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Structure of Naproxen,* $C_{14}H_{14}O_3$

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Abstract. An effective inhibitor of cyclo-oxygenase. $M_r = 230·25$, monoclinic, $P2_1$, $a = 13·3150$ (10), $b = 5·7765$ (4), $c = 7·8732$ (4) Å, $\beta = 93·88$ (1)°, $V = 604·2$ (1) Å^3, $Z = 2$, $D_m = 1·25$ (2) (flotation), $D_x = 1·265$ Mg m^{-3}, $\lambda(\text{Mo } K\alpha_1) = 0·70926$ Å, $\mu(\text{Mo } K\alpha) = 0·095$ mm^{-1}, $F(000) = 244$, $T = 296$ K, final $R(F) = 0·061$ for 1037 observed reflections. The rotation of the carboxyl group with respect to the benezene ring, which seems to be connected with anti-inflammatory potential, is similar to the other two substituted propionic acids already reported. The benzene rings in the naphthyl group are inclined at an angle of 5·2 (2)°.

Introduction. The title compound, an effective inhibitor of the cyclo-oxygenase responsible for biosynthesis of prostaglandins, was obtained from Dr Natarajan, Institute of Basic Medical Sciences, Madras. It exhibits anti-inflammatory, analgesic and antipyretic activity in man (Goodman & Gilman, 1980). The analysis of its structure was undertaken to help to establish the structure–activity relationship in propionic acid derivatives.

Experimental. Single crystals were grown by slow evaporation of a saturated solution in benzene at room temperature. Crystal 0·3 × 0·3 × 0·3 mm, mounted parallel to its long axis (b) and aligned to place this along the instrument φ axis. Picker PDP8E four-circle diffractometer at the National Research Council, Canada. Graphite-monochromatized Mo $K\alpha$ radiation, $\theta/2\theta$ scan technique, line profile analysis (Grant & Gabe, 1978), $2\theta \leq 60°$, 1167 unique reflections with $-15 < h < 15$, $0 < k < 6$, $0 < l < 9$; 1037 with $I_{\text{net}} > 2·5\sigma(I_{\text{net}})$ based on counting statistics. Intensities for measured direct-beam polarization (Le Page, Gabe & Calvert, 1979) and Lorentz effects. Absorption corrections not applied. Unit-cell parameters from the least-squares refinement of the setting angles of 40 reflections with $2\theta > 40°$. Structure solved by direct methods with *MULTAN* (Germain, Main & Woolfson, 1971). E values larger than 1·5 used for phase generation; solution from the set having the highest combined figure of merit. The E map revealed the 17 non-hydrogen atoms. All 14 H atoms located from the ΔF map. Full-matrix refinement was completed with anisotropic temperature factors for non-hydrogen atoms and isotropic for H atoms. Final $R(F) = 0·061$ and $R_w(F) = 0·053$ for observed reflections; $R = 0·074$ and $R_w = 0·053$ for all reflections; $w = 1/\sigma^2(F_o)$ based on counting statistics; goodness of fit 2·6. The final difference synthesis showed no peaks above 0·3 e Å^{-3};

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* IUPAC name: (±)-2-(6-methoxy-2-naphthyl)propionic acid.

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$(\Delta/\sigma)_{\max} = 0{\cdot}2$, $(\Delta/\sigma)_{\text{mean}} = 0{\cdot}1$. All atomic scattering factors from *International Tables for X-ray Crystallography* (1974). No alternative refinement based on the mirror image of the molecule was tried. All calculations performed using the *NRC* PDP8E system programs (Larson & Gabe, 1978) adapted for the Vax Computer at NRC, Canada and the IBM 1130 at University of Madras.

Discussion. Atomic positions and equivalent isotropic temperature factors are listed in Table 1.* The structure of the molecule, and the bond distances and angles are presented in Fig. 1. The bond lengths and angles agree with the standard values within experimental error, except for C(15)—O(16) [1·345 (13) Å] which deviates at the 3σ level from its average observed value of 1·308 Å (Ando, Ashida, Sasada & Kakudo, 1967; Putkey & Sundaralingam, 1970).

The methoxy group shows a tendency to be coplanar with the naphthalene moiety [C(12)—C(3)—O(2)—C(1) 1·8 (11), C(4)—C(3)—O(2)—C(1) −179·9 (6)°], causing an enlargement of the angle C(12)—C(3)—O(2) [126·6 (7)°] and a narrowing of the angle C(4)—C(3)—O(2) [114·2 (6)°]. A similar effect has been observed previously and discussed as being due to some degree of conjugation between O and the benzene ring giving rise to some shortening of the C—O bond (Domiano, Nardelli, Balsamo, Macchia & Macchia, 1979).

It is interesting to note that the plane of the naphthalene ring in this structure is rather distorted [$\sum(\Delta/\sigma)^2 = 464$]; but the two benzene rings in the naphthalene group are themselves planar [$\sum(\Delta/\sigma)^2 = 33$ and 11] and are inclinded at an angle of 5·2 (2)°. This distortion is probably due to the long side chain attached to one of the benzene rings. A quite similar situation has been observed in the structure of 3-(6-methoxy-2-naphthyl)-2,2-dimethylbutyric acid (Stora & Rérat, 1974).

The orientation of the carboxyl group with respect to the naphthalene plane is shown by the Newman projections along C(15)—C(13) and C(8)—C(13), and by the perspective view of the molecule of Fig. 2. Fig. 2(*a*) shows the orientation of the carboxyl group with respect to the —C(H)(CH3)—Ph moiety, Fig. 2(*b*) the orientation of the naphthalene plane with respect to the —C(H)(CH3)—COOH moiety. The chiral centre C(13) in the molecule, characteristic of this compound, is in the *S* configuration for the reported coordinates. However, it could not be experimentally determined owing to the choice of wavelength (Mo *Kα*).

Table 1. *Atomic parameters with their e.s.d.'s in parentheses*

$B_{\text{eq}}(\text{Å}^2)$ is the arithmetic mean of the principal axes of the thermal ellipsoid.

	x	y	z	B_{eq}
C(1)	0·2513 (5)	0·4945 (18)	0·8572 (9)	6·4 (4)
O(2)	0·2808 (3)	0·2819	0·7752 (5)	5·1 (3)
C(3)	0·3804 (5)	0·2454 (17)	0·7588 (8)	4·3 (4)
C(4)	0·4029 (4)	0·0298 (17)	0·6756 (7)	4·1 (3)
C(5)	0·4996 (5)	−0·0248 (16)	0·6474 (7)	3·9 (3)
C(6)	0·5801 (4)	0·1240 (15)	0·6967 (7)	3·1 (3)
C(7)	0·6801 (4)	0·0845 (16)	0·6546 (7)	3·7 (3)
C(8)	0·7571 (4)	0·2335 (16)	0·6951 (7)	3·3 (3)
C(9)	0·7358 (4)	0·4310 (16)	0·7863 (8)	4·4 (4)
C(10)	0·6403 (4)	0·4815 (15)	0·8294 (7)	3·8 (3)
C(11)	0·5597 (4)	0·3311 (15)	0·7850 (7)	3·5 (3)
C(12)	0·4578 (4)	0·3866 (16)	0·8157 (7)	3·6 (3)
C(13)	0·8612 (4)	0·1838 (16)	0·6348 (8)	4·1 (3)
C(14)	0·9040 (5)	0·3976 (17)	0·5436 (8)	5·7 (4)
C(15)	0·9265 (5)	0·1280 (19)	0·7924 (9)	4·6 (4)
O(16)	0·9285 (4)	−0·0983 (14)	0·8327 (6)	5·7 (3)
O(17)	0·9754 (4)	0·2687 (15)	0·8801 (7)	7·8 (3)

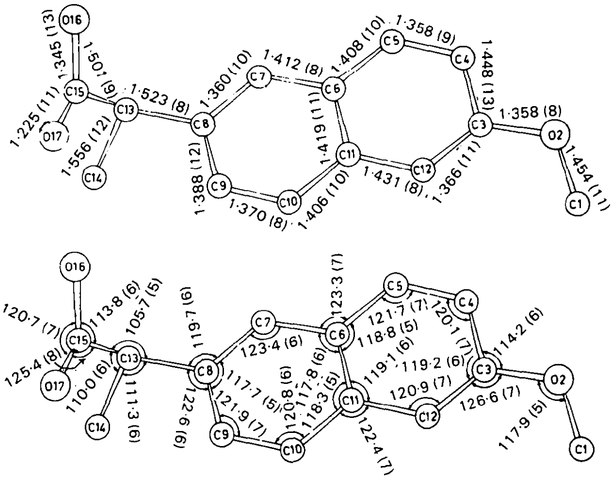

Fig. 1. Bond lengths (Å) and angles (°) in naproxen.

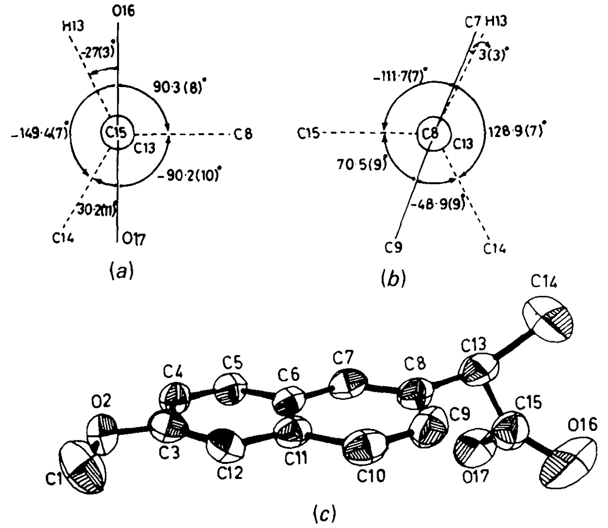

Fig. 2. Newman projections along (*a*) C(15)—C(13) and (*b*) C(8)—C(13). (*c*) Perspective view of the molecule.

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* Lists of structure factors, anisotropic thermal parameters, H-atom parameters and all bond distances and angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39808 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

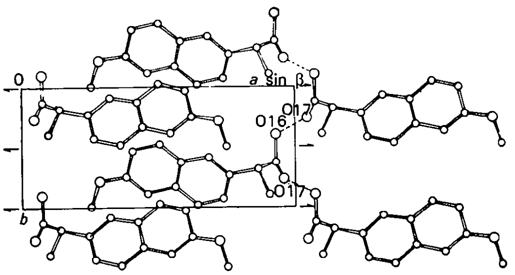

Fig. 3. Packing diagram down the *c* axis.

The rotation of the carboxyl group with respect to the benzene ring in the naphthalene moiety which seems to be connected with the anti-inflammatory potential activity is similar to that of the other 2-substituted propionic acids. The torsion angles τ_3[C(9)–C(8)–C(13)–C(15)] = 70·5 (8)° and τ_4[C(8)–C(13)–C(15)–O(16)(H)] = 90·3 (8)° are comparable with those in other 2-substituted propionic acids [ibuprofen: $\tau_3 = 96{\cdot}4$ (2), $\tau_4 = 89{\cdot}3$ (2)° (McConnel, 1974); flurbiprofen: $\tau_3 = 107{\cdot}7$ (6), $\tau_4 = 77{\cdot}3$ (6)° (Flippen & Gilardi, 1975)]. The theoretical values for the minimum-energy configuration of 2-phenylpropionic acid calculated using CNDO/2 and STD 3G are τ_3 ±60, ±120, τ_4 ±90° (Dupont, Dideberg, Dive, Godfroid & Steiner, 1982).

The packing of the molecules down the *c* axis is shown in Fig. 3. The structure is stabilized by the intermolecular hydrogen bond between O(16) and O(17) of a neighbouring molecule at $(2-x,\ y-\frac{1}{2},\ 2-z)$: O(16)–H(O16) = 1·04 (3), O(16)···O(17) = 2·636 (8) Å, O(16)–H(O16)···O(17) = 163 (3)°.

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(*Z*)-3-(α-Hydroxybenzylidene)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-9-one, $C_{18}H_{14}N_2O_2$

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Abstract. $M_r = 290{\cdot}3288$, monoclinic, $P2_1/c$, $a = 11{\cdot}309$ (5), $b = 11{\cdot}121$ (5), $c = 11{\cdot}672$ (5) Å, $\beta = 110{\cdot}23$ (5)°, $U = 1377{\cdot}34$ Å^3, $Z = 4$, $D_x = 1{\cdot}4002$ Mg m^{-3}, Mo $K\alpha$ radiation, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}054$ mm^{-1}, $F(000) = 608$, $T = 293$ K, $R = 0{\cdot}0689$ for 1115 observed reflexions. The hydroxyl proton is involved in hydrogen bonding to the sp^2-hybridized N atom of the quinazoline ring. The phenyl group is close to coplanar with the pyrroloquinazolinone fragment giving the maximum extended π bonding.

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