which is typical for a double bond. The C–H bonds in the methyl groups range from 0·86 to 1·07 Å with a mean standard deviation of 0·06 Å. The other C–H bonds have distances between 0·88 and 1·06 Å with a mean standard deviation of 0·03 Å. The corresponding isotropic temperature factors lie between 0·10 and 0·16 Å^2 for the methyl H atoms and between 0·05 and 0·10 Å^2 for the other H atoms.

The phenyl ring is planar. For the indene ring system the deviations from planarity are small with a maximum value of 0·02 (1) Å. In the crystalline state the planes through the indene and phenyl rings form an angle of 80·3 (8)° with each other. There are no intermolecular contact distances shorter than the sums of the corresponding van der Waals radii. The packing of the molecules in the unit cell is shown in Fig. 2.

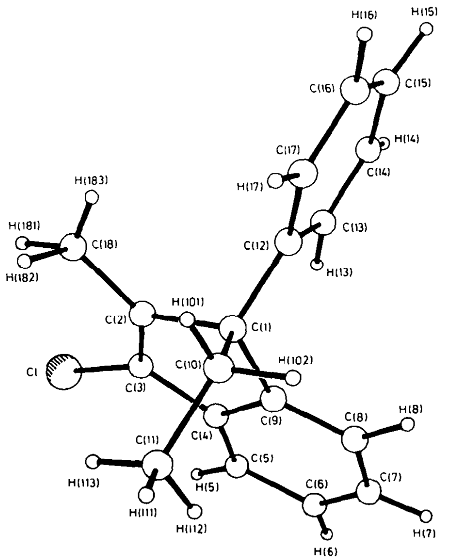

Fig. 1. Perspective view of the $C_{18}H_{17}Cl$ molecule with numbering of the atoms.

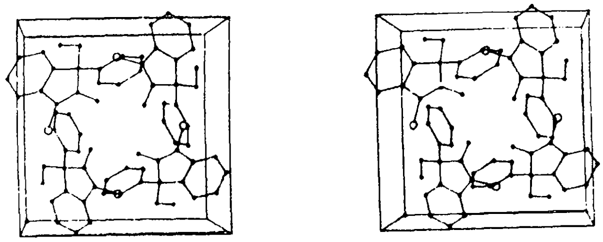

Fig. 2. Stereoscopic view of the molecular packing viewed along **c**.

All calculations were performed on a Univac 1108 computer at the Rechenzentrum der Universität Karlsruhe. The structure plots have been made with the *SHELXTL* system.

One of us (KV) thanks Professor Dr H. Wondratschek for the facilities placed at his disposal. We thank Mr Mattern for technical assistance.

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(–)-2(*R*)-[2,3-Dihydro-2(*R*)-isopropyl-4-oxo-4*H*-1-benzopyran-6-yl]-*N*-[1(*R*)-phenylethyl]propionamide: a Chromanone Amide with Three Chiral Centres

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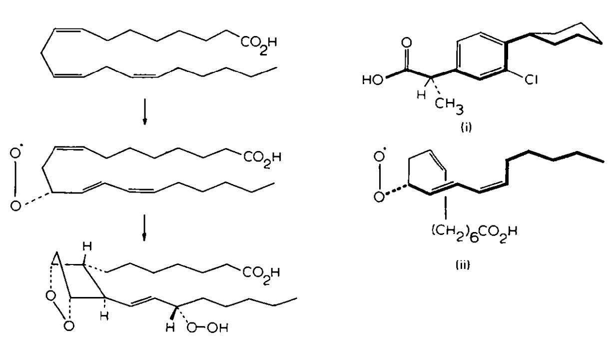
Abstract. $C_{23}H_{27}NO_3$, orthorhombic, $P2_12_12_1$, $Z = 4$, $a = 34{\cdot}314$ (6), $b = 11{\cdot}866$ (2), $c = 5{\cdot}059$ (1) Å, $V = 2059{\cdot}8$ Å^3, $D_c = 1{\cdot}18$ Mg m^{-3}, λ(Cu $K\alpha$, Ni-filtered) = 1·5418 Å, R = 0·049 for 1207 reflexions. All H atoms were located. The compound had been synthesized using an (R)-α-methylbenzylamine; the present study shows that all three asymmetric centres have the same chirality.

0567-7408/80/123193-04$01.00

Introduction. A variety of non-steroidal and anti-inflammatory drugs have been prepared which are believed to act by inhibition of prostaglandin cyclooxygenase. Appleton & Brown (1980) have identified common structural features in a number of these inhibitors and it would seem that these features could be present in the peroxy radical intermediate prior to its cyclization to prostaglandin G (Fig. 1).

The title compound (Fig. 2) was synthesized by Fisons Ltd as part of their anti-inflammatory programme and supplied to us in crystal form by Dr Richard Appleton. The compound contains three chiral centres, at C(9), C(13) and C(16). The chirality at C(16) was known since (*R*)-α-methylbenzylamine was used in the synthesis. The purpose of the present investigation was to determine the chirality at the other two centres because the stereochemistry of these compounds [especially the configuration at C(13)] is crucial to their biological activity. The bold bonds in Fig. 2 indicate the common structural features identified by Appleton & Brown (1980) (*cf.* Fig. 1*b*). Note that the keto function at C(7) is located at a position equivalent to the site in the peroxy radical which is oxygenated in the overall reaction (*cf.* the Cl atom in Fig. 1*b*, i). Appleton & Brown have suggested that a substituent in this position would be sterically acceptable and could bind to the oxygen-orientating site on the enzyme.



(*a*) (*b*)

Fig. 1. (*a*) The prostaglandin cyclooxygenase pathway. Arachidonic acid is converted to prostaglandin G_2 *via* a peroxy radical intermediate. (*b*) (i) 2(*S*)-(3-Chloro-4-cyclohexylphenyl)propionic acid: an example of a potent cyclooxygenase inhibitor. (ii) The peroxy radical, folded to give optimum structural identity (bold lines) with a number of cyclooxygenase inhibitors.

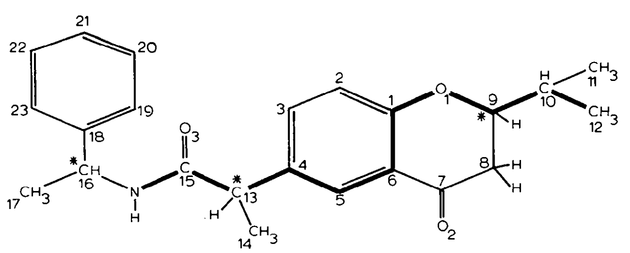


Fig. 2. The title compound and numbering scheme used. Chiral centres are indicated with asterisks. The bold bonds indicate the common structural features with a number of cyclooxygenase inhibitors (*cf.* Fig. 1*b*).

Intensities were measured in the range $3° \le \theta \le 55°$ on an Enraf–Nonius CAD-4 diffractometer with the ω–2θ scan technique and Cu $K\alpha$ (Ni-filtered) radiation.

Table 1. *Fractional atomic coordinates* ($\times 10^4$) *and their e.s.d.'s, and* U_{eq} ($Å^2 \times 10^3$)

H atoms have a common isotropic thermal parameter $U = 0.05$ $Å^2$. For the non-hydrogen atoms $U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33})$.

	x	y	z	U_{eq}
C(1)	3510 (1)	5927 (5)	−1931 (14)	47 (4)
C(2)	3823 (2)	5960 (6)	−190 (17)	60 (5)
C(3)	3928 (2)	5020 (6)	1194 (16)	60 (5)
C(4)	3728 (2)	3997 (5)	873 (14)	45 (4)
C(5)	3429 (1)	3966 (5)	−940 (13)	42 (4)
C(6)	3318 (1)	4918 (5)	−2357 (14)	41 (4)
C(7)	3005 (2)	4878 (6)	−4365 (15)	48 (4)
C(8)	2906 (2)	5969 (6)	−5673 (15)	59 (5)
C(9)	3007 (2)	6979 (5)	−3958 (16)	52 (4)
C(10)	2963 (2)	8120 (6)	−5340 (18)	69 (5)
C(11)	3103 (2)	9080 (6)	−3583 (22)	96 (7)
C(12)	2542 (2)	8309 (6)	−6141 (23)	108 (7)
C(13)	3855 (1)	3000 (5)	2507 (14)	48 (4)
C(14)	3573 (2)	2005 (5)	2556 (17)	68 (5)
C(15)	4256 (2)	2569 (6)	1548 (17)	52 (5)
C(16)	4884 (2)	1788 (5)	2941 (14)	47 (4)
C(17)	4963 (2)	865 (6)	5003 (16)	56 (5)
C(18)	5215 (2)	2642 (5)	2917 (14)	43 (4)
C(19)	5244 (2)	3485 (6)	4792 (16)	57 (5)
C(20)	5568 (2)	4184 (6)	4788 (17)	68 (5)
C(21)	5859 (2)	4060 (6)	2985 (19)	68 (5)
C(22)	5828 (2)	3232 (6)	1067 (16)	61 (5)
C(23)	5508 (2)	2517 (5)	1036 (14)	52 (4)
O(1)	3408 (1)	6911 (3)	−3118 (10)	57 (3)
O(2)	2846 (1)	3996 (4)	−5004 (10)	58 (3)
O(3)	4327 (1)	2453 (5)	−790 (11)	75 (4)
N(1)	4503 (1)	2299 (4)	3484 (11)	49 (4)
H(N1)	4426	2449	5362	
H(C2)	3972	6677	56	
H(C3)	4151	5062	2459	
H(C5)	3288	3240	−1238	
H(C8)	2621	5981	−6069	
H′(C8)	3057	6024	−7363	
H(C9)	2829	6971	−2386	
H(C10)	3132	8136	−6954	
H(C11)	3383	8953	−3139	
H′(C11)	2944	9082	−1927	
H″(C11)	3074	9822	−4489	
H(C12)	2374	8291	−4526	
H′(C12)	2460	7691	−7372	
H″(C12)	2515	9050	−7040	
H(C13)	3892	3264	4367	
H(C14)	3536	1743	693	
H′(C14)	3319	2280	3273	
H″(C14)	3657	1344	3638	
H(C16)	4873	1413	1173	
H(C17)	4853	1070	6765	
H′(C17)	5248	711	5180	
H″(C17)	4823	207	4211	
H(C19)	5048	3557	6419	
H(C20)	5589	4824	6064	
H(C21)	6094	4559	3069	
H(C22)	6036	3154	−307	
H(C23)	5488	1911	−335	

(Preliminary studies had indicated that reflexions at higher angles were so weak that their measurement was not warranted.) Orientation and standard-intensity checks were made at fixed intervals. There were 5168 reflexions (unique and symmetry related) in the range $3° \leq \theta \leq 55°$ but 1310 of these were considered to be too weak to be included in the refinement. The remaining 3858 intensities were merged to give a unique set of 1306 reflexions [$R_{sym} = 0·04$, where $R_{sym} = \sum_h \sum_i |\bar{I}(h) - I(h)i| / \sum_h \sum_i I(h)i$]. In the latter stages of the refinement only reflexions with $F \geq 3\sigma(F)$ were used and this reduced the unique set to 1207 reflexions.

The structure was solved with *MULTAN* (Main, Woolfson, Lessinger, Germain & Declercq, 1974). There were 182 reflexions with $E \geq 1·37$ and these were used for phase generation. The reflexions used in the starting set were as follows:

h	k	l	E	φ	
0	10	0	2·72	360°	A $\sum_1$ reflexion
0	5	2	3·66	90	Origin-fixing reflexions
31	0	1	3·16	90	
17	1	0	2·67	90	
9	0	1	2·56	±90	Multiple assignment.
5	1	1	2·37	±45	

Four sets of phases were generated with combined figures of merit of 3·00, 1·77, 0·42 and 0·30. The peak-search routine of *SHELX* 76 (Sheldrick, 1976) was applied to the electron density distributions calculated from the best set [CFOM = 3·00, $\varphi(901) = -90°$, $\varphi(511) = +45°$] and this revealed 25 of the 27 non-hydrogen atoms. A Fourier synthesis was computed with these 25 atoms and from the resultant electron density map the missing non-hydrogen atoms were located. Five cycles of full-matrix positional and isotropic thermal parameter refinement with *SHELX* 76 followed by eight cycles using anisotropic thermal parameters reduced R from 0·18 to 0·083; at this stage all the H atoms were visible on a difference map. The coordinates of the H atoms were calculated assuming standard geometries and these atoms were included in the refinement but were not themselves refined. Five additional cycles of refinement reduced R to 0·049.

Discussion. The fractional atomic coordinates, bond lengths, bond angles, and torsion angles are given in Tables 1, 2 and 3.* There are no unusual values for these parameters and they provide a good basis for comparison with the values found in other chromone compounds (Morris, Geddes, Sheldrick & Akrigg, 1980) where the presence of large amounts of water in the crystal lattice inhibited the refinements. There is one intermolecular hydrogen bond of length 2·965 Å,

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35623 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Bond distances* (Å) *and angles* (°)

C(1)–O(1)	1·358 (7)	C(10)–C(12)	1·517 (9)
C(1)–C(2)	1·389 (8)	C(13)–C(14)	1·526 (8)
C(1)–C(6)	1·385 (8)	C(13)–C(15)	1·547 (8)
C(2)–C(3)	1·365 (9)	C(15)–O(3)	1·215 (8)
C(3)–C(4)	1·403 (8)	C(15)–N(1)	1·334 (8)
C(4)–C(5)	1·377 (8)	C(16)–N(1)	1·467 (6)
C(4)–C(13)	1·507 (8)	C(16)–C(17)	1·536 (9)
C(5)–C(6)	1·392 (8)	C(16)–C(18)	1·521 (8)
C(6)–C(7)	1·479 (8)	C(18)–C(19)	1·382 (9)
C(7)–O(2)	1·224 (7)	C(18)–C(23)	1·392 (8)
C(7)–C(8)	1·492 (9)	C(19)–C(20)	1·388 (9)
C(8)–C(9)	1·519 (9)	C(20)–C(21)	1·359 (10)
C(9)–O(1)	1·444 (7)	C(21)–C(22)	1·385 (10)
C(9)–C(10)	1·531 (9)	C(22)–C(23)	1·389 (8)
C(10)–C(11)	1·522 (11)		

O(1)–C(1)–C(2)	117·1 (5)	C(11)–C(10)–C(12)	110·2 (6)
O(1)–C(1)–C(6)	123·5 (5)	C(4)–C(13)–C(14)	115·7 (5)
C(2)–C(1)–C(6)	119·4 (6)	C(4)–C(13)–C(15)	110·2 (5)
C(1)–C(2)–C(3)	120·4 (6)	C(14)–C(13)–C(15)	108·2 (5)
C(2)–C(3)–C(4)	121·2 (6)	O(3)–C(15)–C(13)	121·4 (6)
C(3)–C(4)–C(5)	117·7 (6)	O(3)–C(15)–N(1)	124·0 (6)
C(3)–C(4)–C(13)	118·3 (6)	C(13)–C(15)–N(1)	114·5 (7)
C(5)–C(4)–C(13)	124·0 (6)	N(1)–C(16)–C(17)	108·9 (5)
C(4)–C(5)–C(6)	121·8 (5)	N(1)–C(16)–C(18)	113·0 (5)
C(1)–C(6)–C(5)	119·3 (6)	C(17)–C(16)–C(18)	110·5 (5)
C(1)–C(6)–C(7)	118·8 (6)	C(16)–C(18)–C(19)	122·0 (6)
C(5)–C(6)–C(7)	121·9 (5)	C(16)–C(18)–C(23)	118·2 (6)
O(2)–C(7)–C(6)	122·1 (6)	C(19)–C(18)–C(23)	119·6 (6)
O(2)–C(7)–C(8)	121·6 (6)	C(18)–C(19)–C(20)	119·3 (7)
C(6)–C(7)–C(8)	116·2 (6)	C(19)–C(20)–C(21)	121·6 (7)
C(7)–C(8)–C(9)	112·3 (6)	C(20)–C(21)–C(22)	119·4 (6)
O(1)–C(9)–C(8)	109·9 (5)	C(21)–C(22)–C(23)	120·1 (6)
O(1)–C(9)–C(10)	106·1 (5)	C(18)–C(23)–C(22)	119·9 (6)
C(8)–C(9)–C(10)	114·5 (6)	C(1)–O(1)–C(9)	115·1 (4)
C(9)–C(10)–C(11)	111·4 (7)	C(15)–N(1)–C(16)	121·9 (6)
C(9)–C(10)–C(12)	110·2 (6)		

Table 3. *Torsion angles* (°)

O(1)–C(9)–C(10)–C(11)	−53·5 (8)
O(1)–C(9)–C(10)–C(12)	−176·2 (7)
C(8)–C(9)–C(10)–C(11)	−174·9 (6)
C(8)–C(9)–C(10)–C(12)	62·4 (9)
C(3)–C(4)–C(13)–C(14)	166·4 (6)
C(3)–C(4)–C(13)–C(15)	−70·5 (8)
C(5)–C(4)–C(13)–C(14)	−14·1 (9)
C(5)–C(4)–C(13)–C(15)	109·0 (7)
C(4)–C(13)–C(15)–O(3)	−44·9 (9)
C(4)–C(13)–C(15)–N(1)	137·6 (6)
C(14)–C(13)–C(15)–O(3)	82·5 (8)
C(14)–C(13)–C(15)–N(1)	−95·0 (7)
C(13)–C(15)–N(1)–C(16)	174·9 (5)
O(3)–C(15)–N(1)–C(16)	−2·5 (10)
C(15)–N(1)–C(16)–C(17)	−139·4 (7)
C(15)–N(1)–C(16)–C(18)	97·5 (7)
N(1)–C(16)–C(18)–C(19)	43·0 (9)
N(1)–C(16)–C(18)–C(23)	−141·0 (6)
C(17)–C(16)–C(18)–C(19)	−79·2 (8)
C(17)–C(16)–C(18)–C(23)	96·7 (7)

linking N(1) in one unit cell to O(3)—C(15) in an adjacent cell. All three chiral centres were found to have the *R* configuration. Although it is the *S* configuration at C(13) which is critical for activity, the results of the present study were used to identify the other stereoisomers which were produced in the chemical synthesis so that the configurations of the active compounds were known unambiguously.

We thank Fisons Ltd (Pharmaceutical Division) for financial support for this work.

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SQ 14,225: 1-(D-3-Mercapto-2-methylpropionyl)-L-proline

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Abstract. $C_9H_{15}NO_3S$, orthorhombic $P2_12_12_1$, $a = 8\cdot811$ (1), $b = 17\cdot984$ (2), $c = 6\cdot837$ (1) Å, $Z = 4$, $d_m = 1\cdot33$, $d_c = 1\cdot33$ Mg m^{-3}, $\mu_{Cu} = 2\cdot489$ mm^{-1}, $R = 7\cdot1\%$. The title compound is a potent inhibitor of the lung angiotensin-converting enzyme. We present the crystal structure conformation and compare it to the conformation of the molecule obtained from crystallographic studies of SQ 14,225 bound to the aspartyl protease, penicillopepsin. The molecule exhibits an unusual antiplanar conformation of the carboxyl group [O(3)—C(9)—O(2)—H(14) = −163·5°] in the single crystal due to the presence of a strong intermolecular hydrogen bond [O···O = 2·592 (6) Å].

Introduction. SQ 14,225 was designed specifically to inhibit the angiotensin-converting enzyme (kininase II, EC 3.4.15.1) (Cushman, Cheung, Sabo & Ondetti, 1977; Ondetti, Rubin & Cushman, 1977). In the design, the enzyme was assumed to have an active site similar to that of carboxypeptidase A. This assumption was based on the fact that the angiotensin-converting enzyme is a carboxypeptidase which cleaves off dipeptides and contains Zn (Das & Soffer, 1975; Bakhle, 1974). The strong inhibitory action of SQ 14,225 confirms the structural and mechanistic similarity of these two enzymes.

Plate-like crystals of the compound were grown with the vapour-diffusion technique using ethyl acetate as the solvent and petroleum ether as the precipitant. The density was measured by flotation in a mixture of monobromobenzene and monochlorobenzene. For intensity-data collection the crystal was mounted in a direction parallel to the plate surface. For experimental details, see Table 1.

The data were collected on a Picker FACS-1 diffractometer to $2\theta_{max} = 110°$ to obtain 1707 reflections. The background was measured at the beginning and at the end of each scan and was corrected for by the use of the formula $I_{net} = I_{total} - T(B1 + B2)$, where T is the ratio of the scan time to the total background time, and $B1$ and $B2$ are the two background counts. The standard deviation of the intensity was calculated from $\sigma^2(I) = I_{total} + c^2I^2_{total} + T^2[B1 + B2 + c^2(B1^2 + B2^2)]$, where $c = 0\cdot02$ and represents an estimate of the instrumental instability. For reflections with $\sigma^2 \geq 2 \times 10^6$, a value of $\sigma^2(I) = 2 \times 10^6$ was used. The absorption corrections were made using the method of North, Phillips & Mathews (1968). The symmetry-equivalent reflections (hkl and $h\bar{k}l$) were

Table 1. *Experimental details*

Crystal dimensions: 0·35 × 0·12 × 0·60 mm
Extinctions: $h00$: $h = 2n + 1$; $0k0$: $k = 2n + 1$; $00l$: $l = 2n + 1$
Space group: $P2_12_12_1$
Radiation: Ni-filtered, Cu $K\alpha$, operated at 40 kV, 26 mA
Scan type: θ–2θ
Scan width, speed: 2° at 2° min^{-1} in 2θ

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