2-Chloro-9-(ω-dimethylaminopropylidene)thioxanthene

By Michael L. Post and Olga Kennard*

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England

and Alan S. Horn

M.R.C. Neurochemical Pharmacology Unit, Department of Pharmacology, Medical School, Hills Road,
Cambridge CB2 2QD, England

Abstract. α-Chlorprothixene, $C_{18}H_{18}NSCl$, orthorhombic, $Pca2_1$, $a = 19\cdot384$ (8), $b = 10\cdot771$ (4), $c = 7\cdot792$ (3) Å, $Z = 4$, $D_x = 1\cdot29$ g cm^{-3}; in agreement with previously published two-dimensional work by Dunitz, Eser & Strickler [*Helv. Chim. Acta* (1964). **47**, 1897-1902]. The dimethylaminopropylidene chain is almost fully extended and has *cis* configuration about the double bond with respect to the Cl atom. The tricyclic ring system is folded about the central S$\cdots$C direction, with a dihedral angle of 141·6° between the two principal planes.

Introduction. Large crystals were obtained through the courtesy of Dr I. Moller Nielsen of H. Lundbeck and Co., Denmark. Space group and preliminary cell dimensions, determined from Weissenberg and pre-

cession photographs, were in agreement with those published in a previous 2-dimensional study (Dunitz, Eser & Strickler, 1964). Systematic absences were $0kl$ when l odd, $h0l$ when h odd; space groups $Pca2_1$ or $Pcam$, the latter being excluded by Z value and molecular symmetry considerations. For data collection, a crystal was cut approximately $0\cdot40 \times 0\cdot45 \times 0\cdot50$ mm in dimensions and mounted with the crystallographic b axis coincident with the instrument φ axis of a Picker four-circle diffractometer. Data were collected with graphite-monochromated Cu $K\alpha$ radiation ($\lambda = 1\cdot54178$ Å) and the θ–2θ scan mode, operating at a speed of $2°$ min^{-1} in 2θ; the total scan range was $(2 + 0\cdot005 \tan \theta)°$. With $2\theta \le 120°$, 1307 independent reflexions were measured of which 46 had intensities $< 3\sigma$ above background and were classified as unobserved. Lorentz and polarization corrections were applied; no correction for absorption was made.

* External Staff, Medical Research Council.

Table 1. *Final positional* ($\times 10^4$) *and thermal parameters* (Å$^2 \times 10^3$) *with standard deviations in parentheses*

The anisotropic thermal parameter is defined by:

$$T = \exp\left[-2\pi^2(U_{11}a^{*2}h^2 + U_{22}b^{*2}k^2 + U_{33}c^{*2}l^2 + 2U_{12}a^*b^*hk + 2U_{13}a^*c^*hl + 2U_{23}b^*c^*kl)\right].$$

	x	y	z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S	4004 (1)	6621 (1)	3020†	59 (1)	54 (1)	55 (1)	−15 (1)	−4 (1)	−15 (1)
Cl	4875 (1)	1244 (1)	948 (4)	58 (1)	45 (1)	112 (2)	18 (1)	−3 (1)	14 (1)
N	1461 (2)	1751 (4)	1269 (8)	43 (3)	46 (3)	66 (3)	15 (3)	−11 (3)	−17 (2)
C(1)	4051 (2)	3246 (4)	770 (8)	28 (2)	37 (3)	53 (3)	9 (3)	1 (2)	−3 (2)
C(2)	4638 (3)	2756 (5)	1515 (9)	36 (3)	36 (3)	69 (4)	20 (3)	1 (3)	1 (2)
C(3)	5025 (3)	3403 (6)	2687 (10)	40 (3)	64 (4)	74 (5)	24 (4)	−17 (3)	−10 (3)
C(4)	4818 (3)	4584 (7)	3124 (10)	46 (3)	72 (4)	58 (4)	14 (4)	−14 (3)	−22 (3)
C(5)	3681 (3)	8439 (5)	774 (12)	52 (3)	39 (3)	91 (5)	−11 (4)	21 (4)	−16 (3)
C(6)	3393 (3)	8912 (6)	−700 (13)	61 (3)	36 (3)	111 (6)	16 (4)	19 (4)	5 (3)
C(7)	3053 (3)	8133 (5)	−1803 (13)	49 (3)	48 (3)	102 (6)	26 (4)	−3 (4)	−4 (3)
C(8)	3017 (3)	6867 (5)	−1490 (9)	37 (3)	48 (3)	68 (4)	19 (3)	−4 (3)	−8 (2)
C(9)	3227 (2)	5026 (4)	409 (7)	22 (2)	29 (2)	49 (3)	2 (2)	2 (2)	−6 (2)
C(11)	3836 (2)	4450 (4)	1217 (7)	34 (2)	35 (3)	37 (3)	6 (2)	2 (2)	−6 (2)
C(12)	4238 (2)	5116 (5)	2395 (8)	31 (2)	42 (3)	44 (3)	1 (2)	−5 (2)	−15 (2)
C(13)	3640 (2)	7184 (4)	1123 (8)	34 (2)	33 (3)	64 (4)	−10 (3)	14 (3)	−5 (2)
C(14)	3297 (2)	6366 (4)	16 (8)	25 (2)	29 (3)	56 (3)	5 (2)	8 (2)	−3 (2)
C(15)	2643 (2)	4414 (4)	60 (7)	31 (2)	31 (2)	45 (3)	2 (2)	0 (2)	6 (2)
C(16)	2458 (3)	3107 (4)	449 (9)	30 (2)	29 (2)	60 (3)	5 (3)	−4 (2)	−11 (2)
C(17)	1681 (2)	2982 (4)	672 (9)	37 (3)	36 (3)	58 (3)	3 (3)	−3 (3)	9 (2)
C(18)	718 (3)	1743 (6)	1496 (11)	50 (3)	73 (4)	69 (4)	13 (4)	0 (3)	−25 (3)
C(19)	1645 (3)	802 (5)	84 (13)	73 (4)	33 (3)	123 (7)	7 (4)	−2 (5)	−3 (3)

† This parameter was fixed to define the origin and was not refined.

The structure was solved by multi-solution tangent refinement of the phases of 309 $|E|$ values > 1.2. All non-hydrogen atoms were located in the first E map. After five cycles of full-matrix least-squares refinement, with individual isotropic temperature parameters, R was 0·113. At this stage a difference synthesis indicated possible sites for 9 of the hydrogen atoms, the positions agreeing with those calculated with a C–H distance of 1·03 Å. Contributions by all the hydrogen atoms, initially in their calculated positions, were included in subsequent stages and their positional coordinates allowed to refine, but with the C–H vector constrained in magnitude (Sheldrick, 1974). After six cycles of refinement with all non-hydrogen atoms anisotropic and an overall isotropic thermal parameter for hydrogen, R was 0·072. A number of the most intense reflexions appeared to be suffering from secondary extinction and were given zero weight in the later stages of refinement. Convergence was finally attained with R at 0·0595. A weighting scheme based upon counting statistics was used and the function minimized was $\sum w\{||F_o| - |F_c||\}^2$. Final positional and thermal parameters are presented in Tables 1 and 2.*

Table 2. *Final hydrogen atom positional parameters*
$(\times 10^3)$

$U_{iso} = 0.067$ Å^2 throughout.

	x	y	z		x	y	z
H(1)	376	273	−12	H(162)	272	260	152
H(3)	546	298	326	H(171)	144	316	−51
H(4)	512	508	401	H(172)	152	364	158
H(5)	393	902	166	H(181)	58	238	245
H(6)	343	986	−101	H(182)	57	85	187
H(7)	283	848	−294	H(183)	47	198	34
H(8)	274	630	−234	H(191)	218	80	−13
H(15)	226	493	−58	H(192)	139	105	−106
H(161)	260	266	−51	H(193)	149	−9	47

Discussion. The title compound is known to exist as two geometric isomers, the propylidene chain being either *cis* or *trans* about the double bond, with respect to the chlorine substituted on the aromatic ring (Bono-vicino, Arlt, Pearson & Hardy, 1961). The isomer studied here, also known as α-chlorprothixene, is a clinically efficacious neuroleptic drug used in the treatment of major psychoses such as schizophrenia (Klein & Davis, 1969), and has previously been shown by two-dimensional X-ray work (Dunitz, Eser & Strickler, 1964), to have the *cis* configuration (Fig. 1). A variety of pharmacological tests (Moller Nielsen & Neuhold, 1959; Miller, Horn & Iversen, 1974) have shown that

the potency of the *cis* isomer is at least an order of magnitude higher than that of the *trans* (or β) form. This trend has also been observed in a number of other thioxanthene derivatives (Kaiser, Warren & Zirkle, 1974). There is evidence that neuroleptics may act by blocking dopamine receptors in the brain (Horn & Snyder, 1971; Matthysse, 1973; Snyder, 1973) and, since efficacy is sensitive to structural geometry, the conformation of the title compound is of importance in promoting understanding of the mode of action of this and similar drugs under physiological conditions. This particular compound is one of a number of thioxanthene-derived neuroleptics we are at present investigating by X-ray diffraction and pharmacological methods.

Details of the structure are shown in Fig. 2; bond lengths and angles for all the non-hydrogen atoms are presented in Table 3. Principal torsional angles are listed in Table 4. In common with other thioxanthene compounds (Chu, 1973; Chu & Chung, 1974), the tricyclic ring system is folded about the line S···C(9),
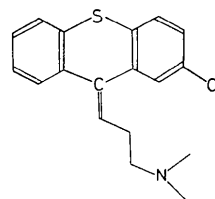

Fig. 1. 2-Chloro-9-(ω-dimethylaminopropylidene)thioxanthene, α-chlorprothixene.
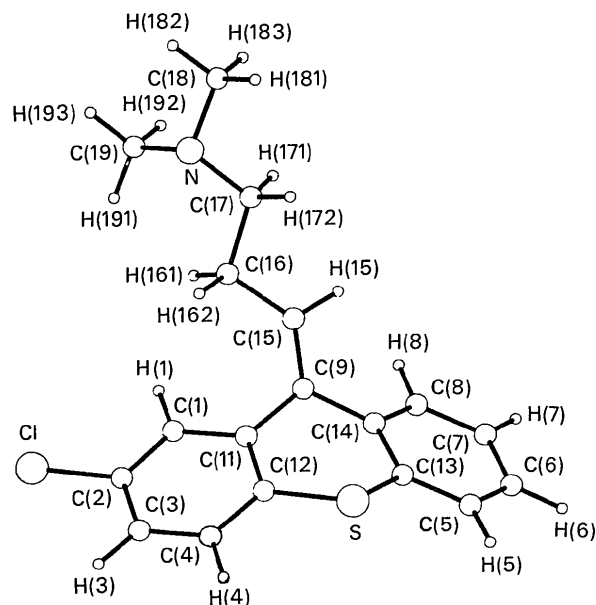

Fig. 2. Molecular diagram of the title compound.

---

* A table of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30400 (10 pp.). Copies may be obtained from The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 3. *Bond distances and bond angles involving non-hydrogen atoms*

Standard deviations are in parentheses.

S——C(12)	1·752 (5) Å	C(11)-C(12)	1·402 (7) Å
S——C(13)	1·746 (5)	C(5)—C(13)	1·381 (7)
Cl—C(2)	1·750 (6)	C(5)—C(6)	1·375 (12)
N——C(17)	1·468 (6)	C(6)—C(7)	1·370 (12)
N——C(18)	1·451 (8)	C(7)—C(8)	1·387 (7)
N——C(19)	1·422 (9)	C(8)—C(14)	1·400 (9)
C(1)—C(11)	1·407 (7)	C(13)—C(14)	1·401 (8)
C(1)—C(2)	1·382 (7)	C(9)—C(11)	1·473 (7)
C(2)-C(3)	1·372 (9)	C(9)—C(14)	1·482 (6)
C(3)-C(4)	1·377 (10)	C(9)—C(15)	1·339 (6)
C(4)-C(12)	1·383 (8)	C(15)-C(16)	1·483 (6)
		C(16)-C(17)	1·522 (7)

C(12)-S——C(13)	101·0 (3)°	C(14)-C(9)—C(15)	120·9 (4)°
C(17)-N——C(18)	109·3 (4)	C(1)—C(11)-C(9)	121·3 (4)
C(17)-N——C(19)	111·8 (5)	C(1)—C(11)-C(12)	118·0 (5)
C(18)-N——C(19)	108·9 (5)	C(9)—C(11)-C(12)	120·7 (5)
C(2)—C(1)-C(11)	119·5 (5)	C(4)—C(12)-S	118·7 (4)
C(1)—C(2)-C(3)	122·5 (6)	C(4)—C(12)-C(11)	120·6 (5)
C(1)—C(2)-Cl	117·7 (5)	C(11)-C(12)-S	120·7 (4)
C(3)—C(2)-Cl	119·8 (5)	C(5)—C(13)-S	118·9 (5)
C(2)—C(3)-C(4)	118·2 (5)	C(5)—C(13)-C(14)	121·4 (6)
C(3)—C(4)-C(12)	121·3 (6)	C(14)-C(13)-S	119·6 (4)
C(13)-C(5)-C(6)	120·3 (7)	C(8)—C(14)-C(9)	121·0 (5)
C(5)—C(6)-C(7)	119·4 (6)	C(8)—C(14)-C(13)	117·2 (5)
C(6)—C(7)-C(8)	121·1 (7)	C(9)—C(14)-C(13)	121·9 (5)
C(7)—C(8)-C(14)	120·5 (6)	C(9)—C(15)-C(16)	129·1 (5)
C(11)-C(9)-C(14)	115·2 (4)	C(15)-C(16)-C(17)	110·3 (4)
C(11)-C(9)-C(15)	123·9 (4)	C(16)-C(17)-N	113·8 (4)

Table 4. *Principal torsional angles*

C(11)-C(9)—C(15)-C(16)	3·2°
C(9)—C(15)-C(16)-C(17)	151·4
C(15)-C(16)-C(17)-N	−172·9
C(16)-C(17)-N——C(18)	178·0

with a dihedral angle of 141·6° between the mean planes of the two aromatic rings. The central hetero ring exhibits boat conformation with the S and C(9) atoms very nearly coplanar with each aromatic ring, the maximum deviation being 0·06 Å. The distance N···Cl is 6·65 Å and considerably longer than the equivalent distance in chlorpromazine (4·82 Å:

McDowell, 1969), a clinically active nitrogen analogue, but in each compound the pyramidally bonded amine nitrogen atom has similar orientation with respect to the substituted aromatic ring. In the present compound the aminopropylidene chain is nearly fully extended (Table 4), but the geometry at the double bond C(9)-C(15) necessarily gives rise to some close intramolecular contacts between hydrogen atoms on C(15) and C(16) and those on the aromatic rings, (2·22–2·39 Å). The slight loss of planarity in the ethylenic moiety [C(16) lies 0·08 Å from the plane C(11), C(9), C(14), C(15)] and the rather large angles C(11)-C(9)–C(15) and C(9)-C(15)-C(16) are probably the result of the chain's accommodating these interactions. All remaining bond lengths and angles in the molecule are as expected.

References

BONOVICINO, G. E., ARLT, H. G. JR, PEARSON, K. M. & HARDY, R. A. JR (1961). *J. Org. Chem.* **26**, 2383–2392.
CHU, S. S. C. (1973). *Acta Cryst.* B**29**, 1690–1696.
CHU, S. S. C. & CHUNG, B. (1974). *Acta Cryst.* B**30**, 235–236.
DUNITZ, J. D., ESER, H. & STRICKLER, P. (1964). *Helv. Chim. Acta*, **47**, 1897–1902.
HORN, A. S. & SNYDER, S. H. (1971). *Proc. Nat. Acad. Sci. Wash.* **68**, 2325–2328.
KAISER, C., WARREN, R. J. & ZIRKLE, C. L. (1974). *J. Med. Chem.* **17**, 131–133.
KLEIN, D. F. & DAVIS, J. M. (1969). *Diagnosis and Drug Treatment of Psychiatric Disorders.* Baltimore: Williams & Wilkins.
McDOWELL, J. J. H. (1969). *Acta Cryst.* B**25**, 2175–2181.
MATTHYSSE, S. (1973). *Fed. Proc.* **32**, 200–205.
MILLER, R. J., HORN, A. S. & IVERSEN, L. L. (1974). In preparation.
MOLLER NIELSEN, I. & NEUHOLD, K. (1959). *Acta Pharmacol. Toxicol.* **15**, 353–362.
SHELDRICK, G. M. (1974). In preparation.
SNYDER, S. H. (1973). *The Neurosciences Third Study Program.* New York: Rockefeller Univ. Press.