Conformations of Some Semi-rigid Neuroleptic Drugs. Part 2.† Crystal Structures of Racemic and of (+)-(*S*)-Octoclothepin{2-Chloro-10,11-dihydro-11-(4-methylpiperazin-1-yl)dibenzo[*b,f*]thiepin} and the Absolute Configuration of the Latter

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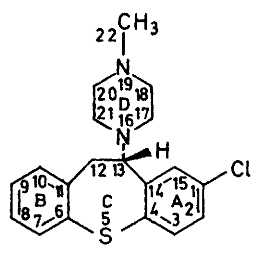
The crystal structures of racemic and of dextrorotatory Octoclothepin, a neuroleptic drug, have been determined from diffractometer data, as has the absolute configuration of the latter. Crystals of racemic Octoclothepin are orthorhombic, space group $Pna2_1$, a = 1 265(4), b = 1 008(2), c = 1 412(5) pm. The structure was solved by Patterson convolution methods and refined by block-diagonal least-squares to R 0.040 (1 083 significant reflections). Crystals of (+)-Octoclothepin are orthorhombic, space group $P2_12_12_1$, a = 1 758(5), b = 1 260(4), c = 787(2) pm. The structure was solved by multisolution direct methods and refined by block-diagonal least-squares to R 0.039 (1 079 significant data). The absolute configuration was determined to be S by means of an R-factor ratio test at termination of refinement (significant at <0.005 probability level) and confirmed by measurement of 50 Friedel pairs with Cu-K_α radiation.

The conformations of racemic and dextrorotatory molecules are practically identical despite different crystal packings. The central seven-membered ring folds about a line through S(5) and C(12), whereby atoms C(12) and C(13) are almost coplanar with the chlorine-substituted benzene ring. Despite removal of the constraint of a 10,11-double bond in the seven-membered heterocycle, the overall molecular conformation bears a strong resemblance to those of Loxapine, Clozapine, and HUF-2046, in that the mean plane of the piperazine ring lies roughly parallel to the plane of one of the benzene rings.

OCTOCLOTHEPIN (I) [1] is a neuroleptic (antischizophrenic) drug, the conformation of which is of interest to those attempting to understand the relationship of chemical structure to antischizophrenic activity. As part of our continuing study of such molecules, we have determined



(I) (+)-(*S*)-Octoclothepin

the crystal structure of the racemate. It later became apparent in pharmacological testing that the separated enantiomers of this optically active molecule showed a several hundredfold difference in biological potency, the activity residing essentially in the (+)-enantiomer.[2] We have, therefore, also determined the crystal structure and absolute configuration of (+)-Octoclothepin.[3]

There are to date only two stereospecific antischizophrenic drugs of known absolute configuration, Butaclamol [4] being one and Octoclothepin the other. Since, however, Butaclamol is a drug of a new chemical type, which may only with difficulty be related to antischizophrenic agents in clinical use, whereas Octoclothepin may fairly easily be related to the forerunner of them all, phenothiazine, a knowledge of the absolute configuration of Octoclothepin is crucial for an understanding of the topography of the neuroleptic drug receptor. The absolute configuration of (+)-Octoclothepin is 11*S*.

EXPERIMENTAL

Crystals of the racemate were grown by slow evaporation of a solution in CH_2Cl_2, crystals of the (+)-enantiomer were of suitable quality as provided.

Crystal Data—(±)-*Octoclothepin*. $C_{19}H_{21}N_2SCl$, $M = 344$. Orthorhombic, a = 1 265(4), b = 1 008(3), c = 1 412(5) pm, U = 1 801.10^6 pm^3, D_c = 1.28 g cm^{-3}, Z = 4. Space group $Pna2_1$ (C^9_{2v}, No. 33) Mo-K_α radiation, λ = 71.07 pm, μ(Mo-K_α) = 3.41 cm^{-1}.

(+)-*Octoclothepin*. $C_{19}H_{21}N_2SCl$, $M = 344$. Orthorhombic, a = 1 758(5), b = 1 260(4), c = 787(2) pm, U = 1 744.10^6 pm^3, D_c = 1.30 g cm^{-3}, Z = 4. Space group $P2_12_12_1$ (D^4_2, No. 19). Mo-K_α radiation; μ(Mo-K_α) = 3.52 cm^{-1}, $[\alpha_D]^{20}$ 51.9° (1% methanol), m.p. 112—114 °C.

Crystals of dimensions 0.2 × 0.3 × 0.5 mm (±) and 0.2 × 0.3 × 0.2 mm (+) were selected 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, 1 503 and 1 481 measurements yielding 1 083 and 107 9 significant [$I \geqslant 3\sigma(I)$] symmetry-independent reflections for racemic and (+)-Octoclothepin respectively. Data were corrected for Lorentz and polarisation effects, but not for X-ray absorption, and placed on an absolute scale by means of a Wilson plot ($\tilde{B}$ 4.71 and 4.27 Å^2 respectively).

Solution of the Structures.—(±)-*Octoclothepin*. An initial attempt was made to solve the structure by the heavy-atom method from a normal, and from a sharpened Patterson synthesis, but without success. Accordingly, a single heavy atom (Cl) was chosen as 'model' for the convolution molecule method,[5] calculation of self-convolution structure

† Part I, T. J. Petcher and H. P. Weber, *J.C.S. Perkin II*, 1976, 1415.

[1] M. Protiva, J. O. Jílek, J. Metyšová, V. Seidlová, I. Jirkoský, J. Metyš, E. Fidlerová, I. Ernst, K. Pelz, and J. Pomykáček, *Farmaco. Ed. Sci.*, 1965, **20**, 721.

[2] T. J. Petcher, J. Schmutz, H. P. Weber, and T. G. White, *Experientia*, 1975, **31**, 1389.

[3] J. O. Jílek, J. Metyšová, J. Pomykacek, and M. Protiva, *Coll. Czech. Chem. Comm.*, 1968, **33**, 1831.

[4] P. H. Bird, F. T. Bruderlein, and L. G. Humber, *Canad. J. Chem.*, in the press.

[5] R. Huber, in 'Crystallographic Computing,' ed. F. A. Ahmed, Munksgaard, Copenhagen, 1970, p. 96 and references cited therein.

factors was omitted, since a rotation search for a ' model ' consisting of one atom is unnecessary, and structure factors for the cross-convolution of Cl with its symmetry-related neighbours were used to provide input to the translation-search functions. The chlorine position was derived from

TABLE 1

Observed and expected intensity differences in Friedel pairs for (+)-(*S*)-Octoclothepin

h	k	l	I_{hkl}	$I_{\bar{h}\bar{k}\bar{l}}$	ΔI_{calc} (%)	ΔI_{obs} (%)
6	1	1	15 218	19 018	−24	−25
5	1	1	17 163	13 992	22	18
3	1	1	21 102	16 887	23	20
2	1	1	40 596	50 137	−19	−24
8	2	1	23 013	21 410	10	7
9	2	1	1 798	1 343	60	25
10	3	1	2 811	3 287	−23	−17
5	3	1	8 833	10 700	−14	−21
4	3	1	2 766	3 335	−33	−21
2	3	1	29 442	26 339	12	11
0	3	1	11 792	11 947	0	−1
2	4	1	7 265	9 096	−18	−25
3	4	1	24 588	21 727	11	12
4	4	1	29 456	26 765	12	9
10	5	1	2 209	1 751	30	21
7	5	1	2 188	2 971	−26	−36
3	5	1	6 011	5 136	20	15
2	5	1	12 472	15 435	−19	−24
4	6	1	6 466	5 528	11	15
9	6	1	8 213	8 796	−11	−7
9	7	1	1 481	2 043	−31	−38
5	7	1	1 672	2 718	−26	−63
4	7	1	1 930	2 471	−26	−28
2	7	1	4 005	4 434	−11	−11
2	8	1	1 767	1 495	24	15
3	8	1	1 909	1 545	14	19
4	8	1	4 124	3 734	14	9
9	8	1	1 657	1 857	−16	−12
10	9	1	3 264	3 680	−11	−13
9	9	1	3 354	2 987	14	11
7	9	1	2 267	2 006	15	12
3	9	1	1 552	1 337	20	14
9	1	2	10 895	12 091	−13	−11
3	1	2	15 010	20 084	−29	−34
6	2	2	5 442	6 057	−14	−11
7	2	2	11 484	9 956	13	13
8	3	2	3 212	4 903	−49	−53
3	3	2	7 093	9 216	−26	−30
2	3	2	8 705	5 794	51	33
1	3	2	14 479	12 456	14	14
4	4	2	13 315	10 590	24	20
6	4	2	3 937	3 007	24	24
9	5	2	1 399	1 600	−21	−14
8	5	2	4 651	5 705	−18	−23
5	5	2	7 856	10 444	−41	−33
6	6	2	10 546	12 023	−14	−14
7	6	2	8 755	7 771	15	12
8	7	2	3 411	3 227	20	5
2	7	2	4 796	4 140	18	14
1	7	2	2 172	2 440	−13	−12
3	4	4	1 475	1 943	−75	−32

I_{hkl}, $I_{\bar{h}\bar{k}\bar{l}}$ are uncorrected integrated intensities (counts)
$\Delta I_{calc} = \{[F_c^2(hkl) - F_c^2(\bar{h}\bar{k}\bar{l})]/F_c^2(hkl)\} \times 100$

the deepest, best-defined minimum in the translation function, a sulphur atom was placed on the origin, and structure factors were calculated anew for the cross-convolution of Cl (now in a known position) and S. The position of the sulphur atom was easily derived from the succeeding translation function (it later turned out that the positions of Cl and S had to be interchanged: for *X*-ray diffraction experiments Cl and S are practically equal atoms, having 17 and 16 electrons respectively). The remaining atoms of the structure were located by straightforward application of the heavy-atom method.

TABLE 2

Final positions ($\times 10^4$ for non-hydrogen atoms, for hydrogen $\times 10^3$) and estimated standard deviations derived from the block-diagonal least-squares refinement. The coordinates of (+)-(*S*)-Octoclothepin are for the correct absolute configuration in a right-handed axial system

(*a*) Racemic Octoclothepin

	X	*Y*	*Z*
C(1)	1 580(4)	3 072(5)	3 465(4)
C(2)	2 633(5)	3 181(6)	3 257(4)
C(3)	3 212(5)	4 118(6)	3 755(4)
C(4)	2 751(4)	4 887(5)	4 455(3)
S(5)	3 680(1)	5 993(1)	4 993(1)
C(6)	2 986(4)	7 519(6)	4 998(4)
C(7)	3 381(5)	8 560(6)	4 466(4)
C(8)	2 850(6)	9 764(7)	4 494(4)
C(9)	1 956(5)	9 915(6)	5 038(5)
C(10)	1 564(4)	8 846(6)	5 558(4)
C(11)	2 077(4)	7 621(6)	5 542(3)
C(12)	1 668(4)	6 449(6)	6 081(3)
C(13)	1 056(4)	5 442(5)	5 458(3)
C(14)	1 689(4)	4 725(5)	4 677(3)
C(15)	1 097(4)	3 819(5)	4 156(3)
N(16)	527(3)	4 407(4)	6 020(2)
C(17)	1 227(4)	3 566(6)	6 585(4)
C(18)	583(5)	2 406(7)	6 974(4)
N(19)	−285(3)	2 881(4)	7 564(3)
C(20)	−963(4)	3 759(6)	6 999(4)
C(21)	−335(4)	4 896(6)	6 607(4)
C(22)	−898(5)	1 787(6)	7 952(5)
Cl	836(1)	1 914(1)	2 819(1)

	X	*Y*	*Z*	B/Å^2
H(2)	293(4)	257(5)	268(3)	3.0(1.3)
H(3)	396(4)	420(5)	361(4)	4.0(1.5)
H(7)	407(4)	844(4)	398(3)	2.4(1.3)
H(8)	311(4)	1 047(4)	412(3)	2.8(1.3)
H(9)	156(4)	1 090(6)	498(5)	6.1(1.7)
H(10)	97(4)	891(5)	597(4)	4.0(1.5)
H(121)	228(4)	603(5)	646(4)	3.9(1.6)
H(122)	111(4)	684(5)	657(3)	2.4(1.3)
H(13)	47(4)	594(5)	508(5)	4.9(1.5)
H(15)	40(4)	368(4)	432(3)	2.2(1.2)
H(171)	169(4)	325(4)	616(3)	2.2(1.3)
H(172)	160(4)	423(5)	716(4)	4.7(1.6)
H(181)	34(5)	191(6)	638(4)	5.9(2.0)
H(182)	113(4)	187(5)	744(3)	3.9(1.5)
H(201)	−124(4)	326(5)	645(3)	2.5(1.3)
H(202)	−154(4)	413(5)	743(4)	4.3(1.6)
H(211)	−77(3)	547(4)	630(3)	2.0(1.2)
H(212)	−2(3)	544(4)	716(3)	1.3(1.1)
H(221)	−45(4)	122(5)	846(4)	4.2(1.5)
H(222)	−120(4)	117(5)	744(3)	3.7(2.4)
H(223)	−152(4)	217(5)	837(4)	4.1(1.5)

(*b*) (+)-(*S*)-Octoclothepin

	X	*Y*	*Z*
C(1)	1 939(3)	1 240(4)	5 572(9)
C(2)	1 689(4)	808(5)	4 090(9)
C(3)	2 054(4)	1 082(5)	2 622(9)
C(4)	2 677(3)	1 775(4)	2 602(9)
S(5)	3 043(1)	2 010(1)	535(2)
C(6)	3 192(3)	3 410(5)	478(9)
C(7)	2 801(3)	3 997(5)	−697(8)
C(8)	2 957(4)	5 080(5)	−812(8)
C(9)	3 458(4)	5 538(6)	296(9)
C(10)	3 835(4)	4 933(5)	1 482(9)
C(11)	3 714(3)	3 838(5)	1 609(7)
C(12)	4 121(3)	3 167(5)	2 861(8)
C(13)	3 636(3)	2 909(4)	4 418(8)
C(14)	2 945(3)	2 171(4)	4 151(7)
C(15)	2 561(3)	1 893(5)	5 615(9)
N(16)	4 090(2)	2 487(3)	5 848(6)
C(17)	4 586(3)	3 286(5)	6 637(8)
C(18)	4 977(3)	2 861(5)	8 149(8)
N(19)	5 408(2)	1 917(4)	7 724(6)
C(20)	4 892(3)	1 127(5)	7 032(8)
C(21)	4 515(3)	1 535(4)	5 440(9)
C(22)	5 802(4)	1 516(6)	9 225(10)
Cl	1 431(1)	970(1)	7 419(2)

TABLE 2 (*Continued*)

	X	Y	Z	B/Å^2
H(2)	124(3)	32(5)	419(8)	3.3(1.7)
H(3)	190(3)	78(4)	160(7)	1.7(1.4)
H(7)	242(4)	368(5)	−141(8)	4.7(1.9)
H(8)	270(3)	549(5)	−182(8)	4.0(1.9)
H(9)	359(4)	625(5)	9(8)	4.0(1.9)
H(10)	420(3)	524(4)	231(8)	2.6(1.5)
H(121)	424(3)	260(5)	215(7)	3.2(1.7)
H(122)	460(3)	354(5)	335(8)	3.3(1.7)
H(13)	340(3)	356(5)	472(8)	3.5(1.8)
H(15)	271(3)	210(5)	683(7)	3.1(1.7)
H(171)	424(3)	392(4)	710(7)	2.1(1.5)
H(172)	496(3)	350(4)	578(8)	3.5(1.7)
H(181)	531(3)	339(5)	856(8)	2.7(1.6)
H(182)	455(3)	270(5)	907(7)	3.4(1.7)
H(201)	447(3)	92(4)	780(7)	1.8(1.5)
H(202)	520(3)	50(5)	673(7)	2.6(1.6)
H(211)	417(3)	105(5)	474(7)	3.0(1.7)
H(212)	492(3)	166(4)	451(8)	2.4(1.5)
H(221)	543(3)	134(5)	1 013(8)	4.0(1.9)
H(222)	612(3)	202(5)	989(8)	4.1(1.9)
H(223)	609(4)	95(5)	884(8)	5.0(2.0)

Block-diagonal least-squares refinement with anisotropic thermal parameters for the heavier atoms, hydrogen atoms with individual isotropic temperature factors, and an isotropic extinction coefficient, which refined to 49(2) assuming an overall isotropic $\bar{T}$ of 0.02 cm, reduced R to a final value of 0.040 for the 1 083 significant reflections and 0.053 for all 1 503 observations.

(+)-*Octoclothepin*. The structure was solved by straightforward application of multisolution direct methods and the first E map calculated revealed all 23 atoms of the structure among the 33 highest peaks. Block-diagonal least-squares refinement using anisotropic thermal parameters for the heavier atoms, hydrogen atoms introduced in calculated positions which were then refined with individual isotropic temperature factors, and an isotropic extinction coefficient which refined to 27(2) assuming an overall isotropic $\bar{T}$ of 0.02 cm, reduced R to a final value of 0.039 (1 079 significant data) and R' to 0.061 (all 1 481 observations). These R factors are for the correct absolute configuration, calculated with inclusion of the effect of anomalous scattering for Cl and S ($\Delta f''$ 0.2 and 0.2 e respectively). The absolute configuration was determined by application of the R-factor ratio test.[6] The ratio 1.0481 for 786 degrees of freedom yielded an indication of S chirality at a significance level of <0.005. To confirm this assignment, structure factors were calculated for several hundred Friedel pairs including the effect of anomalous scattering for Cu-K_α radiation and fifty of these pairs which were expected to show a large anomalous component were re-measured on an Enraf-Nonius CAD4-F diffractometer. The results are presented in Table 1 and fully confirm the assignment. Final positions and estimated standard deviations are presented in Table 2 for both molecules. Thermal parameters and a list of observed and calculated structure factors have been deposited as Supplementary Publication No. SUP 21846 (21 pp., 1 microfiche).*

DISCUSSION

Description of the Structure.—The conformations of racemic and of (+)-Octoclothepin are shown in stereoview with ellipsoids of thermal motion in Figure 1 and molecular geometries are presented in Table 3. Suffi-

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

[6] W. C. Hamilton, *Acta Cryst.*, 1965, **18**, 502.

TABLE 3

Molecular geometry

	Racemate	(+)-(S)-Enantiomer
(a) Distances (pm)		
C(1)–Cl	176	174
C(1)–C(2)	137	136
C(1)–C(15)	138	137
C(2)–C(3)	139	137
C(2)–H	108	99
C(3)–C(4)	139	140
C(3)–H	98	92
C(4)–S(5)	179	177
C(4)–C(14)	139	140
S(5)–C(6)	177	178
C(6)–C(7)	138	137
C(6)–C(11)	139	139
C(7)–C(8)	139	139
C(7)–H	112	95
C(8)–C(9)	138	137
C(8)–H	95	105
C(9)–C(10)	139	138
C(9)–H	112	95
C(10)–C(11)	140	140
C(10)–H	96	100
C(11)–C(12)	150	148
C(12)–C(13)	155	153
C(12)–H_1	104	93
C(12)–H_2	107	106
C(13)–C(14)	154	154
C(13)–N(16)	147	148
C(13)–H	104	95
C(14)–C(15)	139	138
C(15)–H	92	104
N(16)–C(17)	146	145
N(16)–C(21)	146	147
C(17)–C(18)	153	151
C(17)–H_1	90	104
C(17)–H_2	116	101
C(18)–N(19)	146	145
C(18)–H_1	109	99
C(18)–H_2	111	99
N(19)–C(20)	147	145
N(19)–C(22)	146	146
C(20)–C(21)	150	148
C(20)–H_1	99	96
C(20)–H_2	104	106
C(21)–H_1	91	107
C(21)–H_2	103	99
C(22)–H_1	108	99
C(22)–H_2	102	100
C(22)–H_3	107	93
(b) Angles (°)		
C(2)–C(1)–C(15)	123	121
C(2)–C(1)–Cl	118	118
C(15)–C(1)–Cl	120	121
C(1)–C(2)–C(3)	117	118
C(2)–C(3)–C(4)	121	122
C(3)–C(4)–S(5)	112	114
C(3)–C(4)–C(14)	120	118
S(5)–C(4)–C(14)	128	128
C(4)–S(5)–C(6)	103	104
S(5)–C(6)–C(7)	119	119
S(5)–C(6)–C(11)	119	118
C(7)–C(6)–C(11)	123	124
C(6)–C(7)–C(8)	118	118
C(7)–C(8)–C(9)	121	120
C(8)–C(9)–C(10)	120	121
C(9)–C(10)–C(11)	122	121
C(10)–C(11)–C(6)	117	116
C(10)–C(11)–C(12)	122	122
C(12)–C(11)–C(6)	121	122
C(11)–C(12)–C(13)	114	113
C(12)–C(13)–C(14)	117	117
C(12)–C(13)–N(16)	113	113
C(14)–C(13)–N(16)	107	108
C(13)–C(14)–C(15)	114	115
C(13)–C(14)–C(4)	127	127

TABLE 3 (*Continued*)

	Racemate	(+)-(*S*)-Enantiomer
C(4)–C(14)–C(15)	119	118
C(1)–C(15)–C(14)	120	122
C(13)–N(16)–C(17)	115	114
C(13)–N(16)–C(21)	114	113
C(17)–N(16)–C(21)	110	111
N(16)–C(17)–C(18)	109	109
C(17)–C(18)–N(19)	111	111
C(18)–N(19)–C(20)	109	109
C(18)–N(19)–C(22)	112	111
C(20)–N(19)–C(22)	111	110
N(19)–C(20)–C(21)	111	111
C(20)–C(21)–N(16)	110	112

Mean standard deviations: C–C $\leqslant$ 1, C–H $\leqslant$8 pm; C–C–C $\leqslant$0.8°

cient torsion angles for the construction of accurate molecular models are given in Table 4: for our standard numbering of atoms and labelling of rings see (I) and Part 1. The molecular packings, with hydrogen atoms excluded for clarity, are presented in Figures 2 and 3.

The central seven-membered ring folds about a line through sulphur and the CH_2 group C(12), whereby both this atom and the CH group carrying the piperazinyl substituent are coplanar with the chlorine-substituted benzene ring. In both structures, there is a significant and consistent deviation from sp^2 bond angles at the junction of these two rings, [S(5)–C(4)–C(14) 128, C(4)–C(14)–C(13) 127° in both structures] which we are at a loss to explain; the more so that the junction of the seven-membered ring with the unsubstituted benzene ring displays perfectly normal bond angles and no such distortions were observed in the three molecules described in Part 1.

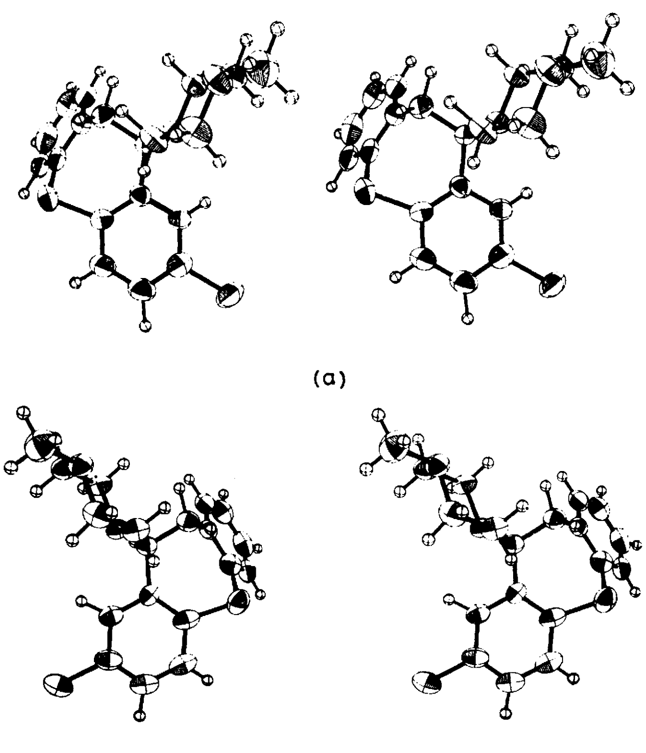


FIGURE 1 Stereo views, showing 50% probability ellipsoids of thermal motion of (a) racemic and (b) (+)-(*S*)-Octoclothepin, this latter in the correct absolute configuration

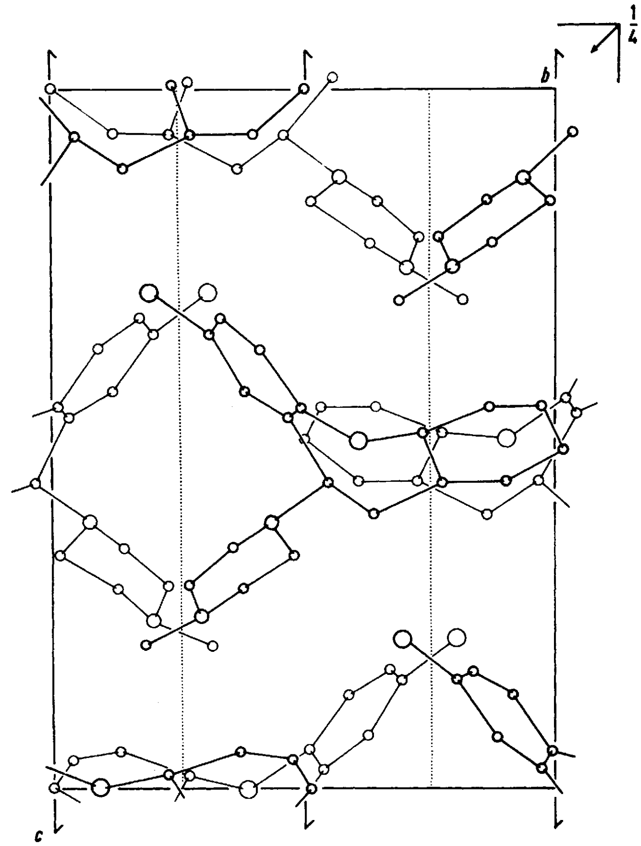


FIGURE 2 Moloecular packing of racemic Octoclothepin, omitting hydrogen atoms, viewed down the crystallographic *a* axis

There are many differences in detail between the conformation of Octoclothepin and that of, *e.g.* Loxapine, but the overall molecular shapes are remarkably similar. The dihedral angle between the planes of the two benzene rings is 117.1 (±) and 120.4° (+). The relaxation of the conditions for partial double bonding C(13)–N(16) by replacement of –N=C– (Loxapine, *etc.*) by $-CH_2-CH-$ (Octoclothepin) is reflected in the normal tetrahedral

TABLE 4

Sufficient torsion angles (°) to describe the molecular conformations

	Racemate	(+)-(*S*)-Enantiomer
C(4)–S(5)–C(6)–C(11)	65	63
S(5)–C(6)–C(11)–C(12)	−3	−2
C(6)–C(11)–C(12)–C(13)	−79	−80
C(11)–C(12)–C(13)–C(14)	64	68
C(12)–C(13)–C(14)–C(4)	−1	−6
C(13)–C(14)–C(4)–S(5)	−1	0
C(14)–C(4)–S(5)–C(6)	−49	−46
C(12)–C(13)–N(16)–C(17)	−62	−58
C(12)–C(13)–N(16)–C(21)	67	70
C(14)–C(13)–N(16)–C(17)	68	73
C(14)–C(13)–N(16)–C(21)	−163	−158

For comparison with the (+)-(*S*)-enantiomer, the torsion angles of the racemic structure correspond to the mirror image of the molecule represented by the fractional co-ordinates in Table 2. To get torsion angles corresponding to those co-ordinates, multiply column 1 above by −1.

angles about N(16) and the torsion angles about the C(13)–N(16) bond (Table 4) which are close to the normal staggered values for sp^3–sp^3 bonds. C(21) is *trans* to C(14) and the lone pair on N(16) is directed towards the hydrogen atom on C(15), which results in a more favourable relationship, in terms of non-bonded contacts, of the

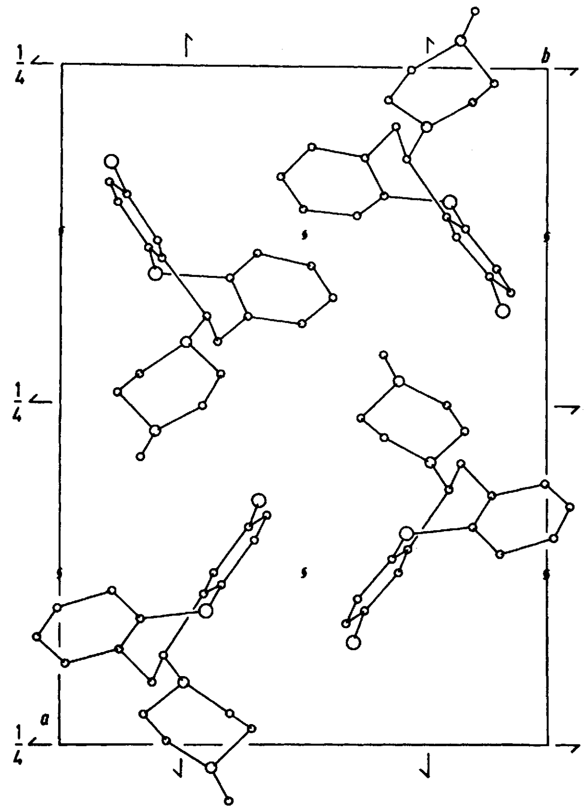


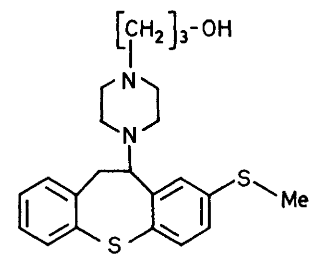
FIGURE 3 Molcular packing of (+)-Octoclothepin, omitting hydrogen atoms, viewed down the crystallographic *c* axis

piperazine ring to the chlorine-carrying benzene ring than in for example Loxapine.

One feature of broad conformational correspondence between Octoclothepin and the molecules discussed in Part 1 lies in the mutual relationship between the piperazine ring and that benzene ring which we have labelled B. The mean planes of these rings are almost parallel [angle between plane normals 17.6 (±) and 23.2° (+): *cf.* 27° Loxapine, Clozapine, and 22° HUF-2046] as was pointed out in Part 1, where partial double-bonding C(13)–N(16) was responsible for this aspect of the conformation. In Octoclothepin, free rotation about the C(13)–N(16) bond to minimise unfavourable non-bonded contracts combines fortuitously with a different conformation of the central seven-membered ring to produce an overall molecular shape which differs very little from that of the related molecules which are 12–13 unsaturated.

One further crystal structure of this type of molecule has recently been published; that of Oxyprothepin (II).[7] The dihedral angle between the planes of the benzene rings is 104° in this analogue of Octoclothepin, but the seven-membered heterocycle folds in the same way about a line through S and the methylene group, and displays the same distortion at the junction of the heterocycle and the substituted benzene ring. Further, the mean plane of the piperazine ring is also approximately parallel to the plane of the unsubstituted benzene ring.

We suggest that the practically constant shape of these molecules, all of which are potent antischizophrenic agents, observed in six crystal structures provides the best available basis for an understanding of neuroleptic drug action. We are convinced that the conformations we observe in the solid state dominate in any population



(II) Oxyprothepin

of conformers in solution (although conformational studies in various media would be more than welcome) and feel sure that examination of the wide range of predominantly flexible molecules currently prescribed for schizophrenia in the light of this conformation as template will lead to synthesis of improved agents for the treatment of this crippling disease.

We thank Dr. M. Protiva, Research Institute of Pharmacy and Biochemistry, Prague, for a gift of (±)-, (+)-, and (−)-Octoclothepin.

[4/2037 *Received, 4th October,* 1974]

7 M. H. J. Koch and G. Evrard, *Acta Cryst.*, 1974, **B30**, 2925.