

The Crystal Structure of Primidone

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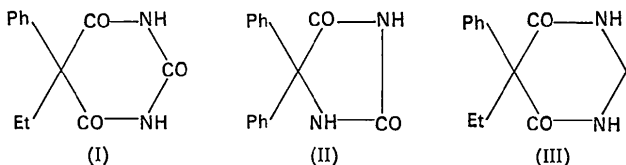
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The crystal structure of the anticonvulsant primidone $C_{12}H_{14}N_2O_2$ has been determined by direct methods and refined by full-matrix least-squares calculations to $R=0.052$ for 1587 observed intensities. The crystals are monoclinic, space group $P2_1/c$, with $a=12.245$ (3), $b=7.088$ (2), $c=14.805$ (4) Å, $\beta=117.82$ (1)°, $Z=4$.

Introduction

After phenobarbitone $C_{12}H_{12}N_2O_3$ [5-ethyl-5-phenylbarbituric acid (I)] and phenytoin $C_{15}H_{12}N_2O_2$ [5,5-diphenylhydantoin (II)], the most frequently used anticonvulsant is primidone $C_{12}H_{14}N_2O_2$ [5-ethyl-5-phenylhexahydropyrimidine-4,6-dione (III)]. Investigated by Bogue & Carrington (1953) and introduced into medicinal use by Handley & Stewart (1952) it is effective in grand mal psychomotor epilepsy and Jacksonian seizures. In man primidone is partly metabolized to phenobarbitone, the resulting plasma levels being capable of exerting significant anticonvulsant effect (Butler & Waddell, 1956; Olesen & Dam, 1967). Gallagher, Smith & Mattson (1970) have demonstrated, however, that primidone has anticonvulsant activity distinct from phenobarbitone.



Compounds which are effective in the treatment of the grand mal form of epilepsy are characterized by having at least one phenyl substituent at the asymmetric carbon. It has been suggested (Lien, 1970; Spinks & Waring, 1963; Camerman & Camerman, 1970) that the configuration of the substituents at this position may well have a bearing on anticonvulsant activity.

Experimental

The compound was supplied in the form of a crystalline powder by Professor R. Spector of Guy's Hospital, London. Crystals obtained by slow evaporation from a solution in absolute ethanol were colourless, acicular shaped, belonging to the monoclinic prismatic crystal class. Weissenberg and precession photographs were taken to obtain approximate cell dimensions. The

systematic absences unambiguously determined the space group as $P2_1/c$. The density was measured by flotation in a mixture of petroleum spirit and chloroform. Accurate values for the cell parameters were determined by least-squares calculations on an automatic four-circle diffractometer (Hilger and Watts Y 290) with $Cu K\alpha_1$ radiation. Crystal data are given in Table 1.

Table 1. Crystal data: primidone

Molecular formula	$C_{12}H_{14}N_2O_2$		
F.W.	218		
Crystal system	Monoclinic		
Habit form	Prismatic, elongated in b		
Space group	$P2_1/c$	D_m	1.267 g cm^{-3}
a	12.245 (3) Å	D_c	1.277 g cm^{-3}
b	7.088 (2)	$F(000)$	464
c	14.805 (4)	$\mu(\text{Cu } K\alpha)$	10.47 cm^{-1}
β	117.82 (1)°	$\lambda(\text{Cu } K\alpha_1)$	1.54051 Å
V_c	1136.45 Å ³	Crystal size	$0.2 \times 0.4 \times 0.2$ mm
Z	4	ω axis	b

Intensities were measured by step-scanning in the $\omega-2\theta$ mode to a limit of $2\theta=100^\circ$. 2110 independent reflections were measured of which 1587 had intensities greater than $3\sigma_c$, where $\sigma_c^2 = N_{B1} + N_{PK} + N_{B2}$; N_{B1} and N_{B2} are the scaled background counts on either side of the peak, and N_{PK} is the scan count. Reflexions with intensities less than $3\sigma_c$ were classed as unobserved and omitted from the refinement. The intensities corrected for Lorentz and polarization factors, were further corrected for vibrational effects and put on an absolute scale (Karle & Hauptman, 1953). Magnitudes for the normalized structure factors, $E(\mathbf{h})$, were calculated. No absorption corrections were applied ($\mu r = 0.2$ to 0.4).

Structure determination and refinement

The structure was determined by direct methods (Karle & Karle, 1966). Phases for 212 out of the 213 reflexions with $|E(\mathbf{h})| > 1.7$ were generated and refined by application of the tangent formula (Karle & Hauptman, 1956) with the computer program *TANFIZ* (Motherwell, Larson & Drew, private communication). An E map

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calculated with the phases determined for the best set ($R_{\text{Karle}}=0.17$) showed all 18 non-H atoms.

The model was refined by full-matrix least-squares calculations with a modified version of Cruickshank & Smith's program with relative weights calculated from $\omega(\mathbf{h}) = (1 - \exp[-(20 \sin^2 \theta / \lambda^2)]) \cdot (1 + 2|F_{\text{min}}| |F_o| +$

Table 2. Observed and calculated structure factors

FOBS are the scaled $|F_o|$ values and FCALC the extinction corrected $|F_c|$ values. * in column O indicates an unobserved reflexion with $I_{\mathbf{h}} < 3\sigma_{\mathbf{h}}$.

h	k	l	FOBS	FCALC	O
0	0	0	100	100	
0	0	1	100	100	
0	0	2	100	100	
0	0	3	100	100	
0	0	4	100	100	
0	0	5	100	100	
0	0	6	100	100	
0	0	7	100	100	
0	0	8	100	100	
0	0	9	100	100	
0	0	10	100	100	
0	0	11	100	100	
0	0	12	100	100	
0	0	13	100	100	
0	0	14	100	100	
0	0	15	100	100	
0	0	16	100	100	
0	0	17	100	100	
0	0	18	100	100	
0	0	19	100	100	
0	0	20	100	100	
0	0	21	100	100	
0	0	22	100	100	
0	0	23	100	100	
0	0	24	100	100	
0	0	25	100	100	
0	0	26	100	100	
0	0	27	100	100	
0	0	28	100	100	
0	0	29	100	100	
0	0	30	100	100	
0	0	31	100	100	
0	0	32	100	100	
0	0	33	100	100	
0	0	34	100	100	
0	0	35	100	100	
0	0	36	100	100	
0	0	37	100	100	
0	0	38	100	100	
0	0	39	100	100	
0	0	40	100	100	
0	0	41	100	100	
0	0	42	100	100	
0	0	43	100	100	
0	0	44	100	100	
0	0	45	100	100	
0	0	46	100	100	
0	0	47	100	100	
0	0	48	100	100	
0	0	49	100	100	
0	0	50	100	100	
0	0	51	100	100	
0	0	52	100	100	
0	0	53	100	100	
0	0	54	100	100	
0	0	55	100	100	
0	0	56	100	100	
0	0	57	100	100	
0	0	58	100	100	
0	0	59	100	100	
0	0	60	100	100	
0	0	61	100	100	
0	0	62	100	100	
0	0	63	100	100	
0	0	64	100	100	
0	0	65	100	100	
0	0	66	100	100	
0	0	67	100	100	
0	0	68	100	100	
0	0	69	100	100	
0	0	70	100	100	
0	0	71	100	100	
0	0	72	100	100	
0	0	73	100	100	
0	0	74	100	100	
0	0	75	100	100	
0	0	76	100	100	
0	0	77	100	100	
0	0	78	100	100	
0	0	79	100	100	
0	0	80	100	100	
0	0	81	100	100	
0	0	82	100	100	
0	0	83	100	100	
0	0	84	100	100	
0	0	85	100	100	
0	0	86	100	100	
0	0	87	100	100	
0	0	88	100	100	
0	0	89	100	100	
0	0	90	100	100	
0	0	91	100	100	
0	0	92	100	100	
0	0	93	100	100	
0	0	94	100	100	
0	0	95	100	100	
0	0	96	100	100	
0	0	97	100	100	
0	0	98	100	100	
0	0	99	100	100	
0	0	100	100	100	

$2|F_o|^2/|F_{\text{max}}|)^{-1}$. A secondary extinction correction (Zachariasen, 1963, 1967) was applied. After two cycles of anisotropic refinement all the H atoms were located from a difference map.

The positional parameters for all atoms, and thermal parameters, anisotropic for the non-H atoms, isotropic for the H atoms, were refined through three cycles to convergence. The final R for the data with $I(\mathbf{h}) > 3\sigma(I)$ was 0.051, 0.071 for all data, and the weighted $R = 0.061$. The value for the coefficient of secondary extinction was $7.7(7) \times 10^{-5}$. Scattering factors used were: O, N and C (Berghuis, Haanappel, Potters, Loopstra, MacGillavry & Veenendaal, 1955) and H (Stewart, Davidson & Simpson, 1965). Structure factors are given in Table 2.

Discussion

The molecule with the numbering scheme is shown in Fig. 1. Fig. 2 shows a view of the molecule looking along C(2)–C(5). Fractional coordinates and thermal parameters are listed in Table 3. Bond lengths and

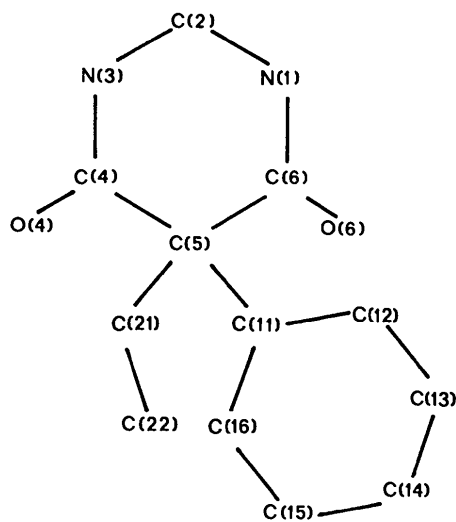


Fig. 1. Atom numbering scheme.

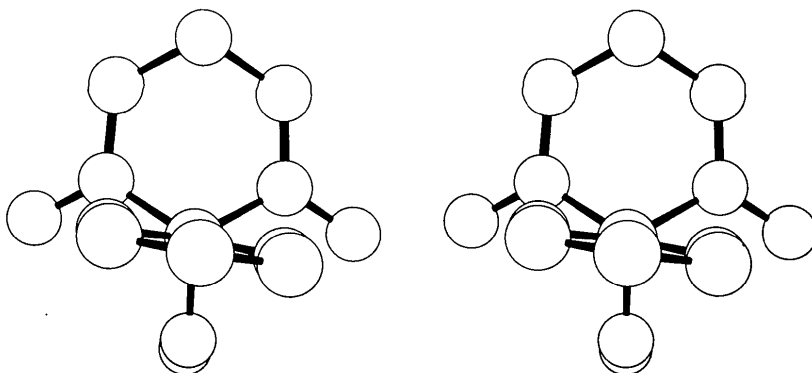


Fig. 2. Stereo view of the molecule of primidone showing the pseudomirror symmetry about the median line C(2)–C(5).

Table 3. Atomic parameters

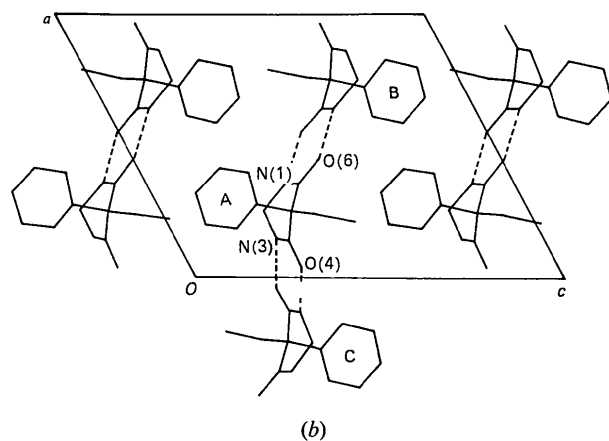
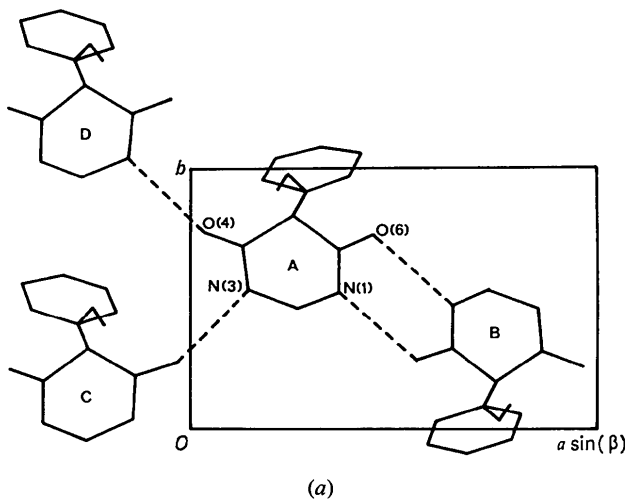
(a) Refined positional and anisotropic thermal parameters for non-H atoms ($\times 10^4$) with e.s.d.'s in parentheses.Anisotropic temperature factor is of the form $\exp \{-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2lhc^*a^*U_{31} + 2hka^*b^*U_{12})\}$.

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	<i>U</i> ₁₂	<i>U</i> ₁₃	<i>U</i> ₂₃
N(1)	0.3603 (2)	0.5216 (3)	0.3801 (2)	315 (10)	310 (10)	434 (12)	79 (9)	101 (9)	6 (9)
C(2)	0.2622 (2)	0.4656 (4)	0.2824 (2)	359 (13)	340 (13)	448 (14)	24 (10)	152 (11)	-55 (12)
N(3)	0.1461 (2)	0.5348 (3)	0.2715 (2)	296 (11)	320 (11)	706 (15)	-47 (9)	170 (11)	-42 (11)
C(4)	0.1351 (2)	0.7042 (3)	0.3048 (2)	305 (13)	313 (12)	570 (16)	46 (10)	186 (11)	98 (11)
C(5)	0.2536 (2)	0.8223 (3)	0.3549 (2)	311 (12)	251 (11)	403 (13)	18 (9)	143 (10)	20 (10)
C(6)	0.3631 (2)	0.6914 (3)	0.4194 (2)	352 (13)	299 (12)	388 (13)	7 (10)	124 (11)	28 (10)
C(11)	0.2768 (2)	0.9127 (3)	0.2710 (2)	392 (13)	211 (11)	432 (14)	32 (9)	198 (11)	-9 (10)
C(12)	0.1814 (3)	0.9521 (4)	0.1753 (2)	566 (18)	437 (16)	460 (15)	-28 (13)	141 (13)	69 (13)
C(13)	0.2050 (4)	1.0433 (5)	0.1030 (3)	1067 (30)	526 (19)	483 (18)	75 (20)	289 (20)	103 (16)
C(14)	0.3221 (5)	1.0960 (5)	0.1257 (3)	1217 (35)	478 (18)	860 (27)	118 (20)	786 (28)	140 (18)
C(15)	0.4164 (4)	1.0616 (5)	0.2203 (4)	766 (25)	546 (19)	1168 (32)	106 (18)	727 (25)	187 (20)
C(16)	0.3954 (3)	0.9721 (4)	0.2941 (3)	437 (16)	406 (15)	723 (20)	47 (12)	323 (15)	106 (14)
C(21)	0.2415 (3)	0.9822 (4)	0.4200 (2)	634 (19)	298 (13)	507 (16)	78 (13)	320 (15)	23 (12)
C(22)	0.2171 (5)	0.9183 (6)	0.5076 (3)	1222 (37)	516 (20)	756 (24)	118 (23)	683 (27)	14 (19)
O(4)	0.0359 (2)	0.7618 (3)	0.2956 (2)	358 (11)	446 (11)	1159 (19)	98 (9)	364 (12)	75 (12)
O(6)	0.4480 (2)	0.7436 (3)	0.5011 (1)	526 (11)	372 (10)	475 (11)	35 (8)	-23 (9)	-26 (8)

Table 3 (cont.)

(b) Refined positional and isotropic thermal parameters for H atoms. \bar{U}_{iso}^2 is the isotropic temperature factor in the expression $B_{iso}^2 = 8\pi^2 \bar{U}_{iso}$.

	<i>x</i>	<i>y</i>	<i>z</i>	$\bar{U}_{iso}^2 (\times 10^4)$
H(11)	0.4209 (29)	0.4456 (45)	0.4094 (22)	162 (74)
H(21)	0.2567 (27)	0.3285 (48)	0.2755 (23)	213 (75)
H(22)	0.2776 (24)	0.5130 (40)	0.2255 (22)	110 (66)
H(31)	0.0858 (33)	0.4616 (52)	0.2427 (25)	295 (90)
H(121)	0.0990 (34)	0.9222 (50)	0.1642 (24)	303 (87)
H(131)	0.1311 (41)	1.0646 (64)	0.0364 (35)	589 (121)
H(141)	0.3420 (32)	1.1548 (53)	0.0747 (28)	393 (96)
H(151)	0.4974 (38)	1.0992 (55)	0.2386 (28)	384 (98)
H(161)	0.4625 (31)	0.9453 (49)	0.3663 (26)	304 (86)
H(211)	0.1767 (26)	1.0638 (42)	0.3737 (21)	115 (65)
H(212)	0.3221 (27)	1.0500 (41)	0.4516 (21)	126 (67)
H(221)	0.1397 (43)	0.8419 (71)	0.4793 (34)	616 (139)
H(222)	0.2902 (40)	0.8372 (69)	0.5555 (33)	588 (127)
H(223)	0.2045 (42)	1.0250 (73)	0.5425 (36)	688 (136)

Fig. 3. Hydrogen-bond scheme viewed (a) along *c* axis, and (b) along *b* axis.

angles (Table 4) exhibit no significant deviations from their expected values except for C(13)–C(14) and C(14)–C(15) which are somewhat low. The torsion angles are listed in Table 5.

The pyrimidine ring *A* exhibits a boat conformation, C(2) and C(5) being displaced by 0.447 and 0.498 Å respectively from the least-squares plane defined for N(1), N(3), C(4), C(6) (plane *A*, Table 6), with C(5) elevated towards the phenyl group. The ring is very symmetrical, corresponding bond lengths and angles on either side of the median line C(2)–C(5) showing no significant differences (Fig. 2).

The phenyl ring *D* is planar to within 0.009 Å (plane *D*, Table 6) with an average bond distance of 1.38 (1) Å. The angle between this plane and the planar portion of the pyrimidine ring is 87°. The rotation of the phenyl ring about C(11)–C(5) is described by the torsion angle C(12)–C(11)–C(5)–C(4) which is +27°.

Table 4. Bond lengths and angles

Standard deviations are given in parentheses.

(a) Bond lengths (Å) for the non-hydrogen atoms

N(1)—C(2)	1.441 (5)	C(6)—O(6)	1.230 (5)
N(1)—C(6)	1.329 (6)	C(11)—C(12)	1.387 (6)
C(2)—N(3)	1.441 (6)	C(11)—C(16)	1.390 (7)
N(3)—C(4)	1.329 (6)	C(12)—C(13)	1.393 (8)
C(4)—O(4)	1.223 (5)	C(13)—C(14)	1.359 (10)
C(4)—C(5)	1.540 (6)	C(14)—C(15)	1.361 (11)
C(5)—C(6)	1.543 (5)	C(15)—C(16)	1.392 (8)
C(5)—C(11)	1.533 (6)	C(21)—C(22)	1.532 (8)
C(5)—C(21)	1.540 (6)		

(b) Bond angles (°) for the non-hydrogen atoms

N(1)—C(2)—N(3)	110.0 (4)	C(6)—C(5)—C(11)	108.4 (3)
C(2)—N(3)—C(4)	122.1 (4)	C(11)—C(5)—C(21)	107.8 (3)
N(3)—C(4)—C(5)	115.8 (4)	C(11)—C(12)—C(13)	120.1 (5)
N(3)—C(4)—O(4)	122.2 (4)	C(12)—C(13)—C(14)	121.0 (6)
O(4)—C(4)—C(5)	122.0 (4)	C(13)—C(14)—C(15)	119.5 (5)
C(4)—C(5)—C(6)	108.8 (3)	C(14)—C(15)—C(16)	121.0 (6)
C(4)—C(5)—C(11)	109.0 (3)	C(15)—C(16)—C(11)	120.1 (5)
C(4)—C(5)—C(21)	111.0 (4)	C(16)—C(11)—C(12)	118.3 (4)
C(5)—C(6)—N(1)	116.0 (3)	C(16)—C(11)—C(5)	119.8 (4)
C(5)—C(6)—O(6)	121.0 (4)	C(21)—C(5)—C(6)	111.7 (3)
O(6)—C(6)—N(1)	122.9 (4)	C(22)—C(21)—C(5)	114.8 (4)
C(6)—N(1)—C(2)	121.8 (3)		

(c) Bond lengths (Å) involving hydrogen atoms

H(11)—N(1)	0.85 (6)	H(151)—C(15)	0.94 (8)
H(21)—C(2)	0.98 (6)	H(161)—C(16)	1.02 (6)
H(22)—C(2)	1.00 (5)	H(211)—C(21)	0.96 (5)
H(31)—N(3)	0.84 (7)	H(212)—C(21)	1.00 (6)
H(121)—C(12)	0.97 (7)	H(221)—C(22)	1.00 (10)
H(131)—C(13)	0.99 (9)	H(222)—C(22)	1.02 (9)
H(141)—C(14)	0.99 (7)	H(223)—C(22)	0.97 (10)

(d) Bond angles involving hydrogen atoms (°)

H(11)—N(1)—C(2)	117 (4)	H(151)—C(15)—C(14)	122 (4)
H(11)—N(1)—C(6)	121 (4)	H(151)—C(15)—C(16)	118 (4)
H(21)—C(2)—N(1)	112 (3)	H(161)—C(16)—C(15)	124 (4)
H(21)—C(2)—N(3)	107 (3)	H(161)—C(16)—C(11)	116 (4)
H(21)—C(2)—H(22)	107 (5)	H(211)—C(21)—C(5)	107 (3)
H(22)—C(2)—N(1)	110 (3)	H(211)—C(21)—C(22)	111 (3)
H(22)—C(2)—N(3)	112 (3)	H(211)—C(21)—H(212)	111 (4)
H(31)—N(3)—C(2)	116 (4)	H(212)—C(21)—C(5)	107 (3)
H(31)—N(3)—C(4)	122 (4)	H(212)—C(21)—C(22)	107 (3)
H(121)—C(12)—C(11)	117 (4)	H(221)—C(22)—C(21)	109 (5)
H(121)—C(12)—C(13)	123 (4)	H(221)—C(22)—H(222)	110 (8)
H(131)—C(13)—C(12)	115 (5)	H(221)—C(22)—H(223)	107 (7)
H(131)—C(13)—C(14)	125 (5)	H(222)—C(22)—C(21)	107 (4)
H(141)—C(14)—C(13)	122 (4)	H(222)—C(22)—H(223)	112 (7)
H(141)—C(14)—C(15)	118 (4)	H(223)—C(22)—C(21)	111 (5)

Molecules of primidone are hydrogen-bonded together to form infinite sheets approximately parallel to (102) (Fig. 3). There are two types of hydrogen bond (Table 7): (i) N(1)—H(11)···O(6) between molecules related by a centre of symmetry, N(1)—O(6) = 2.876 (5) Å; (ii) N(3)—H(31)···O(4) between molecules related by a twofold screw axis, N(3)—O(4) = 2.761 (5) Å.

Configurational similarities in primidone, phenobarbitone and phenytoin

The configurations of the C(5) substituents may be compared by means of the Newman projections (Fig. 4)

Table 5. Torsion angles (°) determined for primidone

The sign of the angle $A-B-C-D$ is positive when a clockwise rotation about $B-C$ is required to bring $A-B-C$ into coincidence with $B-C-D$, viewed along $B-C$.

A	B	C	D	
C(2)—N(1)—C(6)—C(5)				-1
C(2)—N(3)—C(4)—C(5)				+1
C(2)—N(1)—C(6)—O(6)				-2
C(2)—N(3)—C(4)—O(4)				0
N(1)—C(2)—N(3)—C(4)				+141
N(3)—C(2)—N(1)—C(6)				-40
N(1)—C(6)—C(5)—C(4)				+38
N(3)—C(4)—C(5)—C(6)				+141
N(1)—C(6)—C(5)—C(11)				+81
N(3)—C(4)—C(5)—C(11)				-79
N(1)—C(6)—C(5)—C(21)				+19
N(3)—C(4)—C(5)—C(21)				-18
C(4)—C(5)—C(6)—O(6)				+37
C(6)—C(5)—C(4)—O(4)				+142
C(11)—C(5)—C(4)—O(4)				-80
C(11)—C(5)—C(6)—O(6)				+82
C(11)—C(5)—C(21)—C(22)				0
C(12)—C(11)—C(5)—C(4)				+27
C(12)—C(11)—C(5)—C(6)				+146
C(12)—C(11)—C(5)—C(21)				-86
C(16)—C(11)—C(5)—C(4)				+21
C(16)—C(11)—C(5)—C(6)				+140
C(16)—C(11)—C(5)—C(21)				-81
C(21)—C(5)—C(4)—O(4)				+19
C(21)—C(5)—C(6)—O(6)				-20
C(22)—C(21)—C(5)—C(4)				+60
C(22)—C(21)—C(5)—C(6)				-62

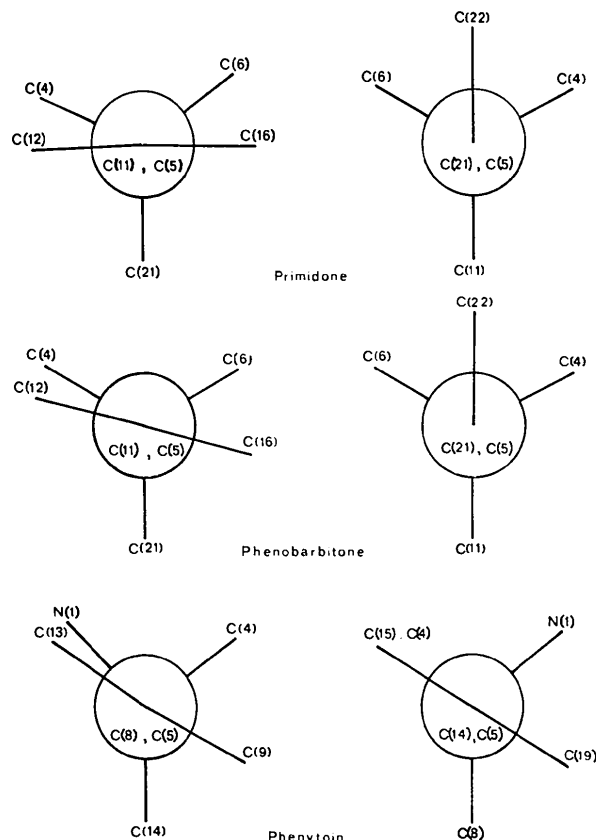


Fig. 4. Newman projections comparing the configuration about C(5) in primidone, phenobarbitone and phenytoin.

Table 6. *Least-squares planes*

Plane	Atom	R.m.s. displacement or deviation (Å)	†Equation of plane
A Pyrimidine	N(1)	0.004	$0.161X^1 + 0.422Y^1 + 0.892Z^1 + 0.990 = 0$
	N(3)		
	C(4)		
	C(6)		
	C(2)*		
	C(5)*		
	O(4)*		
	O(6)*	-0.387	
B	N(3)	0.001	$0.210X^1 - 0.393Y^1 + 0.895Z^1 - 1.695 = 0$
	C(4)		
	O(4)		
	C(5)		
C	N(1)	0.003	$0.492X^1 + 0.355Y^1 - 0.795Z^1 - 0.394 = 0$
	C(6)		
	O(6)		
	C(5)		
D Phenyl	C(11)	0.009	$0.154X^1 - 0.883Y^1 - 0.442Z^1 + 6.34 = 0$
	C(12)		
	C(13)		
	C(14)		
	C(15)		
	C(16)		

* Not included in the calculation of the equation of the plane.

† The equations are defined with respect to orthogonal axes $X^1(a^*)$, $Z^1(c)$, Y^1 expressed in Å.

Table 7. *Hydrogen-bond distances and angles*

X	H	Y	$X \cdots Y$ (Å)	$\angle X-H \cdots Y$ (°)
N(1)	H(11)	O(6 ⁱ)	2.876 (5)	169.6 (3)
N(3)	H(31)	O(4 ⁱⁱ)	2.761 (5)	165.4 (3)

Symmetry code: (i) $1-x, 1-y, 1-z$. (ii) $-x, -\frac{1}{2}+y, \frac{1}{2}-z$.

prepared from the published data for phenobarbitone (Williams, 1973) and phenytoin (Camerman & Camerman, 1971), and that reported herein for primidone. The fragment $\text{Ph}\backslash_{\text{C}}/\text{CO}-\text{NH}$ is a common structural feature, the position of the carbonyl oxygens [O(4) in phenobarbitone, O(6) in primidone and O(6) and O(7) in phenytoin] relative to the centroid of the phenyl rings [C(11) to C(16) in phenobarbitone and primidone; C(8)-C(13) and C(14)-C(19) in phenytoin] being approximately the same. The appropriate distances are listed in Table 8 with the angles between the heterocyclic and phenyl rings.

The relative orientations of the phenyl rings may be influenced by crystal packing and have therefore been omitted from this discussion.

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Calculations were undertaken on the University of London CDC 6600 and University College IBM 360 computers.

Table 8. *Intramolecular distances and dihedral angles*

(a) Intramolecular oxygen-ring centroid/oxygen distances (Å) in primidone, phenobarbitone and phenytoin

Oxygen	Ring centroid or oxygen	Distance (Å)
Primidone		
O(4)	C(11) to C(16)	4.46
O(6)	C(11) to C(16)	4.39
O(4)	O(6)	4.51
Phenobarbitone		
O(4)	C(11) to C(16)	4.34
O(6)	C(11) to C(16)	4.27
O(2)	C(11) to C(16)	5.42
O(4)	O(6)	4.79
Phenytoin		
O(6)	C(8) to C(13)	5.68
O(7)	C(8) to C(13)	3.97
O(6)	C(14) to C(19)	5.51
O(7)	C(14) to C(19)	4.23
O(6)	O(7)	4.56

(b) Dihedral angles (°) in primidone, phenobarbitone and phenytoin

Primidone		
Phenyl-pyrimidine	N(1), N(3), C(4), C(6)	87°
Phenobarbitone		
Phenyl-pyrimidine	N(1), C(2), N(3), C(4), C(6)	86
Phenytoin		
Hydantoin-phenyl	C(8) to C(13)	114
Hydantoin-phenyl	C(14) to C(19)	113
Phenyl C(8) to C(13)-phenyl	C(14) to C(19)	90

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The Crystal Structure of *cis*-9-Isopropylthioxanthene 10-Oxide

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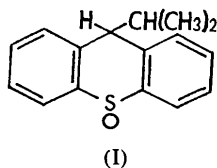
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The crystal structure of *cis*-9-isopropylthioxanthene 10-oxide, $C_{16}H_{16}OS$, has been determined by the heavy-atom method. The refinement was carried out by the least-squares method with anisotropic temperature factors based on three-dimensional data to give a final R value of 0.039 for 2677 reflections. The space group is $P2_1/c$ with $Z=8$, and the unit-cell dimensions are $a=14.356$ (3), $b=8.235$ (2), $c=24.263$ (4) Å, $\beta=106.77$ (3)°. There are two independent molecules in one asymmetric unit of the crystal; however, the two molecules have the same configuration. The distances and angles in the benzenoid rings are normal, and the best planes of the benzene rings make a dihedral angle of 138.8 and 135.5° for the two crystallographically independent molecules. Both the 9-isopropyl and 10-oxide groups are in 'boat-axial' conformation with respect to the central thioxanthene ring. The average sulfur-carbon bond distance is 1.782 (3) Å, and the average sulfur-oxygen bond distance is 1.499 (3) Å. The carbon-sulfur-carbon bond angle is 97.0 (1)°. All these values agree well with those found in other thioxanthene derivatives where the coordination number of the sulfur atom is three. The packing of the molecules in the crystal is determined by the van der Waals interaction.

Introduction

This paper reports the determination of the crystal structure of *cis*-9-isopropylthioxanthene 10-oxide (I)



and is a continuation of the studies on a series of thioxanthene derivatives. The *cis*-isomer of 9-alkylthioxanthene 10-oxide could exist in two conformations; 9-alkyl and 10-oxide groups are both in 'boat equatorial' or in 'boat axial' conformation (Fig. 1). It has been shown that in thioxanthene sulfoxides, the 10-

oxide group prefers the 'boat equatorial' conformation by proton magnetic resonance spectroscopic studies (Evans & Ternay, 1974) and by crystal structure determinations on *cis*-9-methylthioxanthene 10-oxide (Jacobs & Sundaralingam, 1969) and *trans*-thioxanthene-9-ol 10-oxide (Ternay, Chasar & Sax, 1967). The sulfinyl oxygen group governs the stereochemistry of these isomers when the size of the *meso*-substituent is small. However, n.m.r. investigations of *cis*-9-alkylthioxanthene 10-oxides, employing the nuclear Overhauser effect, have shown that the conformation in which the 9-alkyl and sulfinyl oxygen groups are both in the 'boat axial' position becomes significant when the 9-substituent is an ethyl group. Furthermore, *cis*-9-isopropylthioxanthene 10-oxide appears to be conformationally homogeneous in solution (Evans, 1970; Evans, Davenport & Ternay, 1974*a, b*). The purpose of the present study is to determine the conformation of