Table 2. *Atom displacements from the best planes of the phenylene rings in 2-methoxyphenothiazine*

| Plane 1 | | Plane 2 | |
|---|---|---|---|
| S* | 0·172 (3) | S* | 0·123 (3) |
| N* | 0·024 (7) | N* | 0·027 (7) |
| C(1) | −0·014 (9) | C(7) | −0·008 (8) |
| C(2) | 0·019 (9) | C(8) | 0·003 (9) |
| C(3) | −0·006 (9) | C(9) | −0·002 (10) |
| C(4) | −0·025 (10) | C(10) | 0·010 (11) |
| C(5) | 0·017 (9) | C(11) | −0·014 (9) |
| C(6) | −0·003 (9) | C(12) | 0·014 (9) |
| O* | 0·045 (7) | H(N)* | 0·013 |
| C(13)* | 0·26 (1) | | |
| H(N)* | 0·077 | | |
| $\chi^2=5{\cdot}4$ | | $\chi^2=3{\cdot}3$ | |

* Atoms not included in best-plane calculations.

calculation which excludes the N and S atoms gives more planar values, indicating the small displacement of the S and N atoms from the phenylene planes is always toward the outside of the fold.

All of the bond distances and bond angles of the $C_{12}SN$ phenothiazine framework are within the range of values found for a number of other phenothiazine structures, and the methoxy group parameters parallel those of a methoxyphenothiazine drug molecule (Phelps & Cordes, 1974). As shown in Table 2 and Fig. 1, the C and O atoms of the methoxy group are nearly coplanar with the phenylene ring to which the group is attached.

The crystal packing does not result in any intermolecular contacts shorter than the sum of the van der Waals radii for the atoms involved, with the minor exception of the H(N)–N′ (at $-x,y-\frac{1}{2},\frac{1}{2}-z$) distance of 2·55 Å which is 0·15 Å shorter than the non-bonding distance; the N···N′ distance of 3·51 Å is considerably longer than the separation usually attributed to the N–H···N hydrogen bond (Pimentel & McClellan, 1960), however.

We would like to thank the donors of the Petroleum Research Foundation, administered by the American Chemical Society, the University of Arkansas Research Committee, and the fellowship program of the Phillips Petroleum Company, for support of this work.

## References

Bell, J. D., Blount, T. F., Briscoe, O. V. & Freeman, H. C. (1968). *Chem. Commun.* pp. 1656–1657.

Hamilton, W. C. (1965). *Acta Cryst.* **18**, 502–510.

*International Tables for X-ray Crystallography* (1975). Vol. IV. Birmingham: Kynoch Press.

Malrieu, J. P. & Pullman, B. (1964). *Theoret. Chim. Acta*, **2**, 293–301.

Marsau, P. & Gauthier, J. (1973). *Acta Cryst.* B**29**, 992–998.

Phelps, D. P. & Cordes, A. W. (1974). *Acta Cryst.* B**30**, 2812–2816.

Pimentel, G. C. & McClellan, A. L. (1960). *The Hydrogen Bond*, p. 288. San Francisco: Freeman.

Waser, J., Marsh, R. E. & Cordes, A. W. (1973). *Acta Cryst.* B**29**, 2703–2708.

---

*Acta Cryst.* (1975). B**31**, 2544

# *N,N′*-Bis-(3-chloropropionyl)piperazine

By Tien-Ming Ko and J. William Moncrief

*Department of Chemistry, Emory University, Atlanta, Georgia* 30322, *U.S.A.*

(*Received* 29 *April* 1975; *accepted* 30 *April* 1975)

**Abstract.** $C_{10}H_{16}N_2O_2Cl_2$; monoclinic, $P2_1/c$, $a=11{\cdot}371(23)$, $b=7{\cdot}741(11)$, $c=8{\cdot}245(18)$ Å, $\beta=60{\cdot}8(2)^\circ$; $D_c=1{\cdot}40$, $D_x=1{\cdot}42$ g cm$^{-3}$, $Z=2$. The structure, refined to $R_1=0{\cdot}065$, shows considerable steric strain, which may be connected with the oncolytic activity of the compound.

**Introduction.** Colorless crystals of the title compound, recrystallized from water, were obtained from P. G. Huffman, Abbott Laboratory, Chicago, Illinois. Systematic absences $0k0$, $k=2n+1$, and $h0l$, $l=2n+1$ uniquely identified the space group as $P2_1/c$. Two axes of diffraction data $(a,b)$ were collected with Ni-filtered Cu $K\alpha$ radiation on an automated Supper–Pace diffractometer possessing Weissenberg geometry. After Lp corrections the data were correlated (Simpson, 1963) to give 1092 independent reflections, 750 of which were considered observed, having $I>2\sigma(I)$ (Parker, Flynn & Boer, 1968). An additional 152 high-angle reflections accessible with Cu $K\alpha$ radiation were not measured owing to physical limitations of the diffractometer.

The Cl position was located in the Patterson map and then confirmed by direct methods employing the 154 reflections with $E>1{\cdot}45$ and *MULTAN* (Germain, Main & Woolfson, 1971). Reflections in the starting set were 112, 012, $11\bar{1}$, 224, 800, 124 and 434 with the first three used for origin specification. The positions of the other seven non-hydrogen atoms in the asymmetric unit were also located in the $E$ map computed with the set of phases showing the highest figure of merit. A structure factor calculation based on these eight positions resulted in $R_1=0{\cdot}291$.

Full-matrix least-squares refinement of the positions and anisotropic temperature factors of the non-hydrogen atoms with *ORFLS* (Busing, Martin & Levy, 1962) reduced $R_1$ to 0·099. A difference map revealed the positions of all eight H atoms. Four additional cycles of full-matrix least-squares refinement of all positional and thermal parameters (individual isotropic temperature factors for H) produced a final $R_1=0{\cdot}065$ and $wR_1=0{\cdot}063$. The final $R_1$ for all measured data (including zero-intensity reflections) is 0·104. $R_1$ and $wR_1$ are defined by $R_1=\sum||F_o|-|F_c||/\sum|F_o|$ and $wR_1=[\sum w(|F_o|-|F_c|)^2/\sum w|F_o|^2]^{1/2}$. The weighting scheme $w=1/\sigma_F^2$ was employed. The scattering factors were those given in *International Tables for X-ray Crystallography* (1968). A final difference map revealed no peaks exceeding 0·27 e Å$^{-3}$. The final atomic coordinates and thermal parameters are given in Table 1.*

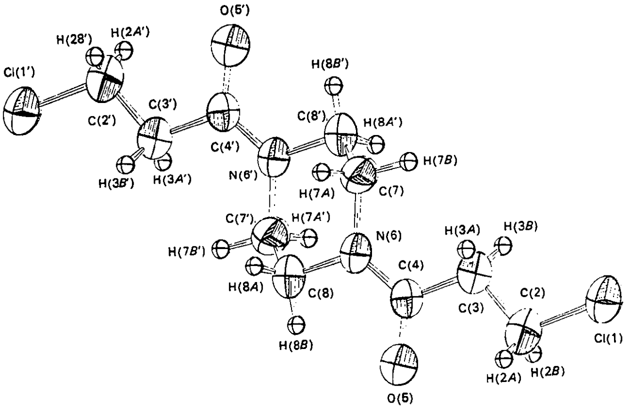

Fig. 1. An *ORTEP* II (Johnson, 1970) drawing of *N*,*N'*-bis-(3-chloropropionyl)piperazine with thermal ellipsoids representing 50% probability.

**Discussion.** Like *N*,*N'*-bis-(3-bromopropionyl)piperazine (Olansky & Moncrief, 1972), this substance has oncolytic activity against certain leukemias, lymphomas and solid tumors (Stein, Carben, Langden & Richards, 1960; Bond, Rohn, Hodes & Yardley, 1962; McNair, Wibin, Hoppe, Schmidt & De Peyster, 1963). Two possible mechanisms of action are alkylation (Emmelot, 1964) involving the $CH_2$–Cl bond and acylation (Moncrief & Heller, 1967) involving the amide group.

Fig. 1 is an *ORTEP* II (Johnson, 1970) drawing of the molecule. Final values of bond distances and angles and their estimated standard errors [*ORFFE* (Busing, Martin & Levy, 1964)] are given in Table 2

Table 2. *Interatomic distances and angles for N,N'-bis-(3-chloropropionyl)- and N,N'-bis-(3-bromopropionyl)piperazine*

| | Chloro | Bromo |
|---|---|---|
| X(1)–C(2) | 1·782 (6) Å | 2·002 (13) Å |
| C(2)–C(3) | 1·482 (7) | 1·485 (17) |
| C(3)–C(4) | 1·505 (7) | 1·511 (13) |
| C(4)–O(5) | 1·263 (6) | 1·211 (12) |
| C(4)–N(6) | 1·316 (6) | 1·345 (12) |
| N(6)–C(7) | 1·498 (6) | 1·456 (12) |
| N(6)–C(8) | 1·461 (6) | 1·464 (12) |
| C(7)–C(8) | 1·515 (8) | 1·519 (18) |
| C(2)–H(2*A*) | 0·914 (62) | |
| C(2)–H(2*B*) | 0·866 (62) | |
| C(3)–H(3*A*) | 0·856 (61) | |
| C(3)–H(3*B*) | 0·939 (62) | |
| C(7)–H(7*A*) | 1·069 (56) | |
| C(7)–H(7*B*) | 1·054 (59) | |
| C(8)–H(8*A*) | 0·989 (58) | |
| C(8)–H(8*B*) | 0·956 (62) | |
| X(1)—C(2)–C(3) | 112·2 (4)° | 112·8 (7)° |
| C(2)—C(3)–C(4) | 113·0 (5) | 111·1 (9) |
| C(3)—C(4)–O(5) | 118·4 (4) | 121·8 (8) |
| C(3)—C(4)–N(6) | 120·4 (4) | 114·5 (8) |
| O(5)—C(4)–N(6) | 121·2 (4) | 123·6 (8) |
| C(4)—N(6)–C(7) | 124·9 (4) | 128·4 (7) |
| C(4)—N(6)–C(8) | 122·0 (4) | 118·0 (7) |
| C(7)—N(6)–C(8) | 113·1 (4) | 112·0 (8) |
| N(6)—C(7)–C(8') | 110·5 (4) | 109·6 (8) |
| N(6)—C(8)–C(7') | 110·9 (4) | 111·1 (8) |
| H(2*A*)–C(2)–H(2*B*) | 114·8 (5·5) | |
| H(3*A*)–C(3)–H(3*B*) | 109·9 (4·1) | |
| H(7*A*)–C(7)–H(7*B*) | 111·0 (4·2) | |
| H(8*A*)–C(8)–H(8*B*) | 118·4 (4·6) | |

Table 1. *Final atomic coordinates and thermal parameters*

$$T=\exp\,[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)\times10^{-4}]$$

| | $x$ | $y$ | $z$ | $\beta_{11}$ | $\beta_{22}$ | $\beta_{33}$ | $\beta_{12}$ | $\beta_{13}$ | $\beta_{23}$ |
|---|---|---|---|---|---|---|---|---|---|
| Cl(1) | 1·0722 (1) | 0·2458 (2) | 0·3654 (2) | 108 (1) | 278 (3) | 420 (4) | 31 (2) | −117 (2) | −30 (3) |
| C(2) | 0·9146 (5) | 0·1754 (8) | 0·3917 (9) | 106 (5) | 267 (11) | 302 (12) | 26 (6) | −73 (7) | −16 (9) |
| C(3) | 0·8159 (4) | 0·3183 (6) | 0·4456 (8) | 96 (5) | 219 (9) | 242 (10) | 10 (5) | −58 (6) | −11 (8) |
| C(4) | 0·6831 (4) | 0·2622 (6) | 0·4641 (5) | 85 (4) | 183 (11) | 230 (8) | −6 (5) | −34 (5) | 2 (6) |
| O(5) | 0·6708 (3) | 0·1074 (5) | 0·4261 (6) | 112 (4) | 216 (8) | 466 (11) | 9 (4) | −98 (5) | −32 (7) |
| N(6) | 0·5827 (3) | 0·3724 (5) | 0·5193 (6) | 80 (4) | 202 (8) | 329 (9) | 12 (4) | −80 (5) | −23 (6) |
| C(7) | 0·5867 (5) | 0·5565 (6) | 0·5725 (7) | 113 (5) | 189 (11) | 360 (15) | 20 (5) | −114 (8) | −56 (9) |
| C(8) | 0·4527 (5) | 0·3229 (8) | 0·5378 (9) | 85 (4) | 228 (10) | 371 (16) | 3 (5) | −78 (7) | −17 (10) |

| | $x$ | $y$ | $z$ | $B$ | | $x$ | $y$ | $z$ | $B$ |
|---|---|---|---|---|---|---|---|---|---|
| H(2*A*) | 0·8793 (62) | 0·0948 (78) | 0·4844 (84) | 3·7 (1·2) | H(7*A*) | 0·5151 (59) | 0·5448 (67) | 0·7168 (79) | 3·7 (1·1) |
| H(2*B*) | 0·9326 (59) | 0·1377 (77) | 0·2832 (85) | 4·5 (1·5) | H(7*B*) | 0·6834 (58) | 0·5848 (68) | 0·5531 (69) | 2·5 (0·9) |
| H(3*A*) | 0·8004 (59) | 0·3595 (78) | 0·5505 (85) | 4·9 (1·6) | H(8*A*) | 0·3867 (63) | 0·3314 (71) | 0·6717 (81) | 4·3 (1·2) |
| H(3*B*) | 0·8694 (62) | 0·3956 (78) | 0·3500 (80) | 6·0 (1·6) | H(8*B*) | 0·4682 (59) | 0·2123 (80) | 0·4792 (76) | 6·6 (1·9) |

---

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31102 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

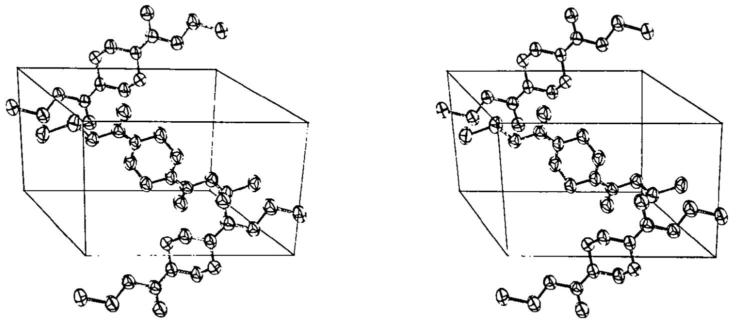

Fig. 2. A stereoscopic drawing (Johnson, 1970) of the contents of the unit cell. The horizontal axis is *a* and the vertical axis is *b*.

with the bromo-derivative values for comparison. Relative to *N*,*N*′-bis-(3-bromopropionyl)piperazine, a longer C(4)–O(5) bond (1·263 to 1·211 Å) with a shorter C(4)–N(6) bond (1·316 to 1·345 Å), a smaller C(4)–N(6)–C(7) angle (124·9 to 128·4°) with a larger C(4)–N(6)–C(8) angle (122·0 to 118·0°) all indicate more conjugation in the amide portion of the chloro compound. The amide groups possess only small deviations from planarity: the angle between the plane defined by C(3), C(4), O(5) and N(6) and the plane of C(4), N(6), C(7) and C(8) is 1°10′. The equations of and the atomic displacements from several calculated least-squares planes are given in Table 3. Perfect coplanarity is not possible because the distances between H(3*A*), H(3*B*) and H(7*A*), H(7*B*) and the distance between O(5) and H(8*B*) in the coplanar case would be shorter than the accepted van der Waals distance of 2·4 Å.

Fig. 2 is a stereoscopic drawing (Johnson, 1970) of the contents of the unit cell. The molecules are packed alternately parallel to two diagonals $xy$ and $\bar{x}y$ with half unit translation in the $z$ direction.

Table 3. *Calculated least-squares planes and atomic displacements*

Equations of least-squares planes (Cartesian coordinates)

(*a*) $0{\cdot}1678X-0{\cdot}2598Y+0{\cdot}9510Z=4{\cdot}2670$

(*b*) $0{\cdot}1601X-0{\cdot}2782Y+0{\cdot}9471Z=4{\cdot}1386$

(*c*) $0{\cdot}1645X-0{\cdot}2703Y+0{\cdot}9486Z=4{\cdot}2067$

Atomic displacements from least-squares planes (Å)

| | (*a*) | (*b*) | (*c*) |
|---|---|---|---|
| Cl(1) | 0·0315 | 0·0095 | 0·0204 |
| C(2) | 0·0710 | 0·0712 | 0·0707 |
| C(3) | 0·0005* | −0·0142 | −0·0094* |
| C(4) | −0·0017* | 0·0021* | −0·0025* |
| O(5) | 0·0006* | 0·0298 | 0·0140* |
| N(6) | 0·0006* | −0·0057* | −0·0071* |
| C(7) | 0·0378 | 0·0018* | 0·0134* |
| C(8) | −0·0092 | 0·0019* | −0·0085* |

* Atoms defining least-squares planes.

This work was supported in part by NSF Grant Number GP 23728 and by a Sloan Fellowship (to J.W.M). The assistance of Leann Olansky and of the Emory University Computing Center is gratefully acknowledged.

## References

Bond, W. H., Rohn, R. J., Hodes, M. E. & Yardley, J. M. (1962). *Cancer Chemother. Rep.* **16**, 209–222.

Busing, W. R., Martin, K. O. & Levy, H. A. (1962). *ORFLS*. Oak Ridge National Laboratory Report ORNL-TM-305.

Busing, W. R., Martin, K. O. & Levy, H. A. (1964). *ORFFE*. Oak Ridge National Laboratory Report ORNL-TM-306.

Emmelot, P. (1964). *Molecular Pharmacology*, Vol. II, pp. 55–198, edited by E. J. Ariens. New York: Academic Press.

Germain, G., Main, P. & Woolson, M. M. (1971). *Acta Cryst.* A**27**, 368–376.

*International Tables for X-ray Crystallography* (1968). Vol. III, 2nd ed., pp. 202–203. Birmingham: Kynoch Press.

Johnson, C. K. (1970). *ORTEP*. Oak Ridge National Laboratory Report ORNL-3794.

McNair, T. J., Wibin, F. A., Hoppe, E. T., Schmidt, J. L. & De Peyster, F. A. (1963). *J. Surg. Res.* **3**, 130.

Moncrief, J. W. & Heller, K. S. (1967). *Cancer Res.* **27**, 1500–1502.

Olansky, L. & Moncrief, J. W. (1973). *Acta Cryst.* B**29**, 357–360.

Parker, W. L., Flynn, J. J. & Boer, F. P. (1968). *J. Amer. Chem. Soc.* **90**, 4723–4729.

Simpson, P. G. (1963). Ph. D. Thesis. Harvard Univ.

Stein, R. J., Carben, J., Langden, J. & Richards, R. K. (1960). *J. Lab. Clin. Med.* **56**, 949.