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The Crystal and Molecular Structure of an Anti-inflammatory Agent, 1-(Cyclopropylmethyl)-4-phenyl-6-methoxy-2(1*H*)-quinazolinone(SL-573)

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The crystal structure of the title compound (SL-573), crystallized from an ethyl acetate solution, has been determined by the single-crystal X-ray diffraction method. The crystals are monoclinic, with the space group $P2_1/a$, and these cell constants: $a=17.395(11)$, $b=8.371(5)$, $c=10.871(7)$ Å, $\beta=99°56(4)'$, and $Z=4$. The intensities were measured visually from equi-inclination integrated Weissenberg photographs taken with Cu $K\alpha$ radiation. The structure was solved by the symbolic addition method. The final R factor was 0.119 for 3284 reflections. The molecules are placed in pairs around the centers of symmetry and are linked by van der Waals' distances less than 3.94 Å. The dihedral angle between the quinazoline and phenyl ring planes was found to be 42.8°.

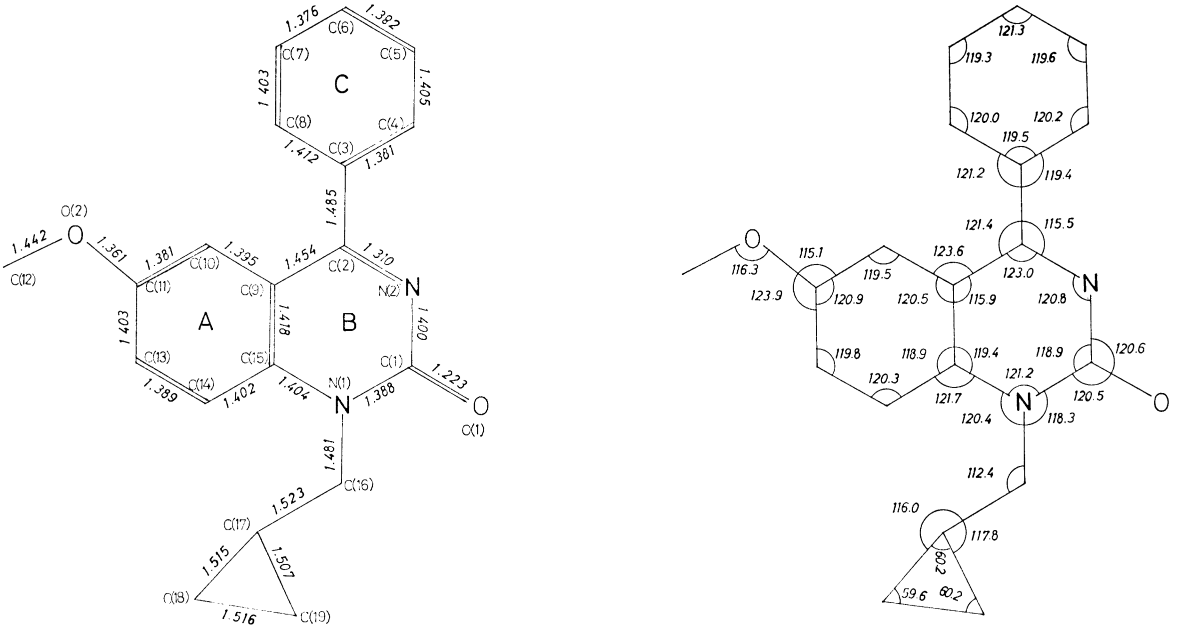
Recently several reports have been published on the syntheses and pharmacology of various quinazolines with marked anti-inflammatory activities.[1-3] Of these, 1-(cyclopropylmethyl)-4-phenyl-6-methoxy-2(1*H*)-quinazolinone(SL-573) has been reported to exhibit not only remarkably anti-inflammatory and analgesic activities in acute inflammation, but also effectiveness in adjuvant-induced chronic inflammation with a low toxicity, especially a minimum gastrointestinal lesion in animal tests.[1] In order to elucidate its pharmacological activities in terms of the molecular conformation, the title compound has now been studied by the X-ray diffraction method.

Experimental

Crystals suitable for X-ray analysis were grown from an ethyl acetate solution. They were rectangular prisms elongated along the b-axis. The unit-cell dimensions were determined from Weissenberg photographs calibrated with NaCl powder patterns superposed on them. The density was measured by flotation in an aqueous solution of KI. The crystal data are listed in Table 1. Crystal specimens with dimensions of 0.527×0.466×0.303 and 0.507×0.327×0.547 mm were selected for data collection around the a and b axes respectively. Weissenberg photographs for the layers of 0kl-12kl and h0l-h6l were taken with nickel-filtered Cu $K\alpha$ radiation. The intensities of 3284 independent reflections were estimated visually. The intensities were corrected for Lorentz and polarization factors, but no corrections were applied for the absorption and the spot shapes. The absolute scale and overall temperature factors ($B=3.81$ Å^2) were determined by Wilson's plot.[4]

Solution and Refinement of the Structure

The symbolic addition procedure[5] was used to solve the structure. Normalized structure factors, $|E_h|$, were calculated, and a set of $\sum_2$ relationships was tabulated. A starting set of three origin-defining reflections and three reflections assigned symbols are shown in Table 2. Each of these reflections had a high $|E_h|$ value and a large number of $\sum_2$ interactions. The signs or symbols of 252 reflections out of 473 with $|E_h|\geqslant 1.4$



(a) (b)

Fig. 1. (a) Bond distances (l/Å) of the molecule and numbering system. (b) Bond angles (φ/°) of the molecule.

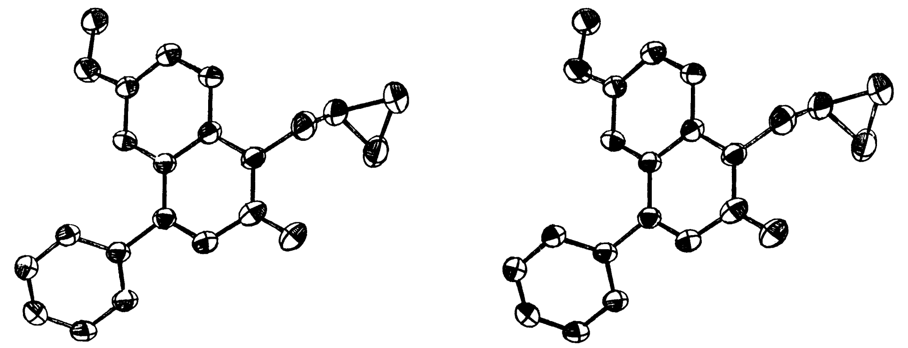


Fig. 2. A stereoview of the molecular structure of SL-573. The thermal ellipsoids are drawn at the 50% probability level. This drawing (0.765 inch/Å) was prepared using the computer program ORTEP (C. K. Johnson, 1965).

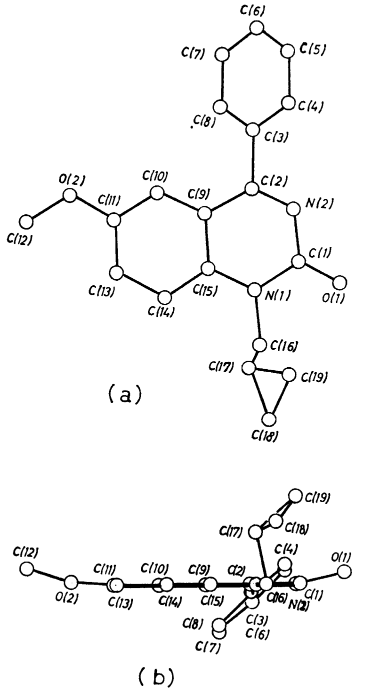


Fig. 3. The molecule viewed (a) normal to the quinazoline ring plane, (b) along the quinazoline ring plane from C(2)–C(3) direction.

TABLE 1. CRYSTAL DATA

Crystal system	monoclinic
Systematic absence	*h*0*l* with odd *l*, 0*k*0 with odd *k*
Space group	$P2_1/a$
a	17.395±0.011 Å
b	8.371±0.005
c	10.871±0.007
β	99°34′±4′
V	1561.0 Å^3
Z	4
D_c	1.304 g/cm^3
D_m	1.307 g/cm^3

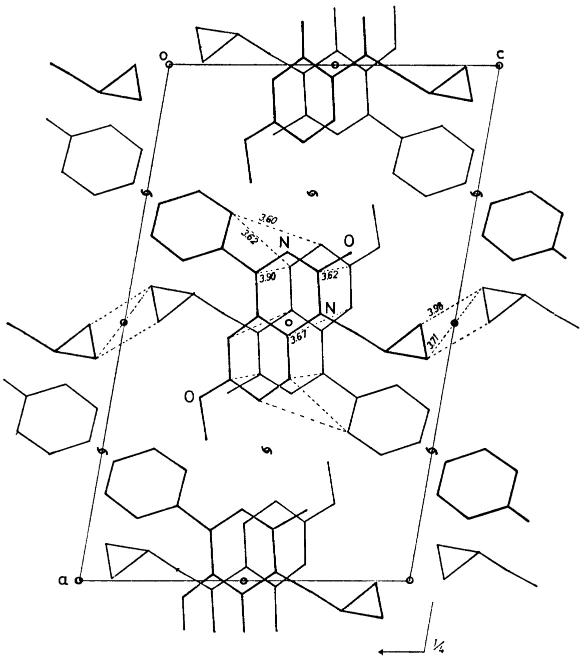


Fig. 4. Projection of the structure along the b axis.

TABLE 2. INITIAL SET

H	$\lvert E_h \rvert$	Sign or symbol
$32\bar{9}$	4.26	+
433	2.67	+
$26\bar{5}$	4.67	+
12, 7, 0	4.75	*a*
11, 3, 3	4.05	*b*
$24\bar{8}$	4.03	*c*

were determined by Σ_2 relationships. The symbols had two possibilities, $a=b=c=(+)$ or $a=b=(-)$ and $c=(+)$. Three-dimentional *E*-maps were computed with each of these phase combinations. The positions of 19 non-hydrogen atoms were obtained from the *E*-map based on the latter combination, $a=b=(-)$ and $c=(+)$. The remaining four atoms were revealed on a subsequent Fourier map. The *R* value, $\Sigma||F_o|-|F_c||/\Sigma|F_o|$, at this stage was 0.411 for all 23 non-

TABLE 3. FINAL ATOMIC PARAMETERS ($\times 10^4$), WITH THEIR STANDARD DEVIATIONS IN PARENTHESES

(a) Fractional atomic coordinates and anisotropic temperature factors$^{a)}$ for non-hydrogen atoms.

Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(1)	4013(3)	8201(6)	5682(5)	25(2)	133(8)	89(5)	12(6)	35(5)	5(10)
C(2)	4032(2)	6865(6)	3780(4)	19(1)	113(7)	63(4)	3(5)	9(4)	25(8)
C(3)	3562(2)	6239(6)	2614(5)	17(1)	134(8)	69(4)	2(5)	7(4)	20(9)
C(4)	2887(3)	5397(7)	2676(5)	20(2)	173(9)	78(5)	−5(6)	12(4)	43(11)
C(5)	2448(3)	4750(8)	1588(6)	23(2)	236(12)	87(5)	−54(8)	8(5)	28(13)
C(6)	2702(3)	4945(8)	457(5)	28(2)	256(13)	69(5)	−28(8)	−3(5)	2(13)
C(7)	3351(3)	5844(8)	360(5)	26(2)	229(12)	66(4)	−14(7)	13(4)	32(12)
C(8)	3798(3)	6474(7)	1445(5)	20(2)	179(9)	71(4)	17(6)	15(4)	40(11)
C(9)	4878(2)	6755(6)	4008(4)	18(1)	112(7)	60(4)	−1(5)	9(4)	16(8)
C(10)	5305(2)	5920(6)	3239(5)	18(1)	125(7)	67(4)	7(5)	0(4)	3(9)
C(11)	6110(2)	5966(6)	3487(5)	19(2)	143(8)	65(4)	13(6)	14(4)	−10(9)
C(12)	7288(3)	4789(10)	3079(6)	20(2)	291(14)	96(6)	57(8)	18(5)	−58(15)
C(13)	6503(3)	6838(7)	4503(5)	21(2)	156(9)	79(5)	0(6)	20(4)	−17(10)
C(14)	6081(3)	7616(6)	5302(5)	19(1)	145(8)	73(4)	−16(6)	10(4)	−34(10)
C(15)	5264(2)	7568(6)	5080(5)	21(2)	111(7)	66(4)	−5(5)	20(4)	5(8)
C(16)	5209(3)	9142(6)	7023(5)	33(2)	110(7)	82(5)	11(6)	31(5)	−51(10)
C(17)	5544(3)	7986(7)	8056(5)	30(2)	151(9)	75(5)	−21(7)	26(5)	−49(10)
C(18)	5690(3)	8666(8)	9366(6)	44(3)	247(13)	76(5)	−44(10)	14(6)	−96(14)
C(19)	5028(3)	7497(8)	8976(6)	47(3)	190(11)	73(5)	−18(9)	43(6)	−16(12)
N(1)	4820(2)	8307(5)	5887(4)	21(1)	119(6)	73(4)	−5(5)	26(3)	−21(8)
N(2)	3634(2)	7517(6)	4570(4)	20(1)	156(7)	74(4)	8(5)	17(3)	−2(8)
O(1)	3638(2)	8732(6)	6448(4)	30(1)	238(9)	99(4)	24(6)	45(4)	−79(10)
O(2)	6474(2)	5142(5)	2671(4)	19(1)	229(8)	89(4)	45(5)	5(3)	−90(9)

a) The anisotropic temperature factors are expressed in this form:

$$\exp\left[-(B_{11}h^2+B_{22}k^2+B_{33}l^2+2B_{12}hk+2B_{13}hl+2B_{23}kl)\right].$$

(b) Atomic coordinates ($\times 10^4$) for hydrogen atoms.

Atom	x	y	z	B(Å^2)	Atom	x	y	z	B(Å^2)
H(1)	2690	5240	3577	3.97	H(10)	5673	9883	6787	4.01
H(2)	1908	4112	1634	4.53	H(11)	5063	6293	9363	4.93
H(3)	2382	4363	−378	4.57	H(12)	4428	7864	8859	4.93
H(4)	3518	6052	−552	4.49	H(13)	6199	8350	10022	5.35
H(5)	4330	7163	1388	3.94	H(14)	5565	9922	9518	5.35
H(6)	5004	5240	2441	3.37	H(15)	5881	7330	7480	4.02
H(7)	7140	6889	4669	3.88	H(16)	6700	4600	2600	4.73
H(8)	6385	8272	6108	3.66	H(17)	7400	4400	2600	4.73
H(9)	4793	9919	7361	4.01	H(18)	7400	4200	4000	4.73

hydrogen atoms. The refinement of the structure was carried out by the block-diagonal least-squares method until the R value reached 0.152. A difference Fourier map using all the reflections indicated the positions of all 18 hydrogen atoms. In further refinement, however, the hydrogen atom coordinates calculated from geometrical considerations were used and were not refined. All the hydrogen atoms were given the same isotropic temperature factors as those of the atoms to which they are attached. The final R value was 0.119 for all the observed reflections. The final atomic parameters are shown in Table 3. The atomic scattering factors were taken from the "Internatioal Tables for X-ray Crystallography".6) A list of the observed and calculated structure factors is kept by the office of the Chemical Society of Japan, (Document No. 7628).

All the calculations were carried out on the IBM 370 computer at the Computer Center of the Sumitomo Chemical Co., Ltd., using UNICS programs7) revised for IBM 370 by Michio Kimura, one of the present authors.

Results and Discussion

The bond distances and angles are shown in Fig. 1. The mean estimated standard deviations of the bond distances and angles for the non-hydrogen atoms were 0.011 Å and 0.7° respectively. The averages of the aromatic C–C bond distances and C–C–C angles in the benzene ring C are 1.393 Å and 120.0° respectively. The six-membered ring, A, has a mean C–C bond distance of 1.393 Å and a mean C–C–C angle of 120.0°. These values are quite reasonable. The C(1)–N(1) bond distance of 1.388 Å is similar to those observed in other heterocyclic rings, for instance, dihydrothymidine8), dihydrouracil9); and 5-methyluridine10).

Table 4. Equations of least-squares planes in the $AX+BY+CZ+D=0$[a)] form

The displacements (l/Å) of atoms from the planes are given in square brackets.

Plane I: Rings A and B

$-0.0925X-0.8447Y+0.5272Z+3.2259=0$

[C(1) 0.088, C(2) −0.077, C(3) −0.238, C(9) −0.003, C(10) 0.071, C(11) 0.054, C(12) 0.458, C(13) −0.035, C(14) −0.053, C(15) −0.017, C(16) 0.011, N(1) 0.002, N(2) −0.015, O(1) 0.218, O(2) 0.102]

Plane II: Rings C and C(2)

$0.5178X-0.8460Y+0.1271Z+1.0888=0$

[C(2) 0.021, C(3) −0.009, C(4) −0.019, C(5) −0.002, C(6) 0.040, C(7) −0.016, C(8) −0.013, C(9) 0.871, N(2) −0.766]

Plane III: Rings A, C(2), and N(1)

$-0.1024X-0.8359Y+0.5393Z+3.2109=0$

[C(1) 0.148, C(2) −0.055, C(3) −0.230, C(9) 0.007, C(10) 0.056, C(11) 0.029, C(13) −0.045, C(14) −0.038, C(15) 0.009, C(16) 0.077, N(1) 0.052, N(2) 0.031, O(2) 0.054]

The dihedral angles between Planes I and II, and Planes II and III, are 42.80° and 43.72° respectively.

a) X, Y, and Z are orthogonal coordinates in Å related to the crystal axes by:

$$\begin{bmatrix} X \\ Y \\ Z \end{bmatrix} = \begin{bmatrix} 1 & 0 & \cos\beta \\ 0 & 1 & 0 \\ 0 & 0 & \sin\beta \end{bmatrix} \begin{bmatrix} a \\ b \\ c \end{bmatrix}$$

Table 5. Intermolecular distances (<4Å)

	Distance		Distance
C(15)···C(10)^{i}	3.67 Å	C(2)···C(14)^{i}	3.90 Å
C(14)···C(2)^{i}	3.90	C(13)···C(2)^{i}	3.81
C(14)···C(4)^{i}	3.62	C(13)···C(4)^{i}	3.60
C(1)···C(11)^{i}	3.62	C(4)···C(14)^{i}	3.62
C(2)···C(13)^{i}	3.81	C(14)···C(3)^{i}	3.93
C(9)···C(9)^{i}	3.63	C(1)···C(10)^{i}	3.77
C(10)···C(1)^{i}	3.77	C(2)···C(11)^{i}	3.84
C(10)···C(9)^{i}	3.79	C(9)···C(10)^{i}	3.79
C(11)···C(1)^{i}	3.62	C(11)···C(2)^{i}	3.84
C(12)···C(1)^{i}	3.77	C(4)···C(13)^{i}	3.60
C(15)···C(9)^{i}	3.77	C(19)···C(18)^{ii}	3.98
C(1)···C(12)^{i}	3.77	C(18)···C(18)^{ii}	3.71
C(3)···C(14)^{i}	3.93		

Symmetry code	Symmetry operation		
none	x	y	z
i	$1-x$	$1-y$	$1-z$
ii	$1-x$	$2-y$	$2-z$

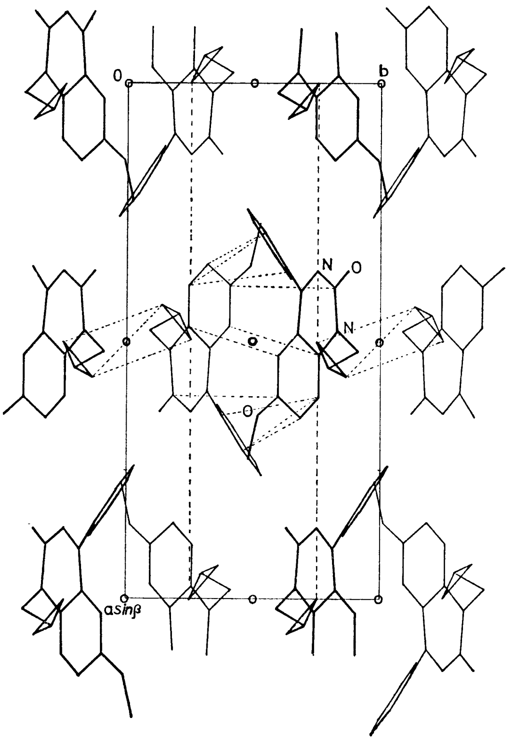


Fig. 5. Projection of the structure along the c axis.

The O(1)–C(1) bond distance of 1.223 Å are comparable with the value of 1.211 Å for 10-methylisoalloxazine hydrobromide dihydrate[11)] and that of 1.213 Å for 3-phenyl-2,4-(1*H*,3*H*)-quinazolinedione.[13)] The molecular conformation and thermal ellipsoids are illustrated by a stereoview in Fig. 2. Interest in the conformation of SL-573 is probably centered on the geometry of the linkage [C(2)–C(3) bond] between the phenyl group and the quinazoline ring. The quinazoline ring is very nearly planar, and the phenyl ring is planar within the limits of accuracy. The least-squares planes and the deviations of atoms from these planes are given in Table 4. The O(2) and C(16) atoms are on the quinazoline ring plane, and the O(1) and C(12) atoms deviate from the plane, as is shown in Fig. 3. The C(2)–C(3) bond length is 1.485 Å, close to the value of 1.477 Å proposed by Dewar and Schmeising[12)], for the C_{sp^2}–C_{sp^2} single bond. This fact suggests that π-bonding is absent in the C(2)–C(3) bond. The steric repulsion caused by the hydrogens prevents the phenyl plane from being coplanar with the quinazoline ring; the dihedral angle between the phenyl and quinazoline planes is 42.8°. An inspection of the intermolecular distances (Table 5) indicates that the packing of the molecules is very efficient. The molecular arrangement in the crystal viewed along the b and c axes is illustrated in Figs. 4 and 5. The molecules are placed in pairs around the centers of symmetry and form tightly packed columns of molecules in the b axis direction. All the intermolecular contacts correspond to the van der Waals interaction. The shortest intermolecular distance is 3.60 Å, while the others are almost all within 3.94 Å.

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