Conformations of Some Semi-rigid Neuroleptic Drugs. Part 1. Crystal Structures of Loxapine, Clozapine, and HUF-2046 Monohydrate {2-Chloro-11-(4-methylpiperazin-1-yl)dibenzo[*b*,*f*][1,4]oxazepine, 8-Chloro-11-(4-methylpiperazin-1-yl)dibenzo[*b*,*e*][1,4]diazepine, and 2-Chloro-11-(4-methylpiperazin-1-yl)dibenzo[*b*,*e*][1,4]diazepine Monohydrate}

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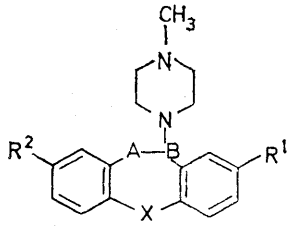
The crystal structures of three closely related rigid neuroleptic drugs have been determined from diffractometer data. Crystals of Loxapine (II) are orthorhombic, space group *Pbca*, with a = 1 796(5), b = 1 413(4), c = 1 301(3) pm, Z = 8. Crystals of Clozapine (III) are also orthorhombic, space group $P2_12_12_1$, with a = 1 804(3), b = 957(1), c = 950(1) pm, Z = 4. Crystals of HUF-2046 (IV) are monoclinic, space group $P2_1/n$, with a = 936(2), b = 1 717(4), c = 1 102(3) pm, β = 102.61(1)°, Z = 4. All three structures were solved by direct methods and refined by block-diagonal least squares to the following R and R' (no. of significant reflections and total no. of observations respectively in parentheses): (II) 0.064 (1 657), 0.081 (2 410); (III) 0.036 (1 295), 0.043 (1 468); (IV) 0.068 (2 469), 0.073 (2 843). Hydrogen atoms were located and their positions were refined in all structures.

The molecular conformations of all three molecules are practically identical, despite the differing substitutions. The dihedral angle between the planes of the two benzene rings is (II) 114, (III) 115, and (IV) 117.5° and a partial double bond between the piperazine ring and the bicyclic system effectively prevents rotation of this former moiety.

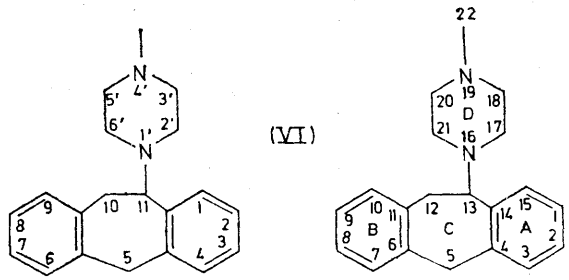
We present here a conformational study of a series of closely related neuroleptic (antischizophrenic) drugs. Several studies of the conformational aspects of antischizophrenic drugs have been made in solution,[1] by theoretical calculation,[2] and above all by crystal-structure analyses,[3] but all such studies have involved relatively flexible molecules and hence are of doubtful value in indicating the steric requirements for drug-receptor interaction. The molecules which we have studied are rigid, biologically potent, and allow direct inference of the topography of the postulated neuroleptic receptor substance(s).

These rigid molecules are all variants of the basic structure (I). Loxapine (II) is 2-chloro-11-(4-methylpiperazin-1-yl)dibenzo[*b*,*f*][1,4]oxazepine,[4] $C_{18}H_{18}N_3OCl$; Clozapine (III), (Leponex®), is 8-chloro-11-(4-methylpiperazin-1-yl)dibenzo[*b*,*e*][1,4]diazepine, $C_{18}H_{19}N_4Cl$; and HUF-2046 (IV) is the 2-chloro-isomer of Clozapine.[5] The crystal structure analyses of these three substances are presented here and structure analyses of both racemic and of the dextrorotatory enantiomer of the thiepine



(I)

	X	A–B	R^1	R^2
(II)	O	–N=C–	Cl	H
(III)	NH	–N=C–	H	Cl
(IV)	NH	–N=C–	Cl	H
(V)	S	$-CH_2-CH-$	Cl	H



(VI)

(V) will be reported in Part 2. In discussing the conformation of these molecules, we shall make use of our standardised crystallographic numbering of atoms. The relationship of this scheme to the conventional chemical numbering is shown in (VI), as is our labelling of the rings A, B, C, and D.

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[2] B. Pullman and P. Courrier, in Proc. Jerusalem Symposia on Quantum Chem. and Biochem., vol. V, eds. E. D. Bergman and B. Pullman, Israel Academy of Sciences and Humanities, Jerusalem, 1973, pp. 547—570, esp. pp. 553—555; B. Pullman, *Aggressologie*, 1968, **9**, 19; L. B. Kier, *J. Theor. Biol.*, 1973, **40**, 211.

[3] J. J. H. McDowell, *Acta Cryst.*, 1969, **B25**, 2175; 1970, **B26**, 954; P. Marsau, *ibid.*, 1971, **B27**, 42; P. Marsau and Y. Cam, *ibid.*, 1973, **B29**, 980; P. Marsau and B. Busetta, *ibid.*, p. 986; P. Marsau and J. Gauthier, *ibid.*, p. 992; S. S. C. Chu, *ibid.*, 1972, **B28**, 3625; M. H. J. Koch and G. Evrard, *ibid.*, 1973, **B29**, 2971; 1974, **B30**, 237; M. H. J. Koch and G. Germain, *ibid.*, 1972, **B28**, 121; L. L. Reed and J. P. Schaefer, *ibid.*, 1973, **B29**, 1886; M. H. J. Koch, *ibid.*, pp. 359, 1538; M. H. J. Koch and O. Dideburg, *ibid.*, p. 2969; J. P. Declercq, G. Germain, and M. H. J. Koch, *ibid.*, 1973, **B29**, 2311; M. L. Post, O. Kennard, and A. S. Horn, *ibid.*, 1974, **B30**, 1644; J. D. Dunitz, H. Eser, and P. Strickler, *Helv. Chim. Acta*, 1964, **47**, 1897; J. M. Bastian and H. P. Weber, *ibid.*, 1971, **54**, 293; M. C. Malmström, S. B. S., and A. W. Cordes, *J. Heterocyclic Chem.*, 1972, **9**, 325; J. P. Schaeffer, *Chem. Comm.*, 1967, 743; M.-R. Callas and P. Marsau, *Comptes rend.*, 1969, **C268**, 2014; B. Busetta and P. Marsau *ibid.*, 1968, **C266**, 692; G. Escobar, J. Clastre, and P. Marsau *ibid.*, 1968, **C267**, 1339; Y. Cam and P. Marsau, *ibid.*, 1970, **C270**, 309.

[4] J. Schmutz, F. Künzle, F. Huniker, and R. Gauch, *Helv. Chim. Acta*, 1967, **50**, 245.

[5] F. Hunziker, E. Fischer, and J. Schmutz, *Helv. Chim. Acta*, 1967, **50**, 1588.

EXPERIMENTAL

Crystals of all three compounds were obtained by slow evaporation of saturated 1 : 1 methanol–water solutions.

Crystal Data.—(i) *Loxapine*, (II). $C_{18}H_{18}ClN_3O$, M = 327. Orthorhombic, a = 1 796(5), b = 1 413(4), c = 1 301(3) pm, U = 3 302 × 10^6 pm^3, D_c = 1.32 g cm^{-3}, Z = 8. Space group *Pbca* (D_{2h}^{15}, No. 61). μ(Mo-K_α) = 2.55 cm^{-1}.

(ii) *Clozapine*, (III). $C_{18}H_{19}ClN_4$, M = 326. Orthorhombic, a = 1 804(3), b = 957(1), c = 950(1) pm, U = 1 640 × 10^6 pm^3, D_c = 1.32, Z = 4. Space group $P2_12_12_1$ (D_2^4, No. 19). μ(Mo-K_α) = 2.53 cm^{-1}.

(iii) HUF-2046, (IV). $C_{18}H_{19}N_4Cl{\cdot}H_2O$, M = 354. Monoclinic, a = 936(2), b = 1 717(4), c = 1 102(3) pm, β = 102.6(1)°, U = 1 728 × 10^6 pm, D_c = 1.37 g cm^{-1}, Z = 4. Space group $P2_1/n$ (non-standard setting of $P2_1/c$, C_{2h}^5, No. 14). μ(Mo-K_α) = 2.49 cm^{-1}.

Crystals of dimensions *ca.* 0.3 × 0.5 × 0.9 mm (II), 0.3 × 0.5 × 0.7 mm (III), and 0.4 × 0.7 × 0.5 mm (IV) were selected from the recrystallised material and preliminary unit-cell dimensions and space groups were determined from precession photographs. Three-dimensional intensity data were collected on a Hilger and Watts linear diffractometer by use of graphite-monochromatised Mo-K_α radiation (λ = 71.07 pm). In each case, all available symmetry-independent reflections out to sinθ/λ 0.55 were measured. For the three compounds, 2 410, 1 468, and 2 483 measurements yielded respectively 1 657, 1 295, and 2 469 significant [$I \geqslant 3\sigma(I)$] diffraction maxima. Data were corrected for Lorentz and polarisation effects and placed on an absolute scale by means of Wilson plots: B = 3.9, 3.2, and 3.3 Å^2.

TABLE 1

Final positions, with estimated standard deviations in parentheses, derived from the block-diagonal least-squares refinement for Loxapine (II)

	x	y	z	B
C(1)	3 711(2)	6 521(3)	6 437(3)	
C(2)	3 735(2)	6 762(3)	7 471(3)	
C(3)	4 094(2)	6 157(3)	8 133(3)	
C(4)	4 417(2)	5 334(2)	7 772(2)	
O(5)	4 796(1)	4 747(2)	8 458(1)	
C(6)	5 562(2)	4 791(3)	8 259(2)	
C(7)	6 026(2)	5 200(3)	8 996(3)	
C(8)	6 783(2)	5 233(3)	8 806(3)	
C(9)	7 068(2)	4 867(3)	7 914(3)	
C(10)	6 604(2)	4 441(3)	7 194(3)	
C(11)	5 834(2)	4 413(2)	7 356(2)	
N(12)	5 394(1)	3 918(2)	6 639(2)	
C(13)	4 736(2)	4 189(2)	6 377(2)	
C(14)	4 379(2)	5 078(2)	6 743(2)	
C(15)	4 026(2)	5 704(2)	6 055(2)	
N(16)	4 363(1)	3 664(2)	5 659(2)	
C(17)	3 547(2)	3 623(3)	5 582(2)	
C(18)	3 325(2)	3 426(3)	4 482(2)	
N(19)	3 638(1)	2 531(2)	4 154(2)	
C(20)	4 451(2)	2 586(3)	4 193(3)	
C(21)	4 705(2)	2 787(3)	5 278(3)	
C(22)	3 401(2)	2 302(4)	3 088(3)	
Cl	3 271(0)	7 292(1)	5 588(1)	
H(2)	350(2)	740(2)	770(3)	3.2(1.0)
H(3)	414(2)	629(2)	889(2)	2.2(0.9)
H(15)	399(2)	551(2)	526(2)	1.9(0.9)
H(7)	579(2)	536(2)	962(2)	2.8(1.0)
H(8)	711(2)	555(2)	934(2)	3.1(1.0)
H(9)	759(2)	488(2)	771(2)	2.8(1.0)
H(10)	681(2)	412(2)	654(2)	2.5(0.9)
H(171)	336(2)	308(2)	599(2)	2.2(0.9)
H(172)	334(1)	423(2)	583(2)	1.0(0.8)
H(181)	348(2)	395(2)	401(2)	2.3(0.9)
H(182)	276(2)	341(2)	444(2)	2.2(0.9)
H(211)	455(2)	225(2)	574(2)	2.1(0.9)
H(212)	524(2)	286(2)	529(2)	2.6(1.0)
H(201)	467(2)	314(2)	368(2)	1.8(0.9)
H(202)	466(2)	192(3)	395(3)	3.7(1.1)
H(221)	282(2)	229(3)	304(3)	6.3(1.4)
H(222)	362(3)	167(3)	296(3)	5.5(1.3)
H(223)	358(3)	284(3)	258(3)	5.9(1.4)

TABLE 2

Final positions, with estimated standard deviations in parentheses, derived from the block-diagonal least-squares refinement, for Clozapine (III)

	x	y	z	B
C(1)	7 322(2)	7 116(4)	9 428(5)	
C(2)	6 714(2)	7 966(4)	9 580(4)	
C(3)	6 038(2)	7 541(4)	9 090(4)	
C(4)	5 955(2)	6 240(4)	8 468(4)	
N(5)	5 263(1)	5 815(3)	7 910(3)	
C(6)	5 301(1)	5 581(4)	6 419(4)	
C(7)	4 923(2)	6 444(4)	5 501(4)	
C(8)	4 968(2)	6 243(4)	4 042(4)	
C(9)	5 402(2)	5 170(4)	3 554(3)	
C(10)	5 768(2)	4 270(4)	4 453(4)	
C(11)	5 734(2)	4 474(4)	5 919(4)	
N(12)	6 085(1)	3 493(3)	6 772(3)	
C(13)	6 460(1)	3 865(3)	7 870(4)	
C(14)	6 548(2)	5 319(3)	8 394(4)	
C(15)	7 243(2)	5 802(4)	8 830(4)	
N(16)	6 867(1)	2 863(3)	8 554(3)	
C(17)	7 044(2)	2 880(4)	10 068(4)	
C(18)	7 825(2)	2 377(4)	10 284(4)	
N(19)	7 923(1)	962(3)	9 716(3)	
C(20)	7 744(2)	980(4)	8 217(4)	
C(21)	6 961(2)	1 483(4)	7 950(4)	
C(22)	8 685(2)	512(4)	9 926(5)	
Cl	5 511(0)	4 955(1)	1 738(1)	
H(1)	788(1)	745(3)	972(3)	0.7(0.8)
H(2)	673(2)	892(4)	1 002(4)	2.7(1.0)
H(3)	567(1)	810(3)	910(3)	0.9(0.8)
H(5)	492(2)	642(4)	813(4)	1.9(0.9)
H(7)	456(2)	729(4)	584(4)	2.3(1.0)
H(8)	465(1)	695(3)	339(3)	1.1(0.8)
H(10)	607(1)	349(3)	409(3)	0.4(0.7)
H(15)	767(1)	518(3)	872(3)	0.8(0.8)
H(171)	662(2)	220(4)	1 054(4)	2.1(1.0)
H(172)	691(2)	376(4)	1 045(4)	2.2(1.0)
H(181)	825(2)	301(4)	989(4)	2.3(1.0)
H(182)	796(1)	229(4)	1 116(4)	1.7(0.9)
H(201)	816(2)	165(4)	771(4)	3.0(1.1)
H(202)	784(2)	4(4)	781(4)	2.5(1.0)
H(211)	654(1)	82(3)	832(3)	0.1(0.6)
H(212)	684(1)	152(3)	690(4)	1.5(0.8)
H(221)	879(2)	51(4)	1 090(4)	2.8(1.0)
H(222)	901(2)	106(4)	943(4)	1.7(0.9)
H(223)	873(2)	−33(4)	948(4)	2.2(1.0)

All three structures were solved by direct methods. In each case, all 23 atoms of the molecule could be located in the first E map. Loxapine, however, would not refine from these initial co-ordinates. It was noticed in this case that in addition to the 23 strong peaks, there was a weaker image of the same set of peaks, translated in the x direction only. Accordingly, small x translations were successively applied to the starting co-ordinates and R was calculated for the 381 reflections having $F_o > 30$. An x-shift of 0.037 gave the best R (0.31) and refinement proceeded smoothly from this modified set of starting positions. In the E map of HUF-2046, there was one additional strong peak. Difference-Fourier syntheses after initial refinement indicated that this peak represented a genuine atom. It was assigned as water of crystallisation after inspection of a packing diagram showed that this additional atom could

take part in a sensible intermolecular hydrogen-bonding scheme.

All structures were refined by block-diagonal least-squares, initially with isotropic, then with anisotropic thermal parameters. Hydrogen atoms were introduced in calculated positions at a late stage, difference-Fourier synthesis being used to aid this process for methyl groups, the N(5) hydrogen atoms, and those of the water molecule. The hydrogen atoms were then refined with isotropic thermal parameters, together with the other atoms. In the final cycles, an isotropic extinction parameter [6] was introduced and refined (IV). Final positions and standard deviations estimated from the block-diagonal refinement are presented in Tables 1—3 and structure factor tables and anisotropic thermal parameters have been deposited as Supplementary Publication No. SUP 21705 (43 pp., 1 microfiche).*

RESULTS

Description of the Structures.—The conformations of the three molecules are shown in stereo view with ellipsoids of thermal vibration in Figure 1. The molecular geometries are given in Table 4. Sufficient torsion angles for the

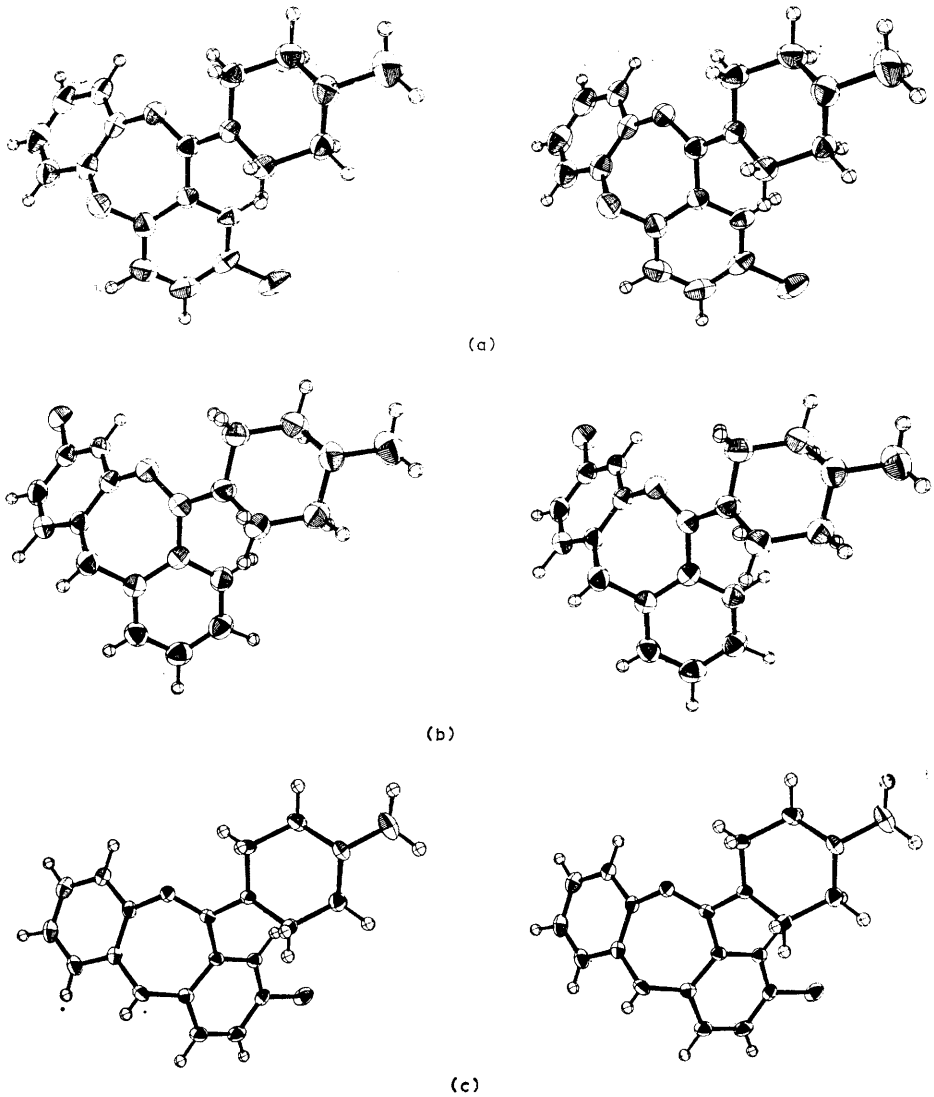

FIGURE 1 Stereoviews, showing 50% probability ellipsoids of thermal motion, of (a) Loxapine (II), (b) Clozapine (III), and (c) HUF-2046 (IV)

and attained final values of 138(6), 112(5), and 288(12), respectively. The final R and R' factors attained for significant reflections and for all observations respectively were: 0.064, 0.081 (II), 0.036, 0.043 (III), and 0.068, 0.073

construction of accurate molecular models are given in Table 5. In all three molecules, the central seven-membered heterocycle (ring c) is in a boat conformation with an almost exact mirror plane passing through O(5) [N(5)] and the centre of the N(12)–C(13) double bond. The dihedral angle between the planes of the benzene rings (defined as the obtuse angle subtended by the plane normals) is 114 in Loxapine, 115 in Clozapine, and 117.5° in HUF-2046.

* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1975, Index issue.

[6] P. Coppens and W. C. Hamilton, *Acta Cryst.*, 1970, **A26**, 71.

TABLE 3

Final positions, with estimated standard deviations in parentheses, derived from block-diagonal least-squares refinement, for HUF-2046 (IV)

	x	*y*	*z*
C(1)	1 689(3)	5 163(1)	1 066(3)
C(2)	1 154(4)	4 768(2)	1 959(3)
C(3)	1 740(4)	4 055(2)	2 355(3)
C(4)	2 853(3)	3 724(1)	1 859(3)
N(5)	3 566(3)	3 040(1)	2 366(2)
C(6)	5 103(3)	3 125(1)	2 817(3)
C(7)	5 722(4)	2 991(2)	4 072(3)
C(8)	7 222(4)	3 065(2)	4 526(3)
C(9)	8 122(4)	3 283(2)	3 733(3)
C(10)	7 512(4)	3 406(2)	2 486(3)
C(11)	6 002(4)	3 336(1)	2 002(3)
N(12)	5 516(4)	3 380(1)	699(2)
C(13)	4 305(3)	3 717(1)	189(3)
C(14)	3 278(3)	4 105(1)	864(3)
C(15)	2 715(3)	4 838(1)	496(3)
N(16)	3 942(3)	3 794(1)	−1 084(2)
C(17)	3 433(3)	3 787(2)	−1 811(3)
C(18)	2 282(4)	4 341(2)	−2 883(3)
N(19)	3 291(3)	4 129(1)	−3 676(2)
C(20)	4 798(4)	4 112(2)	−2 943(3)
C(21)	4 963(3)	3 561(2)	−1 847(3)
C(22)	3 173(5)	4 701(2)	−4 688(3)
Cl	1 057(1)	6 103(0)	664(1)
O(H_2O)	2 208(3)	2 834(1)	4 710(2)

	x	*y*	*z*	*B*
H(2)	46(4)	502(2)	232(3)	0.0(0.7)
H(3)	134(5)	374(2)	292(4)	1.4(1.0)
H(5)	330(4)	287(2)	288(3)	0.2(0.8)
H(7)	508(4)	280(2)	451(3)	0.7(0.8)
H(8)	772(4)	293(2)	537(4)	1.7(1.0)
H(9)	926(4)	337(2)	407(3)	0.2(0.8)
H(10)	811(4)	355(2)	191(3)	0.4(0.8)
H(15)	309(4)	516(2)	−15(3)	0.7(0.9)
H(171)	184(3)	393(1)	−132(3)	0.7(0.7)
H(172)	220(3)	325(1)	−211(3)	0.5(0.7)
H(181)	122(5)	430(2)	−339(4)	3.0(1.2)
H(182)	238(4)	487(2)	−257(4)	0.7(0.8)
H(201)	546(4)	395(2)	−348(3)	0.3(0.8)
H(202)	512(3)	466(1)	−260(3)	0.7(0.7)
H(211)	586(4)	363(2)	−135(3)	0.5(0.9)
H(212)	477(3)	307(1)	−211(3)	0.8(0.6)
H(221)	381(5)	453(2)	−526(5)	3.1(1.2)
H(222)	348(4)	521(2)	−437(3)	0.5(0.8)
H(223)	209(5)	469(2)	−513(4)	1.1(1.1)
H(W1)	245(4)	308(2)	512(4)	1.4(1.0)
H(W2)	188(5)	259(2)	494(4)	1.6(1.0)

The most noticeable feature of the overall molecular conformation is the at first sight unfavourable close approach of C(17) in the piperazine ring to the benzene ring A and the near parallelism of the mean plane of the piperazine ring to that of benzene ring B (Table 6). Closer examination of

TABLE 4

Molecular geometry

(*a*) Distances (pm)	(II)	(III)	(IV)
C(1)–Cl	174		174
C(1)–C(2)	139	137	138
C(1)–C(15)	138	139	138
C(1)–H		110	
C(2)–C(3)	137	137	137
C(2)–H	104	100	94
C(3)–C(4)	138	139	140
C(3)–H	101	85	96
C(4)–O[N](5)	140	142	141
C(4)–C(14)	139	139	141
O[N](5)–C(6)	140	144	142
N(5)–H		87	73
C(6)–C(7)	140	138	140
C(6)–C(11)	138	140	141
C(7)–C(8)	138	140	139

TABLE 4 (*Continued*)

(*a*) Distances (pm)	(II)	(III)	(IV)
C(7)–H	94	109	91
C(8)–C(9)	137	137	139
C(8)–H	103	108	98
C(9)–C(10)	139	138	138
C(9)–H	99		107
C(9)–Cl		175	
C(10)–C(11)	140	141	140
C(10)–H	103	98	97
C(11)–N(12)	141	139	141
N(12)–C(13)	129	129	129
C(13)–C(14)	149	149	150
C(13)–N(16)	137	137	138
C(14)–C(15)	141	140	139
C(15)–H	107	99	107
N(16)–C(17)	147	147	146
N(16)–C(21)	147	145	146
C(17)–H	99	95	89
C(17)–H	100	110	98
C(17)–C(18)	151	150	150
C(18)–N(19)	145	147	147
C(18)–H	101	105	103
C(18)–H	102	88	98
N(19)–C(20)	146	146	147
N(19)–C(22)	149	146	147
C(20)–C(21)	151	152	152
C(20)–H	110	110	100
C(20)–H	106	99	104
C(21)–H	101	102	90
C(21)–H	97	104	89
C(22)–H	103	92	102
C(22)–H	107	95	100
C(22)–H	98	92	97
(*b*) Angles (°)			
C(2)–C(1)–C(15)	123	120	122
C(2)–C(1)–Cl	118		119
C(15)–C(1)–Cl	119		119
C(1)–C(2)–C(3)	118	120	119
C(2)–C(3)–C(4)	121	121	121
C(3)–C(4)–O[N](5)	119	121	121
C(3)–C(4)–C(14)	122	120	118
O[N](5)–C(4)–C(14)	119	119	121
C(4)–O[N](5)–C(6)	110	112	114
O[N](5)–C(6)–C(7)	119	120	120
O[N](5)–C(6)–C(11)	119	119	120
C(7)–C(6)–C(11)	122	121	120
C(6)–C(7)–C(8)	119	121	121
C(7)–C(8)–C(9)	120	118	120
C(8)–C(9)–C(10)	121	122	119
C(8)–C(9)–Cl		119	
C(10)–C(9)–Cl		119	

	(I)	(II)	(III)
C(9)–C(10)–C(11)	120	120	122
C(10)–C(11)–N(12)	118	118	117
C(10)–C(11)–C(6)	118	118	118
C(6)–C(11)–N(12)	124	125	124
C(11)–N(12)–C(13)	123	122	122
N(12)–C(13)–C(14)	124	126	126
N(12)–C(13)–N(16)	118	118	119
C(14)–C(13)–N(16)	118	116	115
C(13)–C(14)–C(15)	121	120	120
C(13)–C(14)–C(4)	120	122	120
C(4)–C(14)–C(15)	118	118	120
C(14)–C(15)–C(1)	119	121	119
C(13)–N(16)–C(17)	124	125	123
C(13)–N(16)–C(21)	119	121	121
C(17)–N(16)–C(21)	111	112	110
N(16)–C(17)–C(18)	110	109	110
C(17)–C(18)–N(19)	110	111	111
C(18)–N(19)–C(20)	109	109	110
C(18)–N(19)–C(22)	111	110	110
C(20)–N(19)–C(22)	109	110	110
N(19)–C(20)–C(21)	110	112	112
C(20)–C(21)–N(16)	110	109	109

Mean standard deviations: C–C ⩽ 0.7 pm
C–H ⩽ 7 pm
C–C–C ⩽ 0.5°

the molecular geometry, particularly of the bond angles at N(16) and the torsion angles about the C(13)–N(16) bond suggests an explanation, however. The torsion angles

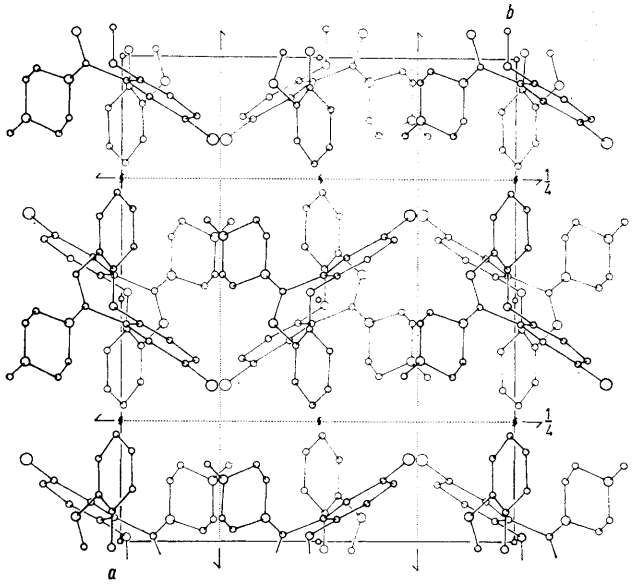

FIGURE 2 Molecular packing of (II) (omitting hydrogen atoms) viewed down the *c* axis

about the C(13)–N(16) bond are such that C(21) is anti-planar to C(14) and that the lone pair on N(12) bisects the angle between the two hydrogen atoms on C(21). The bond

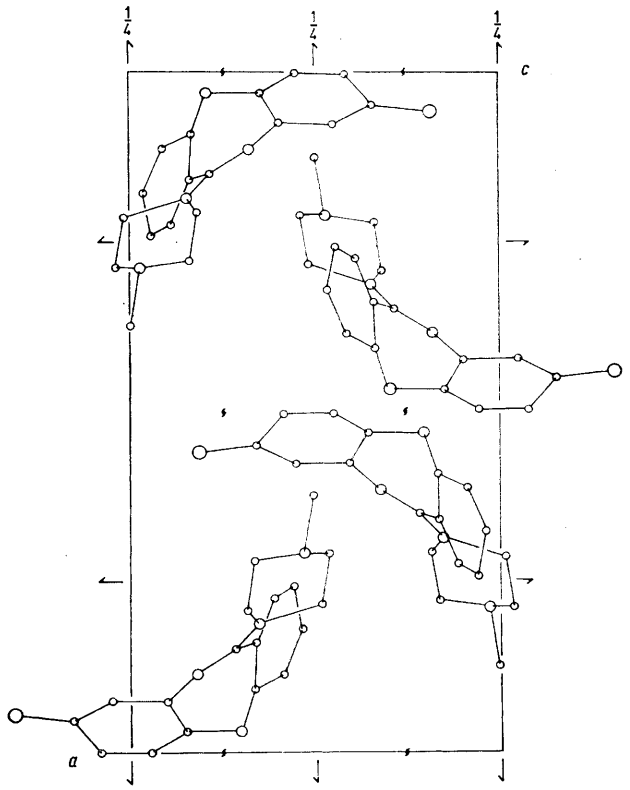

FIGURE 3 Molecular packing of (III) (omitting hydrogen atoms) viewed down the *b* axis

angles about N(16) also suggest a trigonal, rather than a tetrahedral, atom. We interpret these observations in terms of partial double-bonding C(13)···N(16) (mean bond length for the three molecules 137.3 pm), increased torsional rigidity in that bond, and an increased sp^2 character for N(16). This increased sp^2 character has no effect on the conformation of ring D, an almost perfect chair with the C(22) methyl group equatorial, but results rather in an

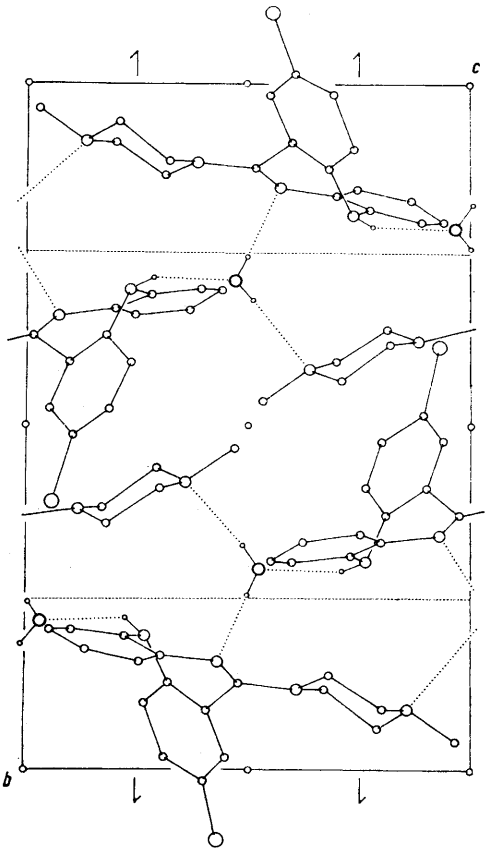

FIGURE 4 Molecular packing of (IV), viewed down the *a* axis. Only those hydrogen atoms involved in hydrogen bonding, indicated by dotted lines, are shown

increase, by unequal amounts, of the C(13)–N(16)–C(17) and C(13)–N(16)–C(21) bond angles so that the N(16)–C(13) bond takes up a position somewhere between equatorial and axial to the piperazine ring.

TABLE 5

Sufficient torsion angles (°) to describe the molecular conformations

	(II)	(III)	(IV)
4–5–6–11	−68	−66	−62
5–6–11–12	−5	−6	−8
6–11–12–13	42	46	46
11–12–13–14	4	−2	1
12–13–14–4	−45	−44	−48
13–14–4–5	0	6	11
14–4–5–6	70	64	58
12–13–16–17	154	151	148
12–13–16–21	4	−9	−5
14–13–16–17	−31	−34	−37
14–13–16–21	180	166	170

Molecular Packing.—Simplified views of the molecular packing arrangements are given in Figures 2—4. In none of the structures are there any intermolecular contacts less than the sum of the van der Waals radii. There are no intermolecular hydrogen bonds in the Clozapine structure, although bonding of the type N–H · · · N would, in principle,

TABLE 6

Interplanar dihedral angles (°) for rings A, B, and D

	(II)	(II)	(IV)
A–B	144	115	117.5
A–D	43	38	42
B–D	27	27	22

be possible. In HUF-2046, the molecules are bound together through the water of crystallisation: one hydrogen atom of the water molecule bonds to N(12) of one drug molecule, and the second bonds to N(19) of a molecule related to the first by the glide plane. The scheme is completed by the N(5) proton of a third drug molecule, related to the first by the two-fold screw axis, acting as

TABLE 7

Hydrogen-bonding distances * (pm) in HUF-2046 (IV)

	D–H	H · · · A	D · · · A
N(5)–H(5) · · · O(H_2O	73	245	314
O(H_2O)–H(W1) · · · N(19)	70	226	289
O(H_2O)–H(W2) · · · N(12)	60	237	297

* D = donor, H = hydrogen, A = acceptor.

donor to the water oxygen atom. Details are given in Table 7. That the molecular conformations of the three molecules are so similar, despite such different packing schemes, indicates quite clearly that we are observing here a preferred molecular conformation, uninfluenced by that bugbear of theoreticians and pharmacologists alike, ' crystal packing forces '. We are confident that the observed conformation persists in solution, and by extension, at the neuroleptic receptor.

DISCUSSION

Since none of these molecules has a chiral centre, we cannot with confidence say whether the asymmetric configuration illustrated in Figure 1, or its mirror image, is the configuration involved in interaction with the neuroleptic receptor. It is, however, of interest to know the approximate rate of interconversion of the two mirror-symmetric conformers in solution. (One can depict this interconversion as a ' wing-flapping ' of the two benzene rings about the central seven-membered heterocycle, accompanied by a concomitant flip of the piperazine ring above and below the plane of ring c.) Clozapine crystallises in a non-centrosymmetric space group. Individual crystals therefore contain exclusively one or the other asymmetric conformer. To test whether the interconversion is rapid, we selected three large single crystals weighing 3.42, 4.56, and 6.69 mg, and dissolved each in 1 ml of ' Uvasol ' grade methanol. Measurements of optical rotation were immediately made at five different wavelengths, and in the case of one solution, at four differing dilutions. All experiments yielded zero rotation within the limits of experimental error.

There are two alternative explanations for this failure to observe optical rotation: either the solutions we used were too dilute for the sensitivity of the apparatus (concentrations ranged from 0.1 to a little better than 0.2 molar); or the molecule immediately equilibrates at room temperature in methanol solution to a 1 : 1 mixture of both conformers upon dissolution. This flexibility could arise, for example, from rapid umbrella inversion at N(5). We consider the latter explanation to be correct.

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