of α-chlorprothixene (free base) (Fig. 5b) has recently been reported (Post, Kennard & Horn, 1974a), in the adenylate cyclase assay it has a Ki = $3{\cdot}7 \times 10^{-8}$ M ,whilst the weaker β-isomer has a value of $9{\cdot}5 \times 10^{-7}$ M (Miller & others, 1974). As α-chlorprothixene has only one nitrogen atom there is no doubt about the relevant distance. The values of A–N=6·24 Å and B–N=7·43 Å (Table 1) are within the range of the previous compounds. In chlorpromazine (Fig. 5c) the values for the distances A–N_1 and B–N_1 in the free base (McDowell, 1969) are 5·12 and 6·81 Å whilst in the hydrochloride (Dorignac-Calas & Marsau, 1972) these values change to 6·70 and 6·18 Å respectively (Table 1). The conformation of the hydrochloride, of course, will be influenced by the requirement of H-bonding to the chloride ion by the charged amino group.

In the two thioxanthenes examined so far, α-flupenthixol and α-chlorprothixene, the distance thought to be relevant for effective blockade of the dopamine receptor has a mean value of 6·03 Å and the other distance is 7·45 Å. It would thus appear that a conformationally asymmetric molecule is required for maximum activity with a difference in distance of the nitrogen atom from the centres of the two aromatic rings of about 1·5 Å. A difference in these distances of 1·7 Å is also found for the

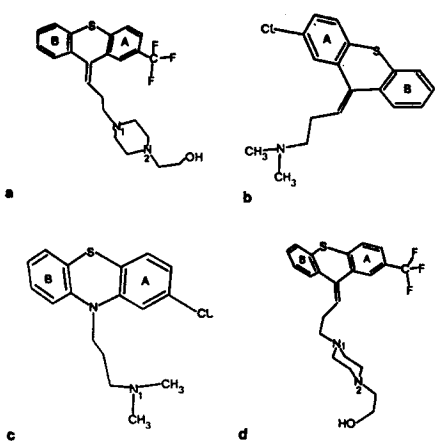

FIG. 5. The conformations of the free bases of α-flupenthixol (a) (Post, Horn & Kennard, unpublished), α-chlorprothixene (b), chlorpromazine (c) and β-flupenthixol (d) (Post, Horn & Kennard, unpublished) viewed in projection in the crystal structure. The drawings were produced from the atomic coordinates using program PLUTOX (Motherwell, unpublished).

free base of chlorpromazine whilst in the hydrochloride it falls to 0·6 Å. In the free base of β-flupenthixol (Fig. 5d) the distances A–N_1 (6·09 Å) and –C(–CF_3)–N_1 (7·00 Å) are greater than in the α-isomer where A–N_1 = 5·82 Å and –C(–CF_3)–N_1 = 5·46 Å (Table 3) the dihedral angles also differ by 8° (Table 2). If this solid-state conformation for the β-isomer is similar to that occurring at the receptor it could be argued that the above differences, in total, could result in the molecule not having an optimal "fit" for the receptor. There is also a small difference (0·36 Å) between the distance A–N_1 (6·09 Å) and B–N_1 (6·45 Å) which means that the β-isomer, at least in the solid state, is less "asymmetric" than the α-isomer. The clinically efficacious antipsychotic phenothiazine, trifluprom azine HCl (Klein & Davis, 1969) exhibits two conformations (A and B) in the solid state (Phelps & Cordes, 1974) conformation B is shown in Fig. 6a. In this conformation A–N_1 = 6·28 Å and B–N_1 = 7·28 Å, it is of interest that the former distance is very similar to the analogous one found in models of loxapine, it is also noteworthy that these two drugs have a very similar antagonistic activity on the dopamine sensitive adenylate cyclase system. In the other conformation A, A–N_1 = 6·38 Å and B–N_1 = 6·42 Å.

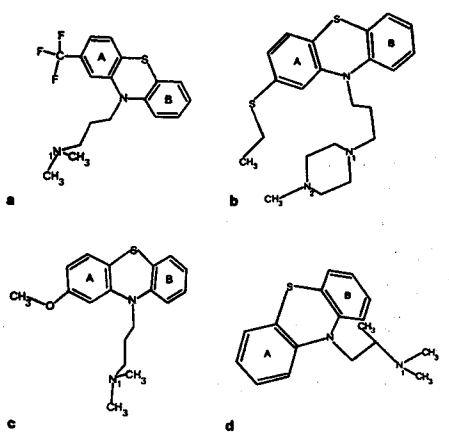

FIG. 6. The conformations of trifluprom azine HCl (a), thiethylperazine free base (b), 2-methoxypromazine maleate (c) and promethazine HCl (d) viewed in projection in the crystal structure. The drawings were produced from the atomic coordinates using program PLUTOX (Motherwell, unpublished).

Thiethylperazine (McDowell, 1970) (free base) (Fig. 6b) has a A–N_1 distance of 5·93 Å (Table 1) and a –S–Et group as the 2-substituent, it is, however, said to be a phenothiazine with only weak antipsychotic activity (Matthysse, 1973; Karobath & Leitich, 1974) and it is not a potent inhibitor of the dopamine sensitive adenylate cyclase system (Table 2) (Karobath & Leitich, 1974). This is probably explicable in terms of the 2-substituent (–S–Et) (cf. Gordon & others (1963) for a discussion of the effect of the –S–CH_3 group) as two other analogues with a –CF_3 (trifluoperazine) or –Cl substituent (prochlorperazine) are potent both clinically and in the above *in vitro* system (Klein & Davis, 1969; Miller & others, 1974).

2-Methoxypromazine (Fig. 6c) is reported to be less active clinically than chlorpromazine (Gosline, Walters & Saunders, 1959) and the maleate salt (Fig. 6c) has A–N_1 = 6·35 Å and B–N_1 = 6·64 Å with a dihedral angle of 157° (Marsau & Gauthier, 1973). It is again possible that it is less efficacious due to the nature of the 2-substituent (Gordon & others, 1963).

Promethazine HBr (Marsau & Busetta, 1973) and HCl (Fig. 6d) (Escobar, Marsau & Clastre, 1968) diethazine HCl (Marsau, 1971) (Fig. 7a) and isothazine HCl (ethoproperazine) (Marsau & Calas, 1971) (Fig. 7b) are all compounds with a two carbon side chain and no 2-substituent and all are known to be weak or ineffective as antipsychotics and neuroleptics (Klein & Davis, 1969; Zirkle & Kaiser, 1970). All three compounds are also known to be weak inhibitors of the dopamine-sensitive adenylate cyclase system (Horn & others, 1974; Miller & others, 1974; Clement-Cormier & others, 1974; Karobath & Leitich, 1974). In promethazine HCl A–N_1 = 6·04 Å and B–N_1 = 5·36 Å, in diethazine A–N_1 = 5·26 Å and B–N_1 = 6·16 Å and in isothazine A–N_1 = 6·17 Å and B–N_1 = 5·20 Å (Table 1). The average difference between the two distances is about 0·8 Å. It has been shown that introduction of a 2-substituent into these compounds increases activity (Zirkle & Kaiser, 1970).

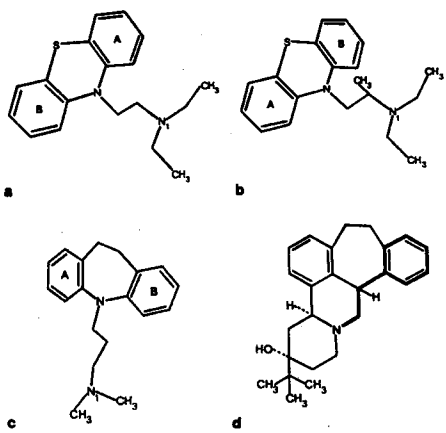

FIG. 7. The conformations of diethazine HCl (a), isothazine HCl (b) and imipramine HCl (c) viewed in projection in the crystal structure. The drawings were produced from the atomic coordinates using program PLUTOX (Motherwell, unpublished). The structural formula of (+)-butaclamol (d) is shown with the phenylethylamine moiety in heavy outline.

The tricyclic antidepressant imipramine (Fig. 7c) is well known to be ineffective as a neuroleptic (Klein & Davis, 1969) although it bears a structural resemblance to chlorpromazine. In the crystal structure of the hydrochloride (Post, Kennard & Horn, 1974b, 1975) there are two conformations (Fig. 7c shows the B form) and the distances A–N_1 are 6·24 Å, 6·53 Å and B–N_1 are 7·21 Å, 6·07 Å, and the dihedral angles are 130° and 123° (Tables 1 and 2). It is probable that its lack of *in vivo* and *in vitro* activity (Klein & Davis, 1969; Karobath & Leitich, 1974; Clement-Cormier & others, 1974) is due to the absence of a 3-substituent (the 3 position in the imipramine ring system is equivalent to the 2 position in the phenothiazines) and the presence of a dimethylene bridge instead of a sulphur atom. Recent nmr studies on imipramine have shown that the tricyclic ring system is not fixed in one conformation but that the central seven membered ring is inverting at a very rapid rate on the nmr time scale (Abraham, Kricka & Ledwith, 1974). It would be of interest to know if this is also true of the neuroleptics (Aroney, Hoskins & Le Fevre, 1968; Aizenshtat & others, 1972; Ternay & Evans, 1974).

The topic of structure-activity studies of neuroleptics is at once made more interest-

ing yet more complex by the reported neuroleptic effects of butaclamol (Fig. 7d) a neuroleptic displaying stereoselective activity due to optical isomerism. In both *in vivo* and *in vitro* (dopamine adenylate cyclase) studies the (+)-isomer (Fig. 7d) of one racemate is much more active than the (−)-isomer (Bruderlein, Humber & Voith, 1975; Miller, Horn & Iversen, 1975; Lippman, Pugsley & Merker, 1975). The Ki value for (+)-butaclamol in the above assay is $8{\cdot}8 \times 10^{-9}$ M. In its structure butaclamol resembles more closely the tricyclic antidepressants than the previously discussed neuroleptics. It lacks a hetero atom bridge and a 2-substituent, it would be of interest, however, to know if the compound would be more potent if it had these atoms. It can be readily seen to contain the phenylethylamine skeleton of dopamine in its structure (in heavy outline in Fig. 7d) which could account for its antagonist activity, as in other potent neuroleptics is also contains a hydroxy "tail".

In conclusion it is apparent, therefore, from the drugs studied that as with any other drug-receptor interaction the overall effect is due to a combination of a favourable conformation and the correct molecular structure. Although these factors are obviously related and interdependent it is clear from the foregoing examples that there is a certain amount of separation in the contribution of these two effects. A more or less correct interatomic distance of about 6 Å of the amine nitrogen atom from the centre of one aromatic ring is *not* a sufficient requirement for activity as this is seen in both active and inactive compounds and in order for a compound to be active it must also possess a non-planar ring system as well as certain other groups that may have direct receptor effects. The increased potency that is seen on varying the nature of the 2-substituent and the type of amino side chain is possibly due to the receptor effects of these groups rather than any strictly conformational actions on the drug itself.

Acknowledgements

The authors would like to thank the M.R.C. for financial support and the S.R.C. for the provision of the diffractometer.

REFERENCES

ABRAHAM, R. J., KRICKA, L. J. & LEDWITH, A. (1974). *J. chem. Soc.*, Perkin II, 1648–1654.

AIZENSHTAT, Z., KLEIN, E., WEILER-FEILCHENFELD, H. & BERGMANN, E. D. (1972). *Israel J. Chem.*, **10**, 753–763.

ANDÉN, N. E., RUBENSON, A., FUXE, K. & HOKFELT, T. (1967). *J. Pharm. Pharmac.*, **19**, 627–629.

ARONEY, M. J., HOSKINS, G. M. & LEFEVRE, R. J. W. (1968). *J. chem. Soc.* (*B*), 1206–1208.

BERGIN, R. & CARLSTROM, D. (1968). *Acta Cryst.*, *B***24**, 1506–1510.

BLOOR, J. E., GILSON, B. R., HAAS, R. J. & ZIRKLE, C. L. (1970). *J. medl Chem.*, **13**, 922–925.

BODEA, C. & SILBERG, I. (1968). *Advan. Heterocyl. Chem.*, **9**, 321–460.

BRUDERLEIN, F. T., HUMBER, L. G. & VOITH, K. (1975). *J. medl Chem.*, **18**, 185–188.

BUNNEY, B., WALTERS, J., ROTH, R. & AGHAJANIAN, G. (1973). *J. Pharmac. exp. Ther.*, **185**, 560–571.

BURKI, H. R., RUCH, W., ASPER, H., BAGGIOLINI, M. & STILLE, G. (1974). *Eur. J. Pharmac.*, **27**, 180–190.

BUSTARD, T. M. & EGAN, R. S. (1971). *Tetrahedron*, **27**, 4457–4469.

CARLSSON, A. & LINDQVIST, M. (1963). *Acta pharmac. tox.*, **20**, 140–144.

CLEMENT-CORMIER, Y. C., KEBABIAN, J. W., PETZOLD, G. L. & GREENGARD, P. (1974). *Proc. Nat. Acad. Sci. U.S.A.*, **71**, 1113–1117.

COSTALL, B., NAYLOR. R. J. & PINDER, R. M. (1974). *J. Pharm. Pharmac.*, **26**, 753–762.

COUBEILS, J. L. & PULLMAN, B. (1972). *Theoret. Chim. Acta* (*Berl.*), **24**, 35–41.

DORIGNA C-CALAS, M. R. & MARSAU, P. (1972). *Comp. Rend. Acad. Sci. Paris*, **274**, 1806–1809.

ERNST, A. M. (1967). *Psychopharmacologia*, **10**, 316–323.

ESCOBAR, C., MARSAU, P. & CLASTRE, J. (1968). *Compt. Rend. Acad. Sci. Paris, Ser. C*, **267**, 1399–1401.

FEINBERG, A. & SNYDER, S. H. (1975). *Proc. Nat. Acad. U.S.A.*, in the press.

GIESECKE, J. (1973). *Acta. Cryst.*, *B***29**, 1785–1791.

GORDON, M., COOK, L., TEDESCHI, D. H. & TEDESCHI, R. E. (1963). *Arzneimittel-Forsch.*, **13**, 318–320.

GOSLINE, E., WALTERS, C. J. & SAUNDERS, J. C. (1959). *Am. J. Psychiat.*, **115**, 939–940.

GOTTFRIES, C. G. (1971). *Br. J. Psychiat.*, **119**, 547–548.

GREEN, A. L. (1967). *J. Pharm. Pharmac.*, **19**, 207–208.

HORN, A. S. & SNYDER, S. H. (1971). *Proc. Nat. Acad. Sci. U.S.A.*, **68**, 2325–2328.

HORN, A. S., CUELLO, A. C. & MILLER, R. J. (1974). *J. Neurochem.*, **22**, 265–270.

IVERSEN, L. L., HORN, A. S. & MILLER, R. J. (1974). In *Pre and postsynaptic receptors.* American College of Neuropsychopharmacology, 1974. pp. 207–243. Editors: Usdin, E. & Bunney, W. New York: Marcel Dekker.

KARREMAN, G., ISENBERG, I. & SZENT-GYORGYI, A. (1959). *Science*, **130**, 1191–1192.

KAROBATH, M. & LEITICH, H. (1974). *Proc. Nat. Acad. Sci. U.S.A.*, **71**, 2915–2918.

KEBABIAN, J. W., PETZOLD, G. L. & GREENGARD, P. (1972). *Ibid.*, **69**, 2145–2149.

KLEIN, D. F. & DAVIS, J. M. (1969). *Diagnosis and Drug Treatment of Psychiatric Disorders.* Baltimore: Williams and Wilkins.

KOCH, M. H. J. (1974). *Mol. Pharmac.*, **10**, 425–437.

LIPPMANN, W., PUGSLEY, T. & MERKER, J. (1975). *Life Sci.*, **16**, 213–224.

MALRIEU, J. P. (1967). In *Molecular Basis of some Aspects of Mental Activity.* Proc. NATO Advan. Study Inst. (1965), pp. 83–93. Editor: Walaas, O. London: Academic Press).

MARSAU, P. (1971). *Acta Cryst.*, *B***27**, 42–51.

MARSAU, P. & BUSETTA, B. (1973). *Ibid.*, **B29**, 986–991.

MARSAU, P. & CALAS, M. R. (1971). *Ibid.*, **B27**, 2058–2062.

MARSAU, P. & GAUTHIER, J. (1973). *Ibid.*, **B29**, 992–998.

MATTHYSSE, S. (1973). *Fedn Proc. Fedn Am. Socs exp. Biol.*, **32**, 200–205.

MCDOWELL, J. J. H. (1969). *Acta Cryst.*, **B25**, 2175–2181.

MCDOWELL, J. J. H. (1970). *Ibid.*, **B26**, 954–964.

MILLER, R. J., HORN, A. S. & IVERSEN, L. L. (1974). *Mol. Pharmac.*, **10**, 759–766.

MILLER, R. J., HORN, A. S. & IVERSEN, L. L. (1975). *J. Pharm. Pharmac.*, **27**, 212–213.

MILLER, R. J., HORN, A. S., IVERSEN, L. L. & PINDER, R. M. (1974). *Nature*, **250**, 238–241.

MOLLER-NIELSEN, I., PEDERSEN, V., NYMARK, M., FRANCK, K. F., BOECK, V., FJALLAN, B. & CHRISTENSEN, A. V. (1973). *Acta pharmac. tox.*, **33**, 353–362.

NYBACK, H. & SEDVALL, G. (1968). *J. Pharmac. exp. Ther.*, **162**, 294–301.

PETCHER, T. J. & WEBER, H. P. (1973). Abstracts of International Union of Crystallography Meeting, Stockholm, July 1973, p. 38.

PETERSEN, P. V. & MOLLER-NIELSEN, I. (1964). *Psychopharmacological Agents*, Vol. I, pp. 301–304. Editor: Gordon, M. New York: Academic Press.

PHELPS, D. W. & CORDES, A. W. (1974). *Acta Cryst.*, **B30**, 2812–2816.

POST, M. L., KENNARD, O. & HORN, A. S. (1974a). *Ibid.*, **B30**, 1644–1646.

POST, M. L., KENNARD, O. & HORN, A. S. (1974b). *Nature*, **252**, 493–495.

POST, M. L., KENNARD, O. & HORN, A. S. (1975). *Acta Cryst.*, **B31**, 1008–1013.

SHEPPARD, H. & BURGHARDT, C. R. (1974). *Mol. Pharmac.*, **10**, 721–726.

SNYDER, S. H. (1974). In *The neurosciences Third study program*, pp. 721–732. Editors: Schmitt, F. O. & Worden, F. G. Cambridge Massachusetts: The MIT Press.

STILLE, G., SAYERS, A., LAUENER, H. & EICHENBERGER, E. (1973). *Psychopharmacologia*, **28**, 325–337.

TERNAY, A. L. & EVANS, S. A. (1974). *J. org. Chem.*, **39**, 2941–2946.

SCHAEFER, J. P. (1967). *Chem. Commun.*, 743–744.

VAN ROSSUM, J. M. (1967). In *Neuropsychopharmacology*, pp. 321–329. Editor: Brill, H. The Hague: Excerpta Medical Foundation.

WOODRUFF, G. N., ELKHAWAD, A. O. & PINDER, R. M. (1974). *Eur. J. Pharmac.*, **25**, 80–86.

WOODRUFF, G. N., ELKHAWAD, A. O., CROSSMAN, A. R. & WALKER, R. J. (1974). *J. Pharm. Pharmac.*, **26**, 740–741.

YORK, D. H. (1972). *Brain Res.*, **37**, 91–99.

ZIRKLE, C. L. & KAISER, C. (1970). In *Medicinal Chemistry*, Vol. II, 1410–1469. Editor: Burger, A. New York: Wiley-Interscience.