and in the conformation of the third ring (Fig. 1); this probably reflects the differences in hydrogen-bond geometry between the two molecules. The third ring has the twist form in molecule *A* and the envelope form in molecule *B*. Another natural product, hirsutic acid (Comer & Trotter, 1967), contains the same group of three five-membered rings but with the opposite stereochemistry at C(10) and C(11). The H–C and H–O bond lengths are in the range 0·85–1·17 Å.

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The X-ray Crystal Structures of Loxapine {2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[*b*,*f*][1,4]oxazepine} and Amoxapine {2-Chloro-11-(1-piperazinyl)dibenz[*b*,*f*][1,4]oxazepine}

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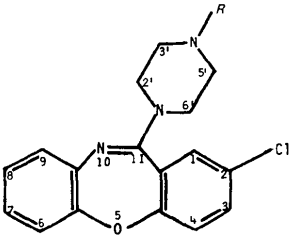
The X-ray crystal structures of the psychoactive agents loxapine {2-chloro-11-(4-methyl-1-piperazinyl)dibenz[*b*,*f*][1,4]oxazepine} and amoxapine {2-chloro-11-(1-piperazinyl)dibenz[*b*,*f*][1,4]-oxazepine} have been determined. Loxapine, $C_{18}H_{18}N_3OCl$, is monoclinic, space group $P2_1/c$, $a = 12{\cdot}953\ (3)$, $b = 10{\cdot}908\ (4)$, $c = 12{\cdot}584\ (4)$ Å, $\beta = 109{\cdot}53\ (3)°$; amoxapine, $C_{17}H_{16}N_3OCl$, is orthorhombic, space group $Pna2_1$, $a = 11{\cdot}765\ (4)$, $b = 9{\cdot}743\ (3)$, $c = 12{\cdot}990\ (2)$ Å. Both structures were solved by the heavy-atom method and refined by standard least-squares methods to $R = 0{\cdot}054$ for loxapine and $R = 0{\cdot}049$ for amoxapine. There are no significant differences between bond lengths and angles in the two structures. The orientation of the piperazine ring with respect to the dibenzoxazepine system is approximately the same in the two molecules. Low-temperature NMR spectra for the two compounds indicate a preferred orientation for the piperazine ring that is consistent with the X-ray results.

Introduction

The chemistry and structure–activity relationships of the psychoactive agents loxapine {2-chloro-11-(4-methyl-1-piperazinyl)dibenz[*b*,*f*][1,4]oxazepine} and amoxapine {2-chloro-11-(1-piperazinyl)dibenz-[*b*,*f*][1,4]oxazepine} have been reviewed by Schmutz (1975).* Loxapine, $C_{18}H_{18}N_3OCl$ ($R = CH_3$), differs structurally from amoxapine, $C_{17}H_{16}N_3OCl$, only by the presence of a methyl group at the 4 position of the piperazine ring. Physiologically, however, loxapine acts as a tranquilizing agent (Latimer, 1969) whereas amox-



$R = CH_3$, Loxapine
$R = H$, Amoxapine

* This article includes a preliminary note on an independent X-ray analysis of the loxapine structure. The data presented are in agreement with results reported here.

apine has antidepressant characteristics (Greenblatt & Osterberg, 1968). Therefore, detailed structural studies for the two compounds were of interest since they might provide information that would be of help in understanding the difference in activity.

Experimental

Irregularly shaped, lamellar, monoclinic crystals of loxapine were obtained by slow evaporation from solutions in methanol/water mixtures. Orthorhombic crystals of amoxapine, in the form of faintly yellow square tablets, were prepared by dissolving material in refluxing methanol and allowing the solution to stand for several days after cooling to room temperature.

Unit-cell dimensions for both compounds were determined with the least-squares refinement program *PARAM* (Stewart, Kundell & Baldwin, 1970) for the values of 2θ measured on the diffractometer for several carefully aligned reflections in the range $20° < \theta < 40°$. The refined cell parameters and other crystal data for the two compounds are collected in Table 1.

Intensities were measured for each crystal in the range $3° < \theta < 66°$, with the $\theta/2\theta$ scan method, on an Enraf–Nonius CAD-3 computer-controlled diffractometer. Ni-filtered Cu $K\alpha$ radiation from a fine-focus tube was used with pulse-height analysis of the diffracted beam to provide further wavelength discrimination.

Neither crystal showed any significant reduction in scattering power as a result of exposure to X-rays. An approximate absorption correction was obtained by measuring the variation of intensity as a function of azimuthal angle ϕ (at $\chi = 90°$) of a carefully aligned reflection. For loxapine, the 206 reflection showed a variation of $\pm 4\%$ in the range $0° < \phi \leq 360°$; the reflection 400 of amoxapine showed a variation of $\pm 10\%$ over the same range. After correction for absorption, Lorentz and polarization effects, normalized structure factors $E(hkl)$ were computed for each crystal. In both cases there was good agreement between the observed and appropriate theoretical distributions of $E(hkl)$ values for centrosymmetric and noncentrosymmetric structures.

Table 1. *Crystal data*

	Loxapine	Amoxapine
Formula	$C_{18}H_{18}N_3OCl$	$C_{17}H_{16}N_3OCl$
M_r	327·8	313·8
Space group	Monoclinic, $P2_1/c$	Orthorhombic $Pna2_1$
a	12·953 (3) Å	11·765 (4) Å
b	10·908 (4)	9·743 (3)
c	12·584 (4)	12·990 (2)
β	109·53 (3)°	90·0°
Cell volume	1675·7 Å^3	1489·0 Å^3
Z	4	4
ρ_{calc}	1·299 g cm^{-3}	1·399 g cm^{-3}
ρ_{obs}	1·30	1·40
Reflections measured	2933	1354
unobserved $[I < 2·5\sigma(I)]$	948	155
Crystal size	160 × 240 × 320 μm	150 × 260 × 400 μm

Structure determination

Both structures were solved by the heavy-atom method. The Cl positions were derived from Patterson syntheses computed with the quantities $[|E(hkl)|^2 - 1]$ as coefficients.

For loxapine, space group $P2_1/c$, the Cl atom was found to be at $y = 0$. An electron density map was computed in which the signs of the terms were determined by the Cl contributions, and amplitudes were obtained from the observed structure factors by Sim weighting (Sim, 1959, 1960; Blow & Crick, 1959). Coordinates for all atoms of the dibenzoxazepine system were found without difficulty. Peaks for the piperazine ring could not be chosen unambiguously because of the false mirror plane generated as a result of the special nature of the Cl contributions ($F_{Cl} = 0$ for $k + l = 2n + 1$). Peaks for the remaining fragment of the structure were found in an electron density synthesis with the signs based on the contributions of Cl and the dibenzoxazepine system.

In amoxapine, space group $Pna2_1$, the Cl atom was set arbitrarily at $z = 0$. An electron density map calculated with Cl phases and coefficients weighted by the Sim method contained peaks corresponding to all the nonhydrogen atoms of the structure.

Refinement

Both structures were refined by the least-squares method applied to F values with the *CRYLSQ* program of the X-RAY 70 system (Stewart, Kundell & Baldwin, 1970). Atomic scattering factors for the calculations were taken from *International Tables for X-ray Crystallography* (1968).

Loxapine

Initial refinement with isotropic thermal parameters and a block-diagonal approximation with unit weights reduced the reliability index R $(= \Sigma||F_o| - |F_c||/\Sigma|F_o|)$ to 0·14. Further anisotropic block-diagonal refinement gave $R = 0·09$, at which point peaks corresponding to all the H atoms could be distinguished in an electron density difference map. Idealized H coordinates were calculated with the non-H parameters at this stage. H atoms were then included in structure factor calculations with anisotropic thermal parameters equal to those of the atoms to which they

Table 2. *Fractional atomic coordinates for nonhydrogen* ($\times 10^4$) *and hydrogen* ($\times 10^3$) *atoms*

Standard deviations are given in parentheses. The B_{iso} values for nonhydrogen atoms correspond to the last isotropic refinement cycle.

(*a*) Loxapine

	x	*y*	*z*	B_{iso} (Å²)
Cl	1931 (1)	12 (1)	1299 (1)	5·64
C(2)	2449 (3)	777 (3)	365 (2)	4·41
C(3)	3552 (3)	1076 (3)	712 (3)	4·96
C(4)	3965 (2)	1642 (3)	9960 (3)	4·50
C(4a)	3273 (2)	1908 (3)	8883 (2)	4·80
C(11a)	2165 (2)	1648 (2)	8539 (2)	3·39
C(1)	1749 (2)	1066 (3)	9298 (2)	3·73
C(11)	1452 (2)	1894 (2)	7357 (2)	3·45
N(10)	1703 (2)	1641 (2)	6466 (2)	3·55
C(9a)	2733 (3)	1189 (3)	6527 (2)	3·77
C(5a)	3726 (2)	1580 (3)	7306 (2)	4·03
O(5)	3717 (1)	2445 (2)	8129 (2)	4·26
C(6)	4729 (2)	1159 (3)	7280 (3)	4·81
C(9)	2787 (3)	368 (3)	5692 (2)	4·66
C(8)	3785 (3)	9934 (3)	5674 (3)	5·89
N(1′)	402 (2)	2293 (2)	7213 (2)	3·76
C(6′)	212 (2)	3250 (3)	7955 (2)	4·10
C(5′)	9033 (2)	3207 (3)	7930 (2)	3·91
N(4′)	8289 (2)	3338 (2)	6779 (2)	4·15
C(3′)	8469 (2)	2364 (3)	6069 (2)	4·56
C(2′)	9637 (2)	2380 (3)	6055 (2)	4·71
C(7)	4753 (3)	317 (3)	6457 (3)	5·20
C(Me)	7150 (2)	3356 (3)	6726 (3)	5·76

	x	*y*	*z*		*x*	*y*	*z*
H(C3)	404	88	1150	H(C3′)*a*	−168	149	639
H(C4)	476	186	1019	H(C3′)*b*	−208	248	522
H(C1)	95	86	907	H(C5′)*a*	−109	395	844
H(C6)	543	146	785	H(C5′)*b*	−110	234	827
H(C7)	547	0	644	H(C6′)*a*	75	310	881
H(C8)	380	−67	508	H(C6′)*b*	37	414	767
H(C9)	209	9	510	H(CMe)*a*	−308	258	692
H(C2′)*a*	−23	322	567	H(CMe)*b*	−324	364	591
H(C2′)*b*	−25	161	557	H(CMe)*c*	−308	382	725

(*b*) Amoxapine

	x	*y*	*z*	B_{iso} (Å²)
Cl	1280 (1)	1612 (1)	0 (0)*	3·27
C(2)	1921 (3)	2804 (3)	817 (2)	2·37
C(3)	3055 (3)	3151 (3)	642 (3)	3·08
C(4)	3535 (3)	4156 (4)	1255 (3)	2·98
C(4a)	2917 (3)	4751 (3)	2036 (2)	2·03
C(11a)	1818 (3)	4363 (3)	2252 (2)	2·23
C(1)	1305 (3)	3379 (3)	1613 (2)	2·52
C(11)	1172 (3)	4976 (3)	3131 (3)	2·36
N(10)	1170 (2)	6253 (3)	3384 (2)	2·31
C(9a)	1806 (3)	7241 (3)	2853 (3)	2·38
C(5a)	2911 (3)	7043 (3)	2490 (2)	2·45
O(5)	3436 (2)	5756 (2)	2629 (2)	2·80
C(6)	3536 (3)	8072 (4)	2019 (3)	2·88
C(9)	1349 (3)	8566 (3)	2764 (3)	3·36
C(8)	1962 (4)	9610 (3)	2296 (3)	3·57
N(1′)	446 (2)	4076 (3)	3645 (2)	2·39
C(6′)	916 (3)	2771 (3)	4006 (3)	2·89
C(5′)	−38 (4)	1789 (4)	4252 (4)	4·31
N(4′)	−757 (3)	2404 (4)	5048 (3)	4·41
C(3′)	−1267 (3)	3669 (4)	4654 (3)	4·30
C(2′)	−331 (3)	4693 (4)	4403 (3)	3·34
C(7)	3046 (4)	9367 (4)	1928 (3)	3·59

* Invariant for Cl.

Table 2 (*cont.*)

	x	*y*	*z*	B_{iso} (Å²)
H(C3)	351	266	8	3·08
H(C4)	434	444	113	2·98
H(C1)	48	311	173	2·52
H(C6)	434	785	172	2·88
H(C7)	351	1015	162	3·59
H(C8)	160	54	19	3·57
H(C9)	56	876	305	3·36
H(C2′)*a*	15	490	511	3·35
H(C2′)*b*	−66	565	412	3·35
H(C3′)*a*	−186	412	524	4·30
H(C3′)*b*	−180	350	396	4·30
H(N4′)	−143	166	525	4·40
H(C5′)*a*	31	82	452	4·30
H(C5′)*b*	−54	157	356	4·30
H(C6′)*a*	143	294	468	2·90
H(C6′)*b*	145	233	340	2·90

were bonded. One cycle of full-matrix anisotropic refinement on non-H atoms led to a final R of 0·054; final positional and thermal parameters are shown in Tables 2 and 3.*

Amoxapine

Isotropic, block-diagonal refinement gave $R = 0{\cdot}064$ for observed reflections and $R = 0{\cdot}080$ for all reflections. The space group $Pna2_1$ is polar so that, even though the amoxapine molecule is not chiral, the anomalous dispersion effects of Cl should be taken into account for proper refinement of the structure (Cruickshank & McDonald, 1967). Structure factors for all reflections gave $R_+ = 0{\cdot}0865$ when the imaginary component of the Cl scattering factor was included with positive sign; with the negative sign $R_- = 0{\cdot}0867$. After applying the Hamilton (1965) significance test it was concluded that the original assignment of data to the $(+h,+k,+l)$ octant was correct. Anisotropic refinement of the data, including the anomalous dispersion effect and keeping the z coordinate of Cl fixed, gave $R = 0{\cdot}077$ for all data. Positions for H atoms were calculated and isotropic temperature parameters of the atoms to which they were bonded were assigned to them. When the H atoms were included, the reliability index for all data was $R = 0{\cdot}067$, which was reduced to $R = 0{\cdot}049$ after a final anisotropic refinement cycle for the non-H atoms. Final positional and thermal parameters are shown in Tables 2 and 3.*

ORTEP drawings (Johnson, 1965) of loxapine and amoxapine molecules with 50% probability thermal ellipsoids are shown in Fig. 1.

* Lists of structure factors for both compounds have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32201 (31 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 3. *Anisotropic thermal parameters* ($\times 10^2$)

Estimated standard deviations are given in parentheses. The temperature factor expression used is $\exp[-\frac{1}{4}(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* + 2B_{23}klb^*c^* + 2B_{13}hla^*c^*)]$.

	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
(*a*) Loxapine						
Cl	9·41 (6)	5·74 (4)	4·75 (4)	0·00 (4)	2·74 (4)	1·15 (4)
C(2)	5·9 (2)	4·1 (2)	3·5 (1)	0·7 (1)	1·6 (1)	0·1 (1)
C(3)	5·2 (2)	5·4 (2)	4·2 (2)	1·1 (1)	0·2 (1)	−0·3 (1)
C(4)	4·3 (2)	5·8 (2)	4·4 (1)	0·4 (1)	0·5 (1)	−0·4 (1)
C(4a)	4·0 (2)	4·1 (1)	4·3 (2)	0·1 (1)	1·1 (1)	−0·1 (1)
C(11a)	3·6 (1)	3·8 (1)	3·4 (1)	0·2 (1)	0·8 (1)	−0·0 (1)
C(1)	4·7 (2)	4·1 (1)	3·7 (1)	0·2 (1)	1·1 (1)	−0·5 (1)
C(11)	3·4 (1)	3·9 (1)	3·7 (1)	−0·1 (1)	0·9 (1)	−0·0 (1)
N(10)	4·1 (1)	4·7 (1)	3·8 (1)	0·3 (1)	1·6 (1)	0·1 (1)
C(9a)	3·9 (2)	4·7 (2)	4·1 (1)	0·7 (1)	1·8 (1)	0·8 (1)
C(5a)	4·7 (1)	4·5 (2)	4·6 (1)	0·4 (1)	2·1 (1)	0·6 (1)
C(6)	4·2 (2)	6·9 (2)	5·6 (2)	1·1 (1)	2·2 (1)	1·8 (2)
C(9)	6·2 (2)	5·7 (2)	4·5 (2)	0·7 (1)	2·8 (1)	0·0 (1)
C(8)	6·6 (2)	7·0 (2)	5·6 (2)	1·4 (2)	3·4 (2)	0·5 (2)
N(1′)	3·6 (1)	5·6 (1)	3·4 (1)	0·7 (1)	0·6 (1)	−0·4 (1)
C(6′)	4·0 (1)	4·6 (2)	4·4 (1)	0·5 (1)	1·1 (1)	−0·5 (1)
C(5′)	4·1 (1)	4·7 (2)	4·3 (1)	0·3 (1)	1·1 (1)	−0·4 (1)
N(4′)	3·2 (1)	4·8 (1)	5·4 (1)	0·3 (1)	1·1 (1)	0·0 (1)
C(3′)	3·9 (2)	6·7 (2)	4·1 (1)	0·6 (1)	0·5 (1)	−0·3 (1)
C(2′)	3·8 (1)	7·9 (2)	3·5 (1)	0·7 (1)	0·4 (1)	−0·1 (1)
C(7)	5·7 (2)	8·1 (2)	5·8 (2)	2·2 (2)	3·4 (2)	1·7 (2)
C(Me)	4·1 (2)	7·5 (2)	8·1 (2)	0·5 (1)	2·3 (1)	−0·4 (2)
O(5)	4·1 (1)	5·0 (1)	5·4 (1)	−0·5 (1)	1·5 (1)	−0·0 (1)
(*b*) Amoxapine						
Cl	4·62 (4)	3·53 (4)	2·41 (3)	−0·84 (3)	0·38 (4)	−1·05 (3)
C(2)	3·6 (2)	2·4 (1)	2·0 (1)	−0·2 (1)	−0·1 (1)	−0·2 (1)
C(3)	3·7 (2)	3·4 (2)	2·4 (2)	0·5 (1)	0·5 (1)	−0·1 (1)
C(4)	2·7 (2)	3·5 (2)	2·8 (1)	−0·1 (1)	0·4 (1)	−0·3 (1)
C(4a)	2·4 (1)	2·6 (1)	2·2 (1)	0·4 (1)	−0·2 (1)	−0·0 (1)
C(11a)	2·7 (1)	2·4 (1)	1·9 (1)	0·5 (1)	−0·3 (1)	−0·1 (1)
C(1)	3·0 (1)	2·7 (1)	2·1 (1)	0·0 (1)	0·3 (1)	−0·1 (1)
C(11)	2·7 (1)	2·7 (1)	2·0 (1)	0·3 (1)	−0·2 (1)	−0·0 (1)
N(10)	2·9 (1)	2·5 (1)	2·5 (1)	−0·0 (1)	0·2 (1)	−0·5 (1)
C(9a)	2·8 (1)	2·6 (2)	2·1 (1)	−0·3 (1)	−0·2 (1)	−0·4 (1)
C(5a)	3·0 (1)	2·7 (1)	2·2 (1)	−0·2 (1)	−0·5 (1)	−0·2 (1)
O(5)	2·6 (1)	3·1 (1)	2·8 (1)	0·2 (1)	−0·4 (1)	−0·4 (1)
C(6)	4·0 (2)	3·5 (2)	3·0 (1)	−0·9 (1)	−0·1 (2)	0·1 (1)
C(9)	4·0 (2)	3·1 (2)	2·8 (1)	0·4 (1)	−0·4 (2)	−0·5 (1)
C(8)	4·9 (2)	2·8 (2)	3·6 (2)	0·1 (1)	−0·5 (2)	0·2 (1)
N(1′)	3·1 (1)	2·5 (1)	2·4 (1)	0·0 (1)	0·7 (1)	−0·2 (1)
C(6′)	3·8 (2)	2·9 (2)	2·8 (2)	0·4 (1)	0·3 (1)	0·5 (1)
C(5′)	5·7 (2)	3·3 (2)	4·5 (2)	−0·8 (2)	0·7 (2)	0·6 (2)
N(4′)	5·2 (3)	4·6 (2)	4·2 (1)	−0·9 (1)	1·1 (2)	0·9 (2)
C(3′)	3·8 (2)	4·8 (2)	4·2 (2)	−0·7 (2)	1·1 (2)	0·1 (1)
C(2′)	3·2 (2)	3·7 (2)	3·3 (2)	0·0 (1)	1·4 (2)	−0·6 (2)
C(7)	5·2 (2)	3·1 (2)	3·7 (2)	−0·8 (2)	−0·1 (2)	0·3 (1)

Discussion

Bond lengths and angles derived for loxapine and amoxapine molecules are shown in Fig. 2. (In this figure, as in other figures and in the text, numerical values in roman type correspond to loxapine while those in italic type are for amoxapine.)

There appear to be no significant differences between bond lengths and angles in the two molecules. In the aromatic rings the average bond length in both compounds is 1·387 (10) Å, which is in good agreement with the literature value of 1·395 (3) Å (Bowen, 1968). The average C(2)—Cl bond length is 1·748 (10) Å, which is longer than the expected 1·70 (3) Å but is comparable,

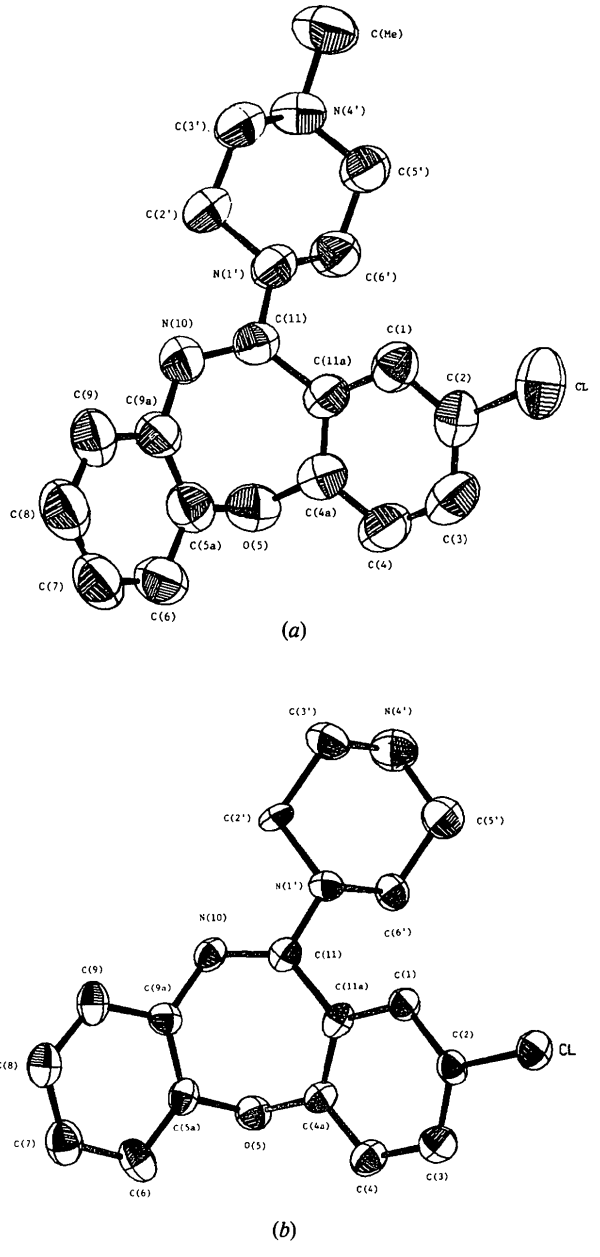


Fig. 1. *ORTEP* drawings of (*a*) loxapine and (*b*) amoxapine, showing 50% probability thermal ellipsoids.

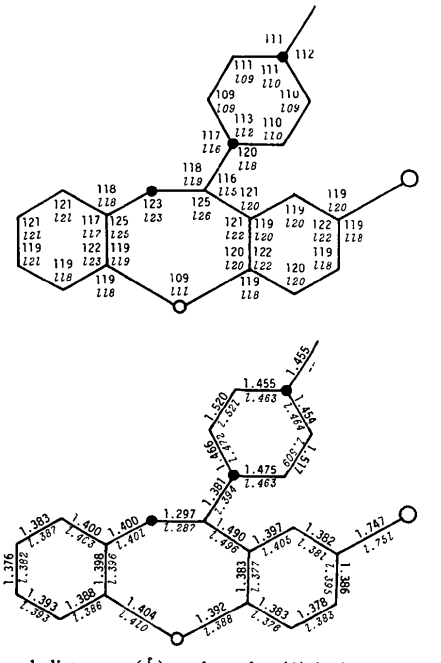


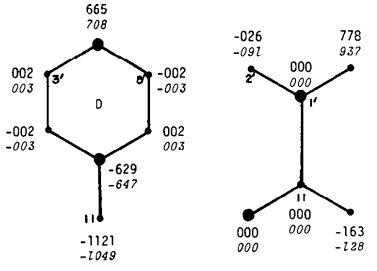
Fig. 2. Bond distances (Å) and angles (°) in loxapine and amoxapine (data for amoxapine in italics). The average estimated standard deviations in the structures are 0·004 Å in bond lengths and 0·3° in bond angles.

for example, with the value of 1·737 (7) Å found in *o*-chlorobenzoic acid (Ferguson & Sim, 1961). Bond distances in the piperazine ring do not differ significantly from those found in the structure of piperazine hexahydrate (Schwarzenbach, 1968). The angles within the ring are approximately tetrahedral, except at N(1′) where in both structures the internal angle is significantly greater [112·5 (2), *112·1 (5)*°]. The external angles at N(1′) in loxapine are substantially larger than those at N(4′), indicating that there may be some electron delocalization into the N(1′)–C(11) bond, although this distance, in both structures, lies within the expected range for C(sp^2)–N(sp^3) bonds (Lide, 1962). In loxapine, the flattening at N(1′), from an approximate tetrahedral configuration, is revealed when the deviations of N(1′) and N(4′) from the planes through the atoms C(2′), C(6′), C(11) and C(3′), C(5′), C(Me) are compared. The deviation for N(1′) is −0·25 while that for N(4′) is 0·44 Å. In amoxapine, N(1′) lies at approximately −0·30 Å from the plane defined by C(2′), C(6′), C(11). The configuration at N(1′) in amoxapine is, therefore, somewhat more tetrahedral than in loxapine. This effect is also demonstrated by comparing deviations from the least-squares plane through C(2′), C(3′), C(5′), C(6′). The deviations of N(1′) from this plane are essentially the same (−0·629, *−0·647* Å), whereas the deviations for C(11) differ by 0·07 (−1·121, *−1·049* Å). In both structures the piperazine ring is in the chair conformation and attached equatorially to C(11). The methyl group in loxapine and the H atom in amoxapine are attached equatorially at N(4′). The four C atoms of the ring are coplanar within experimental error in both structures. Details concerning the deviations of atoms from certain least-squares planes are shown in Fig. 3. Torsion angles (Klyne & Prelog, 1960) for the two rings are shown in Fig. 4; the angles found in amoxapine are larger than those in loxapine and are reflected in the greater deviation in amoxapine of atoms N(1′) and N(4′) from the

planes containing the four C atoms. The conformation of the piperazine ring with respect to the oxazepine ring was analyzed by computing the torsion angles around the C(11)–N(1′) bond and by comparing the deviations of atom C(2′) from least-squares planes through atoms N(10), C(11), N(1′). The torsion angles are 1·2 and *3·9*° respectively, and the deviations from the least-squares planes are –0·026 and *–0·096* Å. Thus, in both structures, the atoms N(10), C(11), N(1′) and C(2′) are almost coplanar. To illustrate this conformational feature, a projection was taken along the C(11)–N(1′) bond (Fig. 5). As a result of the conformation of the piperazine ring, the H atoms attached to C(2′) are almost completely staggered with respect to the C(11)–N(10) bond. The contact distances for H(C2′)*a* and H(C2′)*b* with respect to N(10) are (2·924, *2·865* Å) and (2·398, *2·429* Å) respectively. The latter distances are close to normal van der Waals contacts. The conformation of the piperazine ring leads to contact distances (2·468, *2·562* Å) between H(C1) and H(C6′)*a* in the two structures which are significantly larger than the van der Waals distance. The deviations of atoms in the ring from the plane through N(10), C(11), N(1′) are also shown in Fig. 5. The substantial differences observed again illustrate the more tetrahedral nature of N(1′) in amoxapine than in loxapine.

Bond lengths in the oxazepine rings do not show unusual features when compared with individual values obtained from other structures (Abrahams, 1956; Fraterman & Romers, 1971; Cox & Jeffrey, 1951). In structures containing the –N=C< group, the bond length varies between 1·256 and 1·305 Å (Orioli, Lingafelter & Brown, 1964; Jensen & Jerslev, 1967). Distances found in the present structures are in this range and are short enough to be considered as almost completely double bond in character. The range of values for a pure C(sp^2)–C(sp^2) bond is 1·47–1·48 Å (Lide, 1962), and the values found for the C(11)–C(11a) bonds are in this range. The two C–O distances appear to be single bonds when compared with typical values listed in *International Tables for X-ray Crystallography* (1968).

The overall geometries of the dibenzoxazepine ring systems were studied by calculating least-squares planes through various sets of atoms. Details for the planes and the deviations of the atoms from the planes are shown in Fig. 6. In both structures the aromatic rings are flat within experimental error. The Cl atom appears to be displaced slightly, but significantly, from ring *C*. Atoms N(10), O(5) and C(11) are all displaced slightly from the aromatic rings *A* and *C*. The oxazepine ring *B* is in the boat conformation with atoms C(4a), C(11a), C(5a) and C(9a) coplanar. Atoms N(10) and C(11) form the stern of the boat; in amoxapine the atoms are displaced by equal amounts from the reference plane so that ring *B* forms a symmetrical boat, whereas in loxapine the deviations of N(10) and C(11) are unequal and consequently the ring is slightly unsymmetrical. This lack of symmetry is also reflected in the torsion angles around the ring (Fig. 4). In particular, the torsion angle around the N(10)–C(11) bond is –5·4 in loxapine compared with *–0·9*° in amox-



	Loxapine	Amoxapine
Ring D	C2′ C3′ C5′ C6′	
Plane*	-0.23x+10.06y-4.51z = -0.33	3.56x-0.28y+12.38z = 5.20
Direction cosines of normal	(-0.1550, 0.9219, -0.4105)	(0.3025, -0.0290, 0.5927)
	N10 C11 N1′	
	4.17x+10.32y-1.76z = 1.27	8.39x-1.73y+8.82z = 2.88
	(0.3097, 0.9462, -0.0359)	(0.7127, -0.1774, 0.6787)

*Planes and direction cosines are expressed in direct space coordinates.

Fig. 3. Least-squares planes for the piperazine ring. Deviations of atoms from the planes are shown (Å × 10^3) (data for amoxapine in italics).

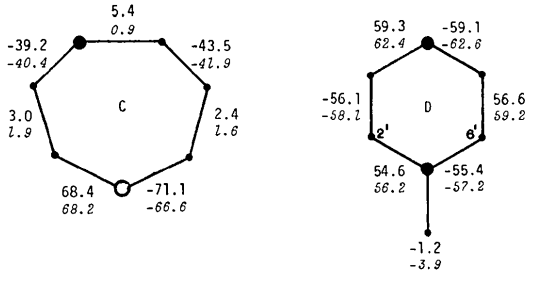
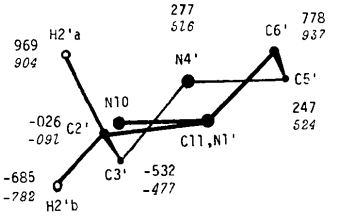


Fig. 4. Torsion angles (°) in the oxazepine and piperazine rings (data for amoxapine in italics).



	Loxapine	Amoxapine
α	1.2°	*3.9*°
β	37.7°	*46.4*°

Fig. 5. A view of the piperazine ring projected along the C(11)–N(1′) bond. Deviations (Å × 10^3) of atoms from the plane through C(11), N(1′), N(10) are shown. The quantity α is the dihedral angle between the reference plane and the plane defined by C(11), N(1′), C(2′); β is the dihedral angle between the reference plane and the plane defined by C(11), N(1′), C(6′).

apine. The torsion angles around the O(5)–C(4a) bond are also substantially different (−71·1, *−66·6°*) and, as a result of this difference, the deviations of atom C(4) from the least-squares plane through C(4a), C(5a), C(9a), C(11a) differ by 0·13 (−0·704, *−0·575* Å). In loxapine, the dibenzoxazepine system is folded so that the angle between the normals to the benzene rings is 113·7°; the corresponding angle for amoxapine is *119·5°*.

There are no intermolecular hydrogen bonds in either structure so that in both cases packing is determined by van der Waals forces. A projection of the loxapine structure along **a** is shown in Fig. 7. The molecules lie in the cell so that the dibenzoxazepine ring systems are roughly parallel to **c** and form chains around $x = \frac{1}{4}$ and $x = \frac{3}{4}$; the piperazine rings lie close to the $x = 0$ plane in such a way that there is overlap between pairs of piperazine rings.

The packing of molecules in the amoxapine structure projected along **a** is shown in Fig. 8. In the projection along **c**, the piperazine rings are related by the twofold screw axis parallel to z. The dibenzoxazepine systems lie parallel to y and partially overlap each other in the z direction. Thus the structure may be considered to consist of layers of overlapping dibenzoxazepine systems running parallel to the y direction, separated by layers containing only piperazine rings which occur in pairs related by the screw axis.

A survey of contact distances ≤4·0 Å reveals that there are no unusually short contacts in either structure. In amoxapine the shortest contact distance is between the O atom of the molecule at (x,y,z) and the Cl atom of the molecule at the symmetry-related position $(\frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} + z)$. The separation is 3·19 (1) Å which

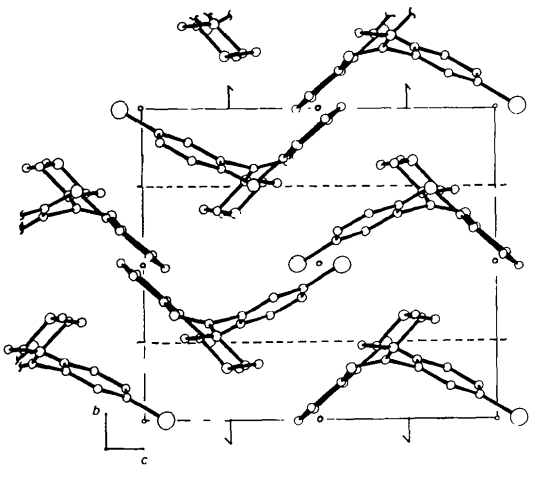


Fig. 7. Loxapine: projection of the structure along **a**.

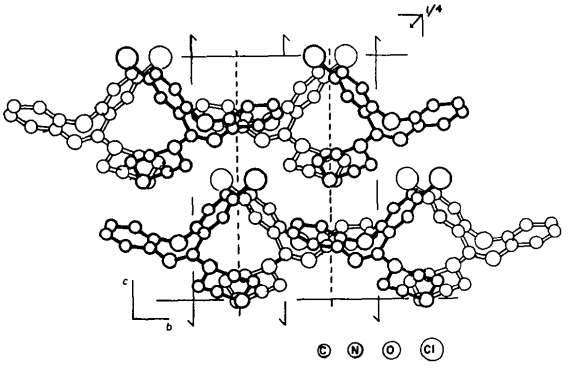
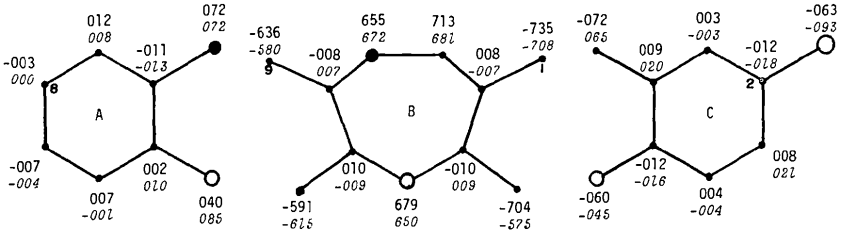


Fig. 8. Amoxapine: projection of the structure along **a**.



	Loxapine	Amoxapine
Ring A	C5a C6 C7	C8 C9 C9a
Plane*	3.30x+8.27y-8.19z = -3.45	4.45x+2.48y+11.56z = 5.91
Direction cosines of normal	(0.0421, 0.7580, -0.6369)	(0.3777, 0.2545, 0.8800)
Ring B	C5a C9a	C4a C11a
	-1.73x+10.37y-2.78z = -1.04	3.37x-2.45y+12.01z = 2.26
	(-0.2332, 0.9503, -0.2986)	(0.2865, -0.2510, 0.9236)
Ring C	C1 C2 C3	C4 C4a C11a
	-4.07x+9.73y+5.16z = 5.12	3.72x-6.97y+8.09z = -0.56
	(-0.1996, 0.8923, 0.3437)	(0.3160, -0.7153, 0.6231)

*Planes and direction cosines are expressed in direct space coordinates

Fig. 6. Least-squares planes in the dibenzoxazepine system. Deviations of the atoms from the planes are shown (Å × 10^3).

is not significantly shorter than the van der Waals O—Cl contact of 3·20 Å (Bondi, 1964).

A survey of the bond distances and angles in the two structures reveals no major differences in molecular geometry that might help explain the different physiological effects displayed by the two compounds. The most striking similarity between the two molecules is the conformation of the piperazine ring with respect to the oxazepine ring. In both cases the bonds N(1')—C(2') and N(10)—C(11) are almost coplanar, though in neither structure are there packing constraints that would lead to this arrangement. As has already been pointed out, this conformation leads to an arrangement that does not involve any overcrowding effects. On the other hand, a minimum steric interaction might be expected if the piperazine ring were oriented with the N(10)—C(11) bond perpendicular to the plane through the C atoms of the ring. Since this does not occur it is tempting to suggest that the observed orientations represent preferred conformations for these molecules. To test this hypothesis NMR studies were carried out on both compounds at low temperatures.

The NMR spectra of loxapine and amoxapine, at ambient temperature in $CDCl_3$, indicate a rapidly interconverting piperazine ring with a complex *AA'BB'* pattern for the ring protons. Multiplets occur at 2·52 and 3·56δ in loxapine and at 2·99 and 3·49δ in amoxapine. Loxapine at −70°C in $CDCl_3$ (just before freezing) shows separate equatorial protons at 4·33 and 3·60δ. Amoxapine under similar conditions shows separate equatorial protons at 4·15 and 3·58δ.

These separations indicate preferred conformations having one equatorial proton *syn* to the C=N and the other *anti* to the C=N of the benzoazepine system. This interpretation of the NMR results is consistent with the conformations observed in the two crystal structures. It has been suggested that preferred conformations of this kind may be stabilized by overlap of unshared electrons with the π cloud of an adjacent double-bond system (Lynch & Cole, 1966).

The assistance of Mr G. O. Morton in running and interpreting the low-temperature NMR spectra is gratefully acknowledged.

Note added in proof:—The complete report of the structure of loxapine (as an orthorhombic polymorph) referred to by Schmutz (1975) has now been published (Petcher & Weber, 1976).

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