Correlation of the Crystal and Molecular Structure with Pharmacologic Activity Associated with 7- and 8-Chloro-1-azaphenoxathiin

Gary E. Martin (1a), James D. Korp (b), James C. Turley (a) and Ivan Bernal (b)

(a) Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Houston, Houston, Texas 77004

(b) Department of Chemistry, University of Houston, Houston, Texas 77004

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The crystal and molecular structure of the 7- and 8-chloro analogs of the 1-azaphenoxathiin system are described. In contrast to previous compounds possessing antipsychotic type activity, the title compounds are both nearly planar, and demonstrate significant substituent location sensitivity, with the 7-chloro analog exhibiting significant biologic activity while the 8-chloro isomer is nearly devoid of activity. The relationship of these compounds to the isosterically related phenothiazines in terms of design and molecular geometry considerations is also described.

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The synthesis of several substituted analogs of the 1-azaphenoxathiin ring system (2,3) as well as the corresponding parent system (4) have recently been reported. The pharmacologic rationale for the synthesis of this system was based on the crystal structure of phenoxathiin (5-7) which, with a dihedral angle of 138°, is spatially quite similar to a relatively large number of active phenothiazines (8-12, see also Table I).

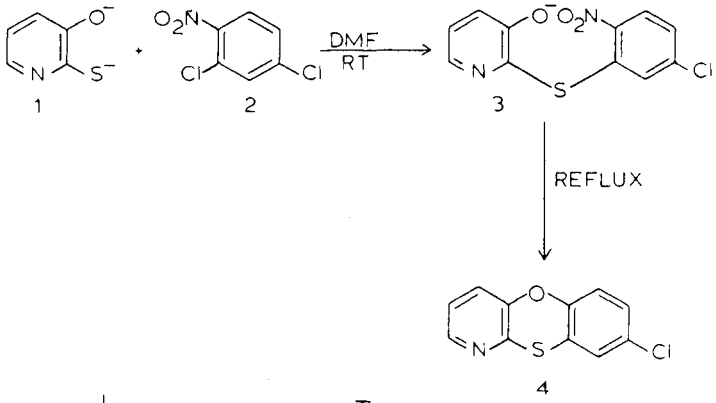
Further molecular design considerations involved the selection of a location for the chloro-substituent, with the location of the chlorine in chlorpromazine (13), that is "*para*" to the sulfur atom, used as a guiding criterion. Thus, the location of the chloro-substituent in the 7-position (2) was positionally analogous to chlorpromazine while the 8-chloro analog was intended to test the relative substituent positional sensitivity of the system.

The final consideration in the design of this system was the decision to employ an aza-substitution which was based on the marked improvement in pharmacologic activity of promazine on aza-substitution (14-16).

Based on the considerations presented above, when the 7-chloro-1-azaphenoxathiin was synthesized (2) and subsequently found to cause a significant decrease in spontaneous, as well as forced motor activity, (see Figure 1) the result was thought to be attributable to spatial similarity to the non-planar phenothiazine nucleus. Further, since the relative activity was somewhat lower than chlorpromazine, which was used as a control, it was thought that the phenoxathiin analog might be occupying the same receptor site, with the difference in activity arising from only partial interaction with the receptor since the molecule did not have the phenothiazine-type side chain.

In the case of the 8-chloro-1-azaphenoxathiin (4), whose synthesis is shown in Scheme I, the relative position of the chloro-substituent is "*meta*" to the sulfur. Pharmacologic testing showed the compound to be essentially devoid of activity (see Figure 1) which, when the crystal structure of 4 was obtained was thought to be attributable

SCHEME I



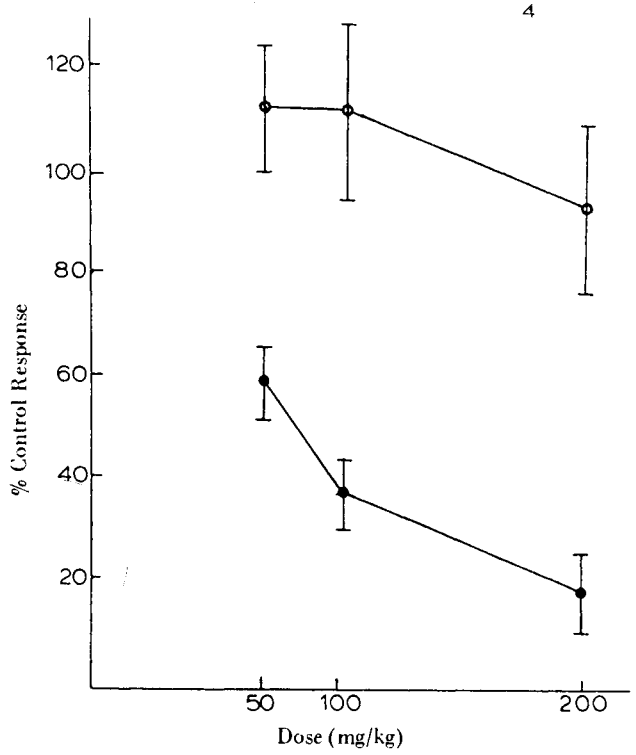
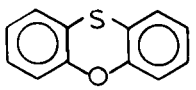
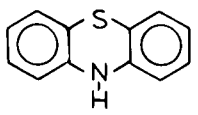
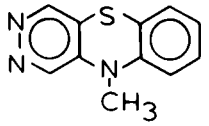
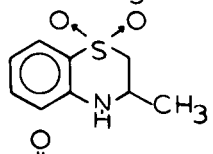
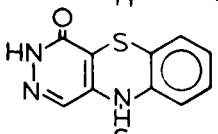
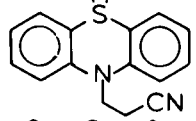
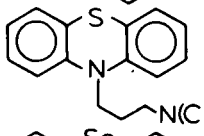
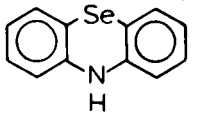
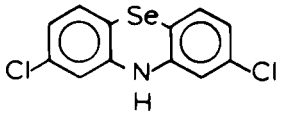
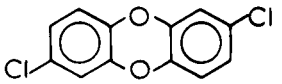
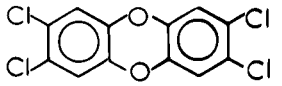
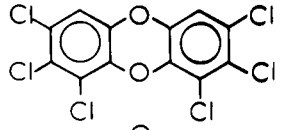
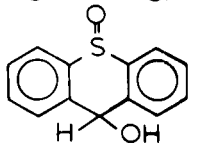


Figure 1. Spontaneous Motor Activity test results for 7-chloro- (•) and 8-chloro-1-azaphenoxathiin (4) (o). Results shown with ± 1 std. dev.

Table 1

A Comparison of Structural Features for Aza-Phenoxathiins and Related Systems.

Compound	C-Y(Å)	C-X(Å)	C-Y-C(°)	C-X-C(°)	Folding Angle(°)	Nature of Y,X	REF
	1.753(43) 1.751(43)	1.401(54) 1.386(52)	97.68(3)	117.63(5)	138.4[c]	S,O	(7)
	1.770(3)	1.406(2)	99.6(-)[c]	121.5(-)[c]	153.3(-)[c]	S,N	(21)
	1.789(4) 1.763(4)	1.423(2) 1.408(3)	100.2(2)	120.6(3)	146.4(-)[c]	S,N	(12)
	1.705(5) 1.734(5)	1.394(4) 1.397(5)	103.8(5)	127.1(9)	Almost planar	S,N	(31)
	1.769(4) 1.747(4)	1.394(4) 1.361(4)	100.5(4)	125.4(7)	4.4[c]	S,N	(26)
	1.77(1) 1.75(2)	1.43(2) 1.41(2)	97.8(7)	118.1(9)	135.4(3)	S,N	(10)
	1.746(8)[a] 1.766(8)	1.47(2) 1.42(2)	97.9(4)	115(1)	134.4(5)	S,N	(11)
	1.729(8) 1.738(8)	1.46(4) 1.40(2)	96.5(4)	117(1)	141.0(5)	S,N	(11)
	1.89(2) 1.89(2)	1.39(2) 1.43(2)	97(1)	122(1)	149.7[c]	Se,N	(24)
	1.921(5)	1.410(5)	95.4(2)	122.9(4)	146.5[c]	Se,N	(25)
	1.378(3)[a] 1.378(3)	1.377(3) 1.379(3)	115.6(2)	115.8(2)	Almost Planar	O,O	(32)
	1.382(4)[b] 1.380(4)		116.3(2)	(b)	Planar	O,O	(33)
	1.40[c] 1.34	1.35[c] 1.36	117[c]	118[c]	Almost Planar	O,O	(34)
	1.75(2) 1.80(2)	1.50(1) 1.51(1)	97.5(7)	112(1)	132.4[c]	SO,CH(OH)	(35)

(a) Two molecules in the asymmetric unit.

(b) Molecule at an inversion center of P1.

(c) Deviation not given in reference

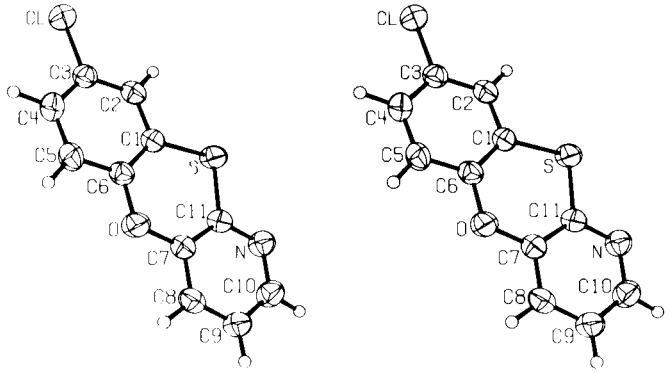
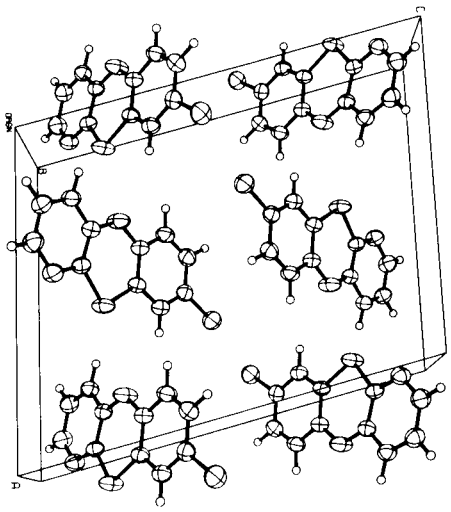


Figure 2. A stereoscopic view of 8-chloro-1-azaphenoxathiin showing the thermal ellipsoids as 50% probability envelopes and labelled according to the numbering scheme used in the crystallographic studies of *both* 8 and 7-chloro derivatives.



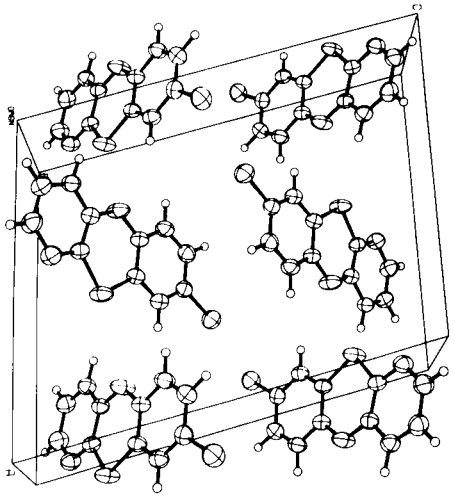


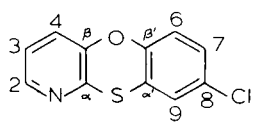
Figure 3. The packing diagram for 8-chloro-1-azaphenoxathiin. Note the orientation of the chlorine with respect to the crystallographic axes and compare with the orientation of the functional group in the 7-chloro derivative. Note that the two molecules crystallize in the same space group with similar cell constants, but that they are not isostructural.

to either the nearly planar nature of the compound (see Figures 2 and 3) or the change in substituent location or both. That such a change in shape would be observed was neither unexpected nor inexplicable. It is well known that the dihedral angle of the related phenothiazine nucleus is quite sensitive to alterations in the electronic nature of its substituents (10,17,18), as seen in the change of the dihedral angle in going from chlorpromazine (139.2°) (9) to 2-methoxypromazine (157.4°) (19). (See also Table I). Further, since chlorpromazine is a very active antipsychotic while 2-methoxypromazine is nearly inactive (20), it appears that the dihedral angle may be an important consideration. This is supported by the observation that phenothiazine (5,6,21) and *N*-methylphenothiazine (22), both of which are spatially similar to 2-methoxypromazine (see Table I) are pharmacologically inactive.

It was thus quite unexpected and rather a surprise when the crystal structure of the active 7-chloro-1-azaphenoxathiin (2) was obtained and found to have essentially the same planarity (see Figure 4) as the 8-chloro compound (**4**). Since both molecules are essentially **planar**, an

Table II

25.2MHz ^{13}C-Nmr Calculated *vs.* Observed Chemical Shift Data of 8-Chloro-1-azaphenoxathiin (**4**) in Deuteriochloroform



Position

δ_C	α	β	α'	β'	2	3	4	6	7	8	9
Calcd.	143.5	147.9	120.2	148.1	144.7	122.9	124.7	118.7	127.3	129.8	128.1
Obs.	142.4	147.5	120.9	148.5	144.9	122.4	123.6	118.3	126.2	129.7	127.5

Table III

Crystallographically Important Data Collection and Data Processing Information

		7-Chloro	8-Chloro
Space Group		$P2_1/a$	$P2_1/a$
Cell Constants	a =	12.377 (4) Å	12.489 (4) Å
	b =	5.412 (1)	5.295 (1)
	c =	14.744 (4)	15.287 (5)
	β =	94.45 (4)°	103.8 (2)°
	Cell Volume =	983.15 Å^3	981.61 Å^3
Density (calc)		1.592 gm-cm^{-3}	1.595 gm-cm^{-3}
Molecular Weight	M.W. =	235.692 gm-mole^{-1}	235.692 gm-mole^{-1}
Standards for Intensity Control (every 30 data points)		[0,2,6; 1,1,5]	[$\bar{9}$,2,1; 4,4,4]
Description of the Crystals: Both were irregular fragments		Maximum dimension: 0.8 mm	Maximum dimension: 0.8 mm
Range for Data Collection		$4.0 \leqslant 2\theta \leqslant 70.0°$	$5.0 \leqslant 2\theta \leqslant 55.0°$
Scan Width for Each Reflection	$\Delta\theta$ =	1.20 + 0.35 tanθ	0.8 + 0.35 tanθ
Maximum Scan Time		6 min.	5 min.
Minimum Accumulated Counts Above Background for Each Reflection		2000	1500
Range of Scan Speeds		0.4 to 5.0° per min.	0.4 to 5.0° per min.
Absorption Coefficient	μ =	5.60 cm^{-1}	5.61 cm^{-1}
Total Number of Independent Data Collected		4078	2841
Number of Data Points Above 3 Standard Deviations		1378	1722
Number of Total Variables		160	160
Final R(F)		0.038	0.035
Final R_w(F)		0.039	0.039
Goodness of Fit		1.54	1.30

Table IV

Non-Hydrogen Atoms Positional (X 10^5) and Thermal Parameters (X 10^4) For 7-Chloro-1-azaphenoxathiin. Hydrogen Atoms Positional (X 10^4) and Thermal Parameters (X 10^3)

Atom	x/a	y/b	z/c	U_{11} or U	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S	104840 (5)	87460 (14)	69866 (5)	230 (3)	502 (5)	813 (6)	35 (4)	83 (3)	141 (4)
Cℓ	83039 (6)	14160 (14)	95993 (5)	675 (5)	586 (5)	637 (5)	19 (5)	88 (4)	181 (4)
N	96458 (16)	123313 (41)	59875 (14)	320 (12)	479 (14)	593 (15)	-17 (12)	41 (11)	69 (13)
O	80039 (12)	83501 (33)	73469 (13)	240 (9)	604 (13)	905 (14)	55 (10)	70 (9)	339 (12)
C1	98460 (18)	68306 (45)	77491 (16)	278 (13)	374 (16)	477 (15)	16 (12)	20 (11)	-48 (13)
C2	104659 (21)	51782 (56)	82886 (19)	276 (16)	621 (21)	594 (19)	71 (16)	10 (14)	51 (17)
C3	100285 (22)	35569 (59)	88616 (21)	425 (17)	624 (22)	549 (19)	164 (18)	-20 (14)	140 (18)
C4	89188 (21)	35341 (48)	89037 (16)	515 (16)	421 (16)	375 (15)	-26 (16)	63 (13)	-18 (14)
C5	82651 (21)	51615 (50)	83934 (17)	320 (15)	444 (17)	487 (17)	37 (14)	53 (13)	33 (14)
C6	87293 (18)	67944 (45)	78274 (17)	306 (13)	368 (16)	476 (15)	56 (13)	2 (12)	-11 (13)
C7	83158 (18)	101538 (46)	67703 (16)	302 (14)	356 (15)	423 (15)	7 (12)	33 (11)	33 (12)
C8	75122 (20)	116698 (52)	63912 (17)	292 (13)	472 (18)	453 (15)	41 (14)	48 (12)	8 (14)
C9	77753 (21)	135308 (57)	58097 (17)	397 (16)	520 (19)	469 (16)	85 (16)	3 (13)	79 (16)
C10	88562 (22)	137978 (56)	56190 (19)	459 (16)	507 (19)	547 (18)	-55 (17)	38 (14)	115 (16)
C11	93842 (18)	105592 (44)	65543 (16)	262 (13)	339 (14)	469 (15)	4 (12)	7 (11)	-21 (13)
H2	11203 (16)	5266 (39)	8257 (13)	37 (7)					
H3	10347 (18)	2515 (41)	9244 (14)	44 (8)					
H5	7495 (18)	5119 (39)	8455 (14)	44 (7)					
H8	6743 (17)	11436 (41)	6558 (13)	48 (7)					
H9	7206 (20)	14548 (47)	5468 (16)	82 (10)					
H10	9076 (17)	15105 (44)	5190 (14)	58 (8)					

Table V

Non-Hydrogen Atoms Positional (X 10^5) and Thermal Parameters (X 10^4) For 8-Chloro-1-azaphenoxathiin. Hydrogen Atoms Positional (X 10^4) and Thermal Parameters (X 10^3)

Atom	x/a	y/b	z/c	U_{11} or U	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S	41800 (4)	86681 (10)	80103 (4)	343 (2)	466 (3)	768 (4)	-39 (2)	247 (2)	-174 (3)
Cℓ	33848 (4)	13471 (11)	54797 (4)	569 (3)	553 (3)	553 (3)	-117 (3)	139 (3)	-110 (3)
N	51862 (13)	123162 (31)	90258 (12)	429 (9)	450 (9)	555 (11)	38 (8)	130 (8)	-71 (8)
O	65615 (10)	85078 (26)	76089 (10)	358 (7)	559 (9)	793 (10)	-71 (7)	240 (7)	-232 (8)
C1	46792 (14)	67681 (32)	72468 (12)	357 (9)	326 (10)	461 (11)	42 (8)	139 (8)	29 (8)
C2	39516 (15)	50498 (37)	67243 (14)	369 (10)	400 (10)	490 (12)	1 (9)	131 (9)	48 (9)
C3	43078 (15)	34803 (35)	61281 (13)	445 (10)	399 (10)	410 (11)	-35 (9)	103 (8)	22 (9)
C4	53861 (16)	35681 (40)	60346 (14)	501 (11)	511 (12)	468 (12)	39 (11)	168 (10)	-47 (11)
C5	61040 (16)	52845 (42)	65467 (15)	372 (10)	556 (13)	534 (13)	23 (10)	177 (9)	-44 (11)
C6	57559 (14)	68862 (34)	71426 (13)	345 (9)	379 (11)	477 (11)	6 (8)	128 (8)	10 (9)
C7	63529 (14)	102645 (34)	82104 (13)	376 (9)	348 (10)	445 (11)	26 (8)	119 (8)	34 (9)
C8	72194 (16)	118388 (38)	85968 (14)	373 (10)	501 (13)	483 (12)	-43 (9)	121 (9)	36 (10)
C9	70552 (17)	136710 (42)	91935 (14)	470 (11)	515 (13)	518 (13)	-95 (11)	75 (10)	-43 (11)
C10	60357 (17)	138513 (43)	93882 (15)	496 (12)	518 (13)	562 (14)	-1 (11)	109 (10)	-114 (12)
C11	53508 (14)	105646 (34)	84455 (13)	342 (9)	350 (10)	468 (12)	17 (8)	96 (8)	27 (8)
H2	3205 (15)	4955 (36)	6777 (12)	46 (5)					
H4	5631 (14)	2300 (34)	5586 (12)	49 (5)					
H5	6891 (15)	5391 (36)	6515 (12)	55 (6)					
H8	7924 (16)	11675 (34)	8421 (13)	52 (6)					
H9	7673 (17)	14672 (38)	9481 (13)	58 (6)					
H10	5926 (15)	15225 (40)	9791 (14)	60 (6)					

attribute generally considered to preclude antipsychotic activity (23), it must be concluded that the profound differences observed in the pharmacologic activity of the two compounds is associated with the change in substituent location, which serves to illustrate the importance of this change.

An important consideration remaining to be discussed is the substantial difference in the dihedral angle between the 1-azaphenoxathiin analogs of this report and the parent phenoxathiin system from which they were derived. It is highly probable that the change is not associated merely with chloro-substitution since a comparison of the dihedral angle of phenoselenazine (24) with the related 3,7-dichlorophenoselenazine (25) shows a relatively small change of only 3.2°, the latter having the smaller dihedral angle (See Table I). A factor which may be responsible is the positioning of the aza-substituent. Thus, in a comparison of 10-methyl-2,3-diazaphenothiazine, which has a dihedral

Table VI

Bond Lengths (Å) and Angles (°) in 7 and 8 Chloro Derivatives

(A) Bond Lengths for Non-Hydrogen Atoms

Bond	7-chloro	8-chloro	Bond	7-chloro	8-chloro
S-C1	1.761 (3)	1.764 (2)	C3-C4	1.380 (4)	1.389 (3)
S-C11	1.757 (2)	1.768 (2)	C4-C5	1.379 (4)	1.381 (3)
Cℓ-CX (a)	1.751 (2)	1.744 (2)	C5-C6	1.372 (4)	1.388 (3)
O-C6	1.385 (3)	1.384 (2)	C6-C1	1.396 (3)	1.393 (3)
O-C7	1.370 (3)	1.376 (3)	C7-C8	1.374 (4)	1.382 (3)
N-C10	1.341 (4)	1.346 (3)	C7-C11	1.401 (3)	1.391 (3)
N-C11	1.329 (3)	1.333 (3)	C8-C9	1.378 (4)	1.380 (3)
C1-C2	1.388 (4)	1.395 (3)	C9-C10	1.396 (4)	1.379 (3)
C2-C3	1.359 (4)	1.383 (3)			

(B) Bond Lengths Involving Hydrogen Atoms

Bond	7-chloro	8-chloro	Bond	7-chloro	8-chloro
C2-H2	0.92 (2)	0.96 (2)	C8-H8	1.00 (2)	0.98 (2)
CX-HX (b)	0.87 (2)	1.06 (2)	C9-H9	1.00 (2)	0.95 (2)
C5-H5	0.97 (2)	1.00 (2)	C10-H10	1.00 (2)	0.98 (2)

(C) Shortest Hydrogen Intermolecular Contacts with S, N and Cℓ

Contact	7-chloro	8-chloro	Contact	7-chloro	8-chloro
S-H8	3.13 (2)	3.07 (2)	Cℓ-H (c)	3.13 (2)	2.87 (2)
N-H8	2.75 (2)	2.81 (2)			

(a) X = 4 for 7-chloro and 3 for 8-chloro. (b) X = 3 for 7-chloro and 4 for 8-chloro. (c) For 7-chloro H3 and for 8-chloro H5.

(D) Bond Angles (deg.)

Angle	7-chloro	8-chloro	Angle	7-chloro	8-chloro
C1-S-C11	100.8 (1)	100.47 (9)	O-C6-C1	123.8 (2)	124.9 (2)
C6-O-C7	123.2 (2)	122.2 (2)	O-C6-C5	114.7 (2)	114.4 (2)
C10-N-C11	118.5 (2)	117.5 (2)	C1-C6-C5	121.6 (2)	120.7 (2)
S-C1-C2	119.3 (2)	117.8 (1)	O-C7-C8	116.3 (2)	116.1 (2)
S-C1-C6	123.9 (2)	123.6 (1)	O-C7-C11	124.7 (2)	125.1 (2)
C2-C1-C6	116.8 (2)	118.6 (2)	C8-C7-C11	118.7 (2)	118.8 (2)
C1-C2-C3	122.9 (2)	120.0 (2)	C7-C8-C9	119.4 (2)	118.8 (2)
C2-C3-C4	118.7 (2)	121.4 (2)	C8-C9-C10	118.5 (3)	118.8 (2)
Cℓ-CX-CY (d)	120.8 (2)	119.4 (1)	N-C10-C9	122.5 (3)	123.2 (2)
Cℓ-CX-CZ (e)	118.3 (2)	119.3 (2)	S-C11-N	114.3 (2)	113.6 (1)
C3-C4-C5	120.9 (3)	118.5 (2)	S-C11-C7	123.2 (2)	123.5 (1)
C4-C5-C6	119.2 (2)	120.8 (2)	N-C11-C7	122.4 (2)	122.9 (2)

(d) For 7-chloro, X = 4; Y = 3. For 8-chloro, X = 3; Y = 2. (e) For 7-chloro, X = 4; Z = 5. For 8-chloro, X = 3, Z = 4.

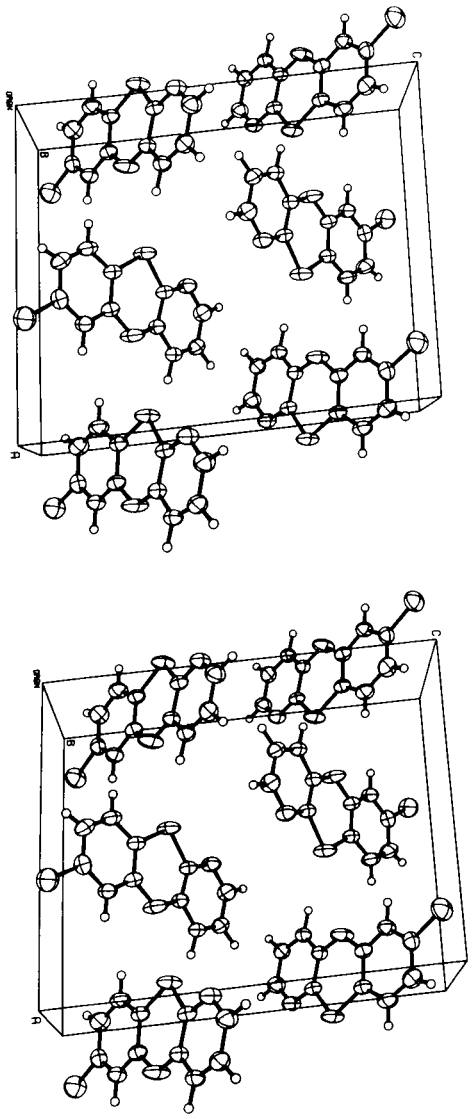


Figure 4. Packing diagram for 7-chloro-1-azaphenoxathiin.

angle of 146.4° (12) with its 3,4-dihydro-4-oxo-2,3-diazaphenothiazine analog (26), which is essentially planar (see Table I), it is likely that the oxo-substituent, which electronically approximates a ring nitrogen, is responsible for the opening of the dihedral angle. Further studies into this aspect are presently underway and will be forthcoming.

In summary, a new antipsychotic agent has been designed based on accumulated X-ray crystal structure data and structure-activity-relationships (SAR) from the isosterically related phenothiazines, and shown to have the intended activity. Although the original intention was to design a class of compounds which were also spatially comparable to the phenothiazines, a characteristic thought to be requisite for antipsychotic activity (23), rather unexpectedly a compound which was essentially planar resulted and which, more surprisingly, still had the desired pharmacologic activity. Additional studies are at present underway which will attempt to unravel the unexpected and at present inexplicable association of antipsychotic activity with a planar system.

Table VII

Least Squares Planes Passing Through the Atoms Defining the Pyridine and Benzene Rings of 7 and 8 Chloro-1-azaphenoxathiin and Deviations From Those Planes (Å)

A. 7-Chloro-1-azaphenoxathiin (a)

(1) Plane Defined by C1, C2 . . . . . .C6

0.03937x + 0.67379y + 0.73788z = 11.34980

C1 . . . . -0.009	C6 . . . 0.007
C2 . . . . 0.001	S . . . .-0.103
C3 . . . . 0.007	Cℓ . . .-0.060
C4 . . . .-0.009	O . . . 0.021
C5 . . . . 0.001	

(2) Plane Defined by C7, C8 . . . . C11 and N

0.08675x + 0.62841y + 0.77303z = 11.97586

C7 . . . .-0.004	N . . .-0.002
C8 -0.001	S . . .-0.006
C9 . . . . 0.005	O . . .-0.001
C10 . . .-0.003	
C11 . . . 0.006	

(3) Angle Between Planes (1) and (2) = 4.27°

B. 8-Chloro-1-azaphenoxathiin

(1) Plane Defined by C1, C2 . . . . . .C6

0.10124x - 0.68500y + 0.72147z = 5.62233

C1 . . . . 0.007	C6 . . .-0.007
C2 . . . .-0.002	S . . . 0.044
C3 . . . .-0.004	O . . .-0.011
C4 . . . . 0.004	Cℓ . . .-0.017
C5 . . . . 0.002	

(2) Plane Defined by C7, C8 . . . . C11 and N

0.11832x - 0.64402y + 0.75580z = 6.29829

C7 . . . .-0.004	N . . . 0.004
C8 . . . . 0.004	S . . . 0.004
C9 . . . .-0.001	O . . .-0.023
C10 . . .-0.003	
C11 . . . 0.000	

(3) Angle Between Planes (1) and (2) = 3.22°

(a) Expressed as px + qy + rz = s, in orthogonal Å/space.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Infra-red spectra were obtained on a Perkin-Elmer Model 283 spectrometer as potassium bromide pellets. ^{1}H-Nmr spectra were recorded on a Varian Associates Model EM-360 spectrometer and chemical shifts are reported in parts per million (δ) downfield from TMS. ^{13}C-Nmr spectra were obtained on a Varian Associates Model

XL-100 Fourier transform spectrometer operating at 25.2 MHz, equipped with a Nicolet TT-100 data system and on NT-440 frequency synthesizer. ^{13}C-Nmr spectra were run in deuteriochloroform and chemical shifts are reported in parts per million (δ) downfield from TMS. Typical fixed instrument parameters were pulse width 4 μsec (22° flip angle), pulse delay 10.00 seconds, sweep width 5KHz. Mass spectra were obtained on a Hewlett-Packard Model 5930 GCMS system equipped with a Model 5933-A data system at an electron energy of 70eV.

Disodium Salt of 2-Mercapto-3-pyridinol (**1**).

To a solution of 0.078 mole of sodium methoxide in 200 ml. of absolute methanol was added 5.00 g. (0.039) mole of 2-mercapto-3-pyridinol as in the procedure of Martin (2). The resultant salt obtained by this procedure was used without further purification.

8-Chloro-1-azaphenoxathiin (**4**).

To a solution of 1.12 g. (0.0059 mole) of nitro-2,4-dichlorobenzene in 30 ml. of dry distilled DMF under dry argon purge was added 1.00 g. (0.0059 mole) of the disodium salt of 2-mercapto-3-pyridinol (**1**), the entire system maintained at room temperature with continual stirring. Stirring was continued at room temperature for 8 hours after which the system was brought to reflux for 24 hours. At the end of the reflux, the solution was cooled to room temperature and then poured into 100 ml. of ice cold distilled water, after which it was extracted with 1.5 l. ether divided into six equal portions. The ether extracts were then combined and back extracted with 1.5 l. of distilled water after which they were dried over anhydrous sodium sulfate. The dried ether extracts were then concentrated to an oil which was chromatographed over a 250 g. silica gel column eluted with cyclohexane: ethyl acetate (4:1), the product obtained on crystallization directly from the eluted fractions to yield 0.093 g. of **4** (6.7% yield) m.p. 119-121°: ir ν max: 3440, 2920, 1600, 1565, 1470, 1445, 1415, 1285, 1272, 1220, 1190, 865, 800, 795, 735, 720 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 8.05, dd, H-2, 1H, 7.1, m, 5H; ^{13}C-nmr calculated chemical shifts of **4** were based on the 1-azaphenoxathiin model (4) and the additivity parameters of the chloro-substituent (27,28). Calculated *vs.* observed ^{13}C-nmr data are shown in Table II; ms: m/e (% relative intensity): 235 (100), 236 (14), 237 (39), 200 (26.7), 202 (3).

Anal. Calcd. for $C_{11}H_6ClNOS$: C, 56.17; H, 2.55; N, 5.95. Found: C, 56.34; H, 2.75; N, 5.73.

Pharmacologic Materials and Methods.

All pharmacologic testing was done in male Swiss-Webster mice (Texas-Inbred, Houston, Texas) weighing 20-25 g. and acclimatized to laboratory conditions for 3-4 days before testing. All animals were permitted food and water *ad libitum*, and all received doses of the test compound suspended in 5% tween-80 + 95% isotonic saline while control animals received an injection of only the vehicle. Spontaneous motor activity was measured in photocell cages obtained from Woodard Research Corporation.

Spontaneous Motor Activity Testing.

The effect of the test compounds in reducing spontaneous motor activity was measured by placing two animals treated with identical doses of the test compound in the photocell cages. Testing was conducted 60 minutes after an intraperitoneal injection of the test dosage or the vehicle in the case of control animals. The test consisted of a 15 minute counting period immediately following a 5 minute acclimatization period. Further, each dosage was tested in a factorial design in each of the three activity cages to negate any difference in sensitivity among the cages. Control animals were tested simultaneously with the test dosages and after the same time intervals. The ED_{50} of both compounds (defined as the dosage which caused a 50% decrease in the level of performance relative to the control values) was then calculated, where possible, from a semi-logarithmic least squares analysis. The percentage control activity was then plotted against test dosage for each compound, as shown in Figure 1.

X-Ray Data Collection and Data Processing.

The instrumentation, data processing programs and techniques of data collection have already been described in previously published documents (29,30). Therefore, we are giving (Table III) those details which are unique to the studies of the two molecules herein described. Both crystals were irregular fragments obtained from chloroform solutions which were allowed to evaporate slowly at room temperature. The largest dimension of neither crystal exceeded 0.8 mm and, since the fragments were fairly uniform in dimensions and the absorption coefficients are very small (See Table III) no absorption problems were expected nor corrected for. All the information presented here was derived from data collected with MoKα (λ = 0.71069 Å) radiation which was monochromatized with a dense graphite crystal, assumed to be ideally imperfect. Lattice constants and the orientation matrices were obtained from the automatic centering of a number of reflections. In the case of the 7-chloro, 33 reflections were centered which lie in the range of $22° \leqslant 2\theta \leqslant 30°$ while in the case of the 8-chloro compound, a set of 30 reflections having 2θ values between 20° and 27° were used. Each set was processed with program PARAM of the X-Ray '72 system (36) to determine the cell constants listed in Table III. A set of 15 reflections well distributed in reciprocal space and having strong intensities were recentered, automatically, and used to define the orientation matrix for data collection in both instances. Systematic absences show, in both cases, the space group to be $P2_1/a$. However, while the space groups are the same and the cell constants are similar, the two substances are *not* iso-structural.

Intensities were measured using the θ-2θ scan technique. Two standard reflections were used to monitor the stability of the electronics and the possibility of crystal decay in the x-ray beam. There were some minor problems with the diffractometer performance (an attenuator was inserted a few times while not being needed; see refinement of the structures) but there was no difficulty with crystal decay. The details of data collection, such as the number of data points sampled in reciprocal space, length of scan, duration of scans, etc., are summarized in Table III. Standard deviations in the intensities, $\sigma(I)$, were estimated from the expression $\sigma^2(I) = I_{tot} + 2\,\Sigma I_{bg}$ where, I_{tot} is the total intensity of the peak and I_{bg} is the total counts for the background at each end of the peak. In both cases, only those reflections for which $I \geqslant 3\sigma(I)$ were classified as "observed", the remaining being classified as "less thans". In the X-Ray '72 System of programs, the "less than" reflections are used in the least squares refinement provided that F(calc) is greater than F(obs). Lorentz and polarization effects were accounted for and in the least squares refinements the weights used were $w = 1/[\sigma|F|]^2$, where $|F|$ values were calculated on the assumption that Poisson's counting statistics were obeyed.

Solutions and Refinements of the Structures.

Both structures were solved by the multiple-entry tangent formula program MULTAN (37). The E-map based on the starting set of phases giving the highest absolute figure of merit contained all the non-hydrogen atoms, in both cases. Refinement of the positions and anisotropic thermal parameters of the heavy

atoms yielded the final discrepancy indices listed in Table III. The discrepancy indices are defined as

$$R(F) = \Sigma(||Fo|-|Fc||)/\Sigma|Fo|$$

$$\text{and } R_w(F) = [\Sigma w(|Fo|-|Fc|)^2/\Sigma wFo^2]^{1/2}$$

Final shifts in all the parameters were less than 0.1σ for both structural analyses. The atomic scattering factors for the non-hydrogen atoms were calculated from numerical Hartree-Fock (38) wave functions; those for hydrogen of Stewart, Davidson and Simpson (39) were used. The estimated standard deviations were computed from the inverse matrix of the final full-matrix least squares cycle of refinement. No unusually high correlations were found in any of the variables refined during that cycle. Final positional and thermal parameters are presented in Tables IV and V, and bond lengths, angles and least squares planes given in Tables VI and VII were calculated using the data in Tables IV and V. The numbering scheme for both molecules is that given in the stereo drawing of the 8-chloro compound depicted in Figure 2. The hydrogen atoms have identifying numbers which match those of the carbons to which they are bonded. When the refinement was completed for both substances, it was noted that there was a small number of reflections for which the difference between observed and calculated F's was unusually high. All of these data points were noted to have F_o's of zero intensity while the F_c's were indicative of observable intensity in most cases. Examination of the raw data shows that *in all cases* the diffractometer, automatically, inserted an *un-needed* attenuator (attenuation factor 21.90 times) and the resulting intensities were nearly zero in all cases. This problem was tested for, once again, and is now corrected. All other data points were normal and data processing was smooth as can be noted from the standard deviations and R factors listed in the various tables.

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