Nonsteroidal Antiinflammatory Drugs. V. The Crystal and Molecular Structure of (±)-(2*S**)-2-[4-((1*S**,2*R**)-2-hydroxycyclopentylmethyl)-phenyl]propionic Acid

Tadashi HATA,* Sadao SATO, and Chihiro TAMURA
Analytical and Metabolic Research Laboratories, Sankyo Co. Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140

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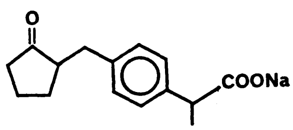
Synopsis. The crystal structure of the title compound was determined by X-ray diffraction techniques and was refined to a final R index of 0.094 for 1249 reflections. The cyclopentane ring takes a half-chair conformation in which the two substituents are attached at equatorial positions. The molecules form centrosymmetric tetramers by the two hydrogen bonds through the carboxyl and hydroxyl groups.

A new antiinflammatory agent, sodium (±)-2-[4-(2-oxocyclopentylmethyl)phenyl]propionate (loxoprofen sodium) (**1**), may exhibit the inhibitory activity for prostaglandin synthesis after the conversion to an active metabolite of (+)-(2*S*)-2-[4-((1*R*,2*S*)-2-hydroxycyclopentylmethyl)phenyl]propionic acid.[1] Since the molecule of this metabolite has three asymmetric carbons, the eight optical isomers can be theoretically considered, wherein the above metabolite is found to be the most active. Since the structure of (±)-(2*S**)-2-[4-((1*R**,2*R**)-2-hydroxycyclopentylmethyl)phenyl]propionic acid (cis-OH isomer) has been determined,[2] the structure determination of the title compound **2**, racemic trans-OH isomer, has been performed for comparison with the isomers and related compounds.



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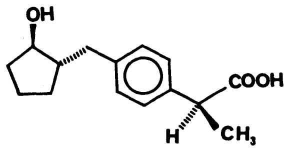

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Experimental

Colorless prisms were grown by slow evaporation of a solution of the substance in a mixture of ether and hexane at room temperature. The lattice parameters and intensity data were collected from a 0.1×0.1×0.6 mm crystal on a Rigaku AFC-5 diffractometer with monochromated Cu*Kα* radiation. Twenty reflections with 32°<2*θ*<49° were used to determine the cell parameters. Space group was assigned from systematic absences. The crystal data were as follows; $C_{15}H_{20}O_3$, M=248.3, monoclinic, $P2_1/n$, a=20.275(1), b=5.479(1), c=12.005(1)Å, β=94.43(1)°, V=1329.6(3)Å^3, Z=4, D_c=1.24 gcm^{-3}, μ(Cu*Kα*) 6.9cm^{-1}. An ω—2θ scanning mode was employed up to 2θ=130° and 2270 reflections were measured. For the structure solution and refinement 1249 unique measurements with $F>3\sigma(F)$ were used. No significant variation in the intensities of the three standard reflections was found. The intensities were corrected for the Lorentz and polarization factors, but not for absorptoion. The structure was solved by the direct method using MULTAN78,[3] and refined by the full-matrix least-squares method with anisotropic thermal parameters. H atom positions, except for two H atoms at C(16), were determined from a difference Fourier synthesis and refined with isotropic thermal parameters. The two remaining H atoms were placed geometrically and included in the refinements with fixed contributions to *Fc*. The final refinement converged at R=0.094 and R_w=0.037. The weighing sheme in the final stage was $w=1/\sigma^2(F)$. Atomic scattering factors were taken from Ref. 4. The final fractional atomic coordinates and equivalent isotropic thermal parameters are given in Table 1.[5]

Results and Discussion

The atom labelling and the anisotropic thermal ellipsoids are shown in Fig. 1. Bond lengths and angles are given in Table 2. The C(1)–C(2) bond length of 1.354(8)Å is shorter than the normal bond length of the benzene ring due to some structural requirement and the others are all normal within the limits of experimental error.

The torsional angles of C(2)–C(1)–C(7)–C(9) and C(1)–C(7)–C(9)–O(10) of the propionic acid side chain are 122.0(6) and 126.5(7)°, respectively. These values are larger than those of 96.4 and 89.3° in ibuprofen,[6] 107.7 and 77.3° in flurbiprofen,[7] 111.7 and 90.2° in naproxen,[8] and 114.7 and 94.9° in one of the two independent molecules in the cis-OH isomer.[2] Another molecule in the cis-OH isomer has angles of 162.6

Table 1. Fractional Atomic Coordinates and Equivalent Isotropic Thermal Parameters, with e.s.d.'s in Parentheses

Atom	10^4x	10^4y	10^4z	B_{eq}/Å^2	Atom	10^4x	10^4y	10^4z	B_{eq}/Å^2
C(1)	2448(2)	6230(11)	125(4)	2.5(2)	O(10)	4047(2)	4333(8)	−385(3)	4.8(2)
C(2)	2022(3)	8138(11)	98(5)	3.1(2)	O(11)	3789(2)	7837(10)	362(5)	6.0(2)
C(3)	1546(3)	8405(12)	863(5)	2.9(2)	C(12)	987(3)	6988(14)	2541(5)	3.4(2)
C(4)	1507(2)	6719(11)	1707(4)	2.3(2)	C(13)	327(2)	5820(13)	2114(5)	3.2(2)
C(5)	1952(3)	4788(12)	1760(5)	3.5(2)	C(14)	−140(3)	5348(14)	2993(5)	3.8(2)
C(6)	2411(3)	4532(13)	959(5)	3.3(2)	C(15)	−815(3)	5110(18)	2355(7)	5.4(3)
C(7)	2952(2)	5956(12)	−775(5)	3.0(2)	C(16)	−793(3)	6753(14)	1354(5)	6.6(3)
C(8)	2804(3)	3739(15)	−1507(6)	4.1(2)	C(17)	−77(3)	7491(18)	1259(7)	5.1(3)
C(9)	3653(3)	5882(13)	−239(5)	3.2(2)	O(18)	38(2)	3218(11)	3601(4)	5.3(2)

Table 2. Bond Lengths (l/Å) and Bond Angles (θ/°), with e.s.d.'s in Parentheses

C(1)	-C(2)	1.354(8)	C(14)	-C(15)		1.522(8)	C(1)	-C(7)	-C(9)	110.7(4)
C(1)	-C(6)	1.372(9)	C(14)	-O(18)		1.408(9)	C(8)	-C(7)	-C(9)	111.3(5)
C(1)	-C(7)	1.552(8)	C(15)	-C(16)		1.505(11)	C(7)	-C(9)	-O(10)	125.2(6)
C(2)	-C(3)	1.390(8)	C(16)	-C(17)		1.520(9)	C(7)	-C(9)	-O(11)	111.4(5)
C(3)	-C(4)	1.377(8)	C(2)	-C(1)	-C(6)	118.0(5)	O(10)	-C(9)	-O(11)	123.3(5)
C(4)	-C(5)	1.389(8)	C(2)	-C(1)	-C(7)	120.7(5)	C(4)	-C(12)	-C(13)	111.8(5)
C(4)	-C(12)	1.517(8)	C(6)	-C(1)	-C(7)	121.3(5)	C(12)	-C(13)	-C(14)	114.9(5)
C(5)	-C(6)	1.396(9)	C(1)	-C(2)	-C(3)	122.6(6)	C(12)	-C(13)	-C(17)	112.1(6)
C(7)	-C(8)	1.515(10)	C(2)	-C(3)	-C(4)	119.8(5)	C(14)	-C(13)	-C(17)	103.6(5)
C(7)	-C(9)	1.514(7)	C(3)	-C(4)	-C(5)	118.1(5)	C(13)	-C(14)	-C(15)	104.8(5)
C(9)	-O(10)	1.189(8)	C(3)	-C(4)	-C(12)	120.2(5)	C(13)	-C(14)	-O(18)	110.9(5)
C(9)	-O(11)	1.310(9)	C(5)	-C(4)	-C(12)	121.7(5)	C(15)	-C(14)	-O(18)	112.0(6)
C(12)	-C(13)	1.535(8)	C(4)	-C(5)	-C(6)	120.6(6)	C(14)	-C(15)	-C(16)	105.6(6)
C(13)	-C(14)	1.495(8)	C(1)	-C(6)	-C(5)	120.8(6)	C(15)	-C(16)	-C(17)	107.9(5)
C(13)	-C(17)	1.560(10)	C(1)	-C(7)	-C(8)	111.7(5)	C(13)	-C(17)	-C(16)	104.6(6)

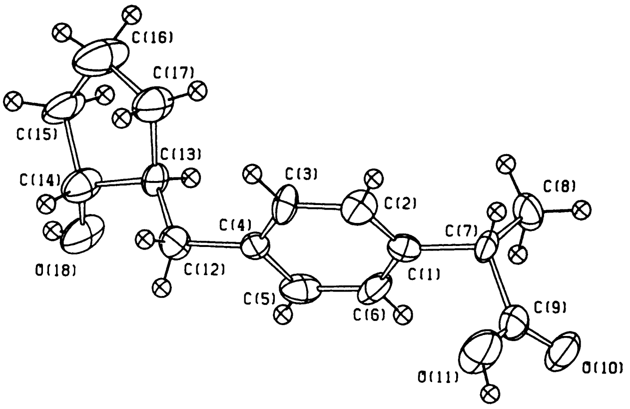

Fig. 1. ORTEP plot of the title compound with thermal ellipsoids at the 50% probability level.

and 96.2°. The former angle is larger than that in the title compound and the latter is smaller.

The cyclopentane ring adopts half-chair conformations with the two equatorial hydroxyl and methylphenyl groups, in which the C(13) and C(14) atoms are displaced by −0.27(1) and 0.31(1)Å from the plane through C(15)-C(16)-C(17). The two independent molecules of the cis-OH isomer also take half-chair forms, however, both hydroxyl groups in these molecules are attached at axial positions. The rotational angle of C(3)-C(4)-C(12)-C(13) is 86.1(8)°, compared with 100.7 and 76.6° in the two independent molecules of the cis-OH isomer. In these molecules, the steric hindrances between the benzene and cyclopentane rings are avoided in such a way that the arrangement of C(3)-C(4)-C(12)-C(13) is nearly perpendicular. The torsional angle of C(4)-C(12)-C(13)-C(14) is 162.8(5)° and the two hydrogen atoms attached at the methylene C(12) atom straddle the H(C14) atom. On the other hand, in the cis-OH isomer, the two corresponding hydrogen atoms straddle the hydroxyl oxygen atom instead of the hydrogen atom, since the oxygen atom is located on the same side of the plane through the cyclopentane ring as the H(C14) atom in the title compound.

The molecules form centrosymmetric tetramers by the two hydrogen-bonds between the carboxyl and hydroxyl groups. The O(18) atom donates the hydogen to $O(10^{\mathrm{i}})$ and accepts one from $O(11^{\mathrm{ii}})$ [(i) $-1/2-x$, $1/2-y$, $1/2-z$; (ii) $1/2-x$, $-1/2+y$, $1/2-z$]. The distances of these hydrogen bonds are 2.801(6) and 2.606(6)Å, respectively.

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References

1) K. Matsuda, Y. Tanaka, S. Ushiyama, K. Ohnishi, and M. Yamazaki, *Biochem. Pharmacol.*, **33**, 2473 (1984).

2) T. Hata, S. Sato, and C. Tamura, *Acta Crystallogr.*, in press.

3) P. Main, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq, and M. M. Woolfson, "MULTAN78, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data," Univs. of York, England, and Louvain, Belgium (1978).

4) "International Tables for X-ray Crystallography," Kynoch Press, Birmingham (1974), Vol. IV.

5) Lists of structure factors, anisotropic thermal parameters and atomic parameters for hydrogen atoms have been deposited as Document No. 8640 at the Office of the Chemical Society of Japan.

6) J. F. McConnell, *Cryst. Struct. Comm.*, **3**, 73 (1974).

7) J. L. Flippen and R. D. Gilardi, *Acta Crystallogr., Sect. B*, **31**, 926 (1975)

8) K. Ravikumar, S. S. Rajan, V. Pattabhi, and E. J. Gabe, *Acta Crystallogr., Sect. C*, **41**, 280 (1985).