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Nonsteroidal Antiinflammatory Drugs. III. Structure of (*E*)-4-(2-Hydroxyiminocyclopentylmethyl)phenylacetic Acid

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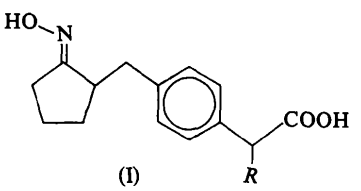
Abstract. $C_{14}H_{17}NO_3$, $M_r = 247{\cdot}3$, monoclinic, $P2_1/c$, $a = 10{\cdot}428\ (2)$, $b = 12{\cdot}039\ (2)$, $c = 10{\cdot}889\ (1)$ Å, $\beta = 109{\cdot}54\ (12)°$, $V = 1288{\cdot}3\ (4)$ Å^3, $Z = 4$, $D_x = 1{\cdot}28$ g cm^{-3}, graphite-monochromated Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å, $\mu = 7{\cdot}4$ cm^{-1}, $F(000) = 528$, $T = 298$ K, final $R = 0{\cdot}0697$ for 1511 reflections. The molecules form centrosymmetric tetramers through two hydrogen bonds between the carboxyl and hydroxyimino groups. The steric hindrance between the benzene and cyclopentane rings is avoided in such a way that the two rings are nearly perpendicular.

Introduction. In the search for non-steroidal antiinflammatory drugs, a number of cycloalkylmethylphenylacetic and -propionic acid derivatives have been synthesized, among which (*E*)-2-[4-(2-hydroxyiminocyclopentylmethyl)phenyl]propionic acid (I*a*) exhibited particularly potent activity (Terada, Naruto, Wachi, Tanaka, Iizuka & Misaka, 1984). Since the title compound (I*b*) has the same cycloalkyl moiety, the structure determination has been undertaken for comparison with related antiinflammatory drugs.



(I)

(*a*) $R = CH_3$
(*b*) $R = H$

Experimental. Colorless prisms grown from ether solution by slow evaporation at room temperature; approximate crystal dimensions $0{\cdot}1 \times 0{\cdot}5 \times 0{\cdot}6$ mm. Rigaku-Denki AFC-5 automated diffractometer, graphite-monochromated Cu $K\alpha$. Sixteen reflections with $18 < 2\theta < 28°$ used to determine cell parameters. No absorption correction. $2\theta_{max} = 130°$, ω–2θ scan, range of *hkl*: −12–11, 0–14, 0–12. No significant variation in intensities for three standard reflections. 2202 reflections measured; 1512 unique with $F \geq 3\sigma(F)$ used for structure solution and refinement. Structure solved by direct methods using *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). Full-matrix least-squares refinement based on F for non-H atoms with anisotropic thermal parameters. H-atom positions determined from difference Fourier synthesis and refined with isotropic thermal parameters. One intense low-angle reflection, 102, seriously affected by secondary extinction excluded. Final refinement converged at $R = 0{\cdot}0697$, $wR = 0{\cdot}0597$, $S = 0{\cdot}82$; $w = 1/\sigma(F)$; $(\Delta/\sigma)_{max}$ 0·01 for non-H atoms, 0·38 for H atoms. Max. peak height on final $\Delta\rho$ map 0·2 e Å^{-3}. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974). Calculations carried out with the *DIRECT-SEARCH* program system described by Koyama & Okada (1975).

Discussion. Fractional atomic coordinates and equivalent isotropic thermal parameters are given in Table 1.* The atom labeling and the anisotropic thermal ellipsoids are shown in Fig. 1. Bond lengths and angles are given in Table 2.

The molecules form centrosymmetric tetramers using the two hydrogen bonds between the carboxyl and hydroxyimino groups. The O(9) atom is hydrogen bonded to O(18^{i}) and the O(10) atom to N(17^{ii}) [(i) $-1 + x, \frac{1}{2} - y, \frac{1}{2} + z$; (ii) $-x, \frac{1}{2} + y, \frac{1}{2} - z$]. The distances O(9)···O(18) and O(10)···N(17) are 2·846 (6) and 2·663 (5) Å, respectively. In centrosymmetric crystals, carboxyl groups usually form centrosymmetric dimers by hydrogen bonding. The title compound, however, does not since the N atoms of the basic hydroxyimino groups have a stronger proton affinity than the carboxyl groups.

The torsional angle C(6)–C(1)–C(7)–C(8) of the acetic acid side chain is 24·4 (7)° and that of C(1)–C(7)–C(8)–O(9) is −128·6 (5)°. These angles

* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42647 (3 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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have been reported to be 101·5 and 25·7° in (2-ethoxy-5-indanyl)acetic acid (Hata, Sato & Tamura, 1986) and 112·6 and 7·7° in 4-(phenoxymethyl)-phenylacetic acid (Bats & Canenbley, 1984*a*). In the two independent molecules of 4-(benzyloxy)-phenylacetic acid (Bats & Canenbley, 1984*b*), the former angles are 85·8 and 38·2° and the latter are −98·4 and −90·7°, respectively. Thus, it may be noted that the side chain of acetic acid rotates freely.

The torsional angle C(3)–C(4)–C(11)–C(12) is 95·7 (6)°, which is nearly rectangular, and thus steric hindrance between the benzene and cyclopentane rings is avoided. The torsional angle C(4)–C(11)–C(12)–C(16) is −174·2 (4)°, corresponding to the stable staggered orientation. Therefore, the two hydrogen atoms of the C(11) methylene group straddle the hydroxyimino N(17) atom.

The cyclopentane ring system adopts an envelope form in which the C(13) atom is displaced by 0·41 (2) Å from the plane through the other four atoms. This ring deviates from the plane of the benzene ring on the same side as the carboxyl group. The conformation in which the C_α-phenyl group substituent is rotated by 180° is equivalent in energy because of the twofold rotation symmetry of the phenyl group. Therefore, in solution, the two substituent groups can also be located on opposite sides of the benzene plane as observed in the crystalline state of ibuprofen (McConnell, 1974).

Table 1. *Fractional atomic coordinates* (×10⁴) *and equivalent isotropic thermal parameters* (Å²), *with e.s.d.'s in parentheses*

	x	*y*	*z*	B_{eq}
C(1)	−1839 (4)	3231 (3)	3142 (4)	2·9 (1)
C(2)	−1741 (5)	2387 (3)	2329 (4)	4·0 (1)
C(3)	−563 (5)	2240 (4)	2036 (5)	5·0 (2)
C(4)	548 (4)	2923 (4)	2541 (4)	4·0 (1)
C(5)	455 (5)	3772 (4)	3355 (4)	4·3 (1)
C(6)	−742 (4)	3916 (4)	3646 (4)	4·4 (2)
C(7)	−3135 (5)	3333 (4)	3471 (6)	4·3 (2)
C(8)	−3419 (4)	4460 (3)	3887 (5)	3·8 (1)
O(9)	−3678 (4)	4638 (3)	4861 (4)	8·4 (2)
O(10)	−3387 (4)	5267 (3)	3114 (3)	6·3 (1)
C(11)	1854 (6)	2734 (6)	2236 (6)	5·9 (2)
C(12)	1959 (5)	3416 (4)	1138 (5)	5·4 (2)
C(13)	1930 (8)	4639 (4)	1163 (8)	8·0 (3)
C(14)	2560 (9)	5061 (5)	221 (9)	9·2 (3)
C(15)	3620 (6)	4181 (4)	201 (6)	5·0 (2)
C(16)	3181 (4)	3164 (3)	725 (4)	3·6 (1)
N(17)	3690 (3)	2202 (3)	828 (3)	3·8 (1)
O(18)	4773 (3)	2159 (3)	330 (3)	5·5 (1)

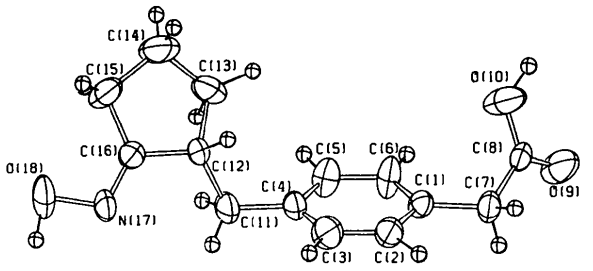

Fig. 1. *ORTEP* plot (Johnson, 1965) of the title compound with thermal ellipsoids at the 50% probability level.

Table 2. *Bond lengths* (Å) *and bond angles* (°), *with e.s.d.'s in parentheses*

C(1)–C(2)	1·374 (6)	C(8)–O(10)	1·293 (6)
C(1)–C(6)	1·368 (6)	C(11)–C(12)	1·484 (9)
C(1)–C(7)	1·515 (8)	C(12)–C(13)	1·473 (7)
C(2)–C(3)	1·381 (8)	C(12)–C(16)	1·518 (8)
C(3)–C(4)	1·377 (7)	C(13)–C(14)	1·480 (14)
C(4)–C(5)	1·378 (7)	C(14)–C(15)	1·536 (10)
C(4)–C(11)	1·523 (9)	C(15)–C(16)	1·486 (7)
C(5)–C(6)	1·399 (7)	C(16)–N(17)	1·264 (5)
C(7)–C(8)	1·491 (7)	N(17)–O(18)	1·408 (6)
C(8)–O(9)	1·199 (7)		

C(2)–C(1)–C(6)	118·2 (4)	O(9)–C(8)–O(10)	120·3 (4)
C(2)–C(1)–C(7)	118·5 (4)	C(4)–C(11)–C(12)	113·9 (5)
C(6)–C(1)–C(7)	123·3 (4)	C(11)–C(12)–C(13)	122·1 (6)
C(1)–C(2)–C(3)	120·5 (4)	C(11)–C(12)–C(16)	115·1 (4)
C(2)–C(3)–C(4)	121·8 (5)	C(13)–C(12)–C(16)	103·2 (5)
C(3)–C(4)–C(5)	118·0 (5)	C(12)–C(13)–C(14)	108·3 (6)
C(3)–C(4)–C(11)	121·2 (5)	C(13)–C(14)–C(15)	105·1 (5)
C(5)–C(4)–C(11)	120·8 (4)	C(14)–C(15)–C(16)	104·3 (6)
C(4)–C(5)–C(6)	119·9 (4)	C(12)–C(16)–C(15)	110·2 (4)
C(1)–C(6)–C(5)	121·7 (5)	C(12)–C(16)–N(17)	121·7 (4)
C(1)–C(7)–C(8)	115·4 (4)	C(15)–C(16)–N(17)	128·0 (5)
C(7)–C(8)–O(9)	123·9 (5)	C(16)–N(17)–O(18)	111·4 (4)
C(7)–C(8)–O(10)	115·8 (5)		

The hydroxyimino N(17) atom deviates from the least-squares plane of the benzene ring by 0·48 Å and the distance of N(17) from the center of the benzene ring is 5·75 Å, which are comparable to the values of 0·42 and 5·06 Å, respectively, in naproxen (Ravikumar, Rajan, Pattabhi & Gabe, 1985). The two six-membered rings in both molecules were superimposed using a new program *SUPIM* (Hata, 1986), which minimized the sum of the squares of the distances between the corresponding atoms in each molecule. After the fitting, the distance between the N(17) atom in the title compound and the methoxy oxygen atom in naproxen is only 1·01 Å. This difference and its direction are within the limits of the distance and angular distribution of hydrogen bonds, as reported by Murray-Rust & Glusker (1984). Therefore, both atoms may interact with the same receptor site.

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X-ray Structure and Molecular-Packing Analysis of a Glucofuranosoimidazolidine-2-thione

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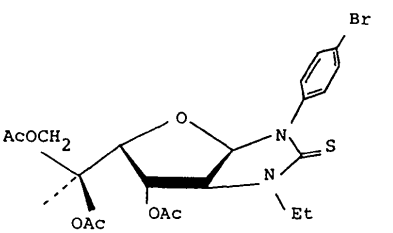
Abstract. 1-(4-Bromophenyl)-3-ethyl-(3,5,6-tri-*O*-acetyl-1,2-dideoxy-α-L-glucofuranoso)[2,1-*d*]imidazolidine-2-thione,* $C_{21}H_{25}BrN_2O_7S$, $M_r = 529{\cdot}40$, orthorhombic, $P2_12_12_1$, $a = 12{\cdot}056$ (7), $b = 22{\cdot}420$ (9), $c = 8{\cdot}841$ (2) Å, $V = 2390$ (2) Å^3, $Z = 4$, $D_m = 1{\cdot}47$ (2), $D_x = 1{\cdot}47$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·7107 Å, $\mu = 1{\cdot}82$ mm^{-1}, $F(000) = 1088$, room temperature, final $R = 0{\cdot}070$ for 1668 observed reflexions. The sugar ring adopts the ^4E conformation and the imidazolidine ring is almost planar. The dihedral angle in the bicyclic system is 71·1 (4)°. The crystal cohesion is mainly due to van der Waals interactions. The lattice energy was computed in the atom–atom approach using van der Waals potential functions and the calculations account satisfactorily for the features of the crystal packing.

Introduction. The structure determination of 1-(*p*-bromophenyl)-3-ethyl-(3,5,6-tri-*O*-acetyl-1,2-dideoxy-α-L-glucofuranoso)[2,1-*d*]imidazolidine-2-thione (I) was undertaken as part of a continuing research project on imidazole *C*-glycosides. Recently, some compounds derived from 2-(alkylamino)-2-deoxyheptoses and 2-(alkylamino)-2-deoxyhexoses have been reported (Estrada, Conde & Márquez, 1983, 1984; Conde, Millan, Conde & Márquez, 1985*a*,*b*) and in this paper we report the structure of a tetra-*O*-acetyl derivative. The application of aminonitrile synthesis to the preparation of the new 2-(ethylamino)-2-deoxyhexose having L-*gluco* configuration and its reaction with 4-bromophenyl isothiocyanate to afford the title compound has been recently reported (Galbis Pérez, Palacios Albarrán, Jiménez Requejo & Avalos González, 1984). Its chemical nature was established from elemental analysis and spectroscopic IR and ^{1}H NMR data and the X-ray analysis was suggested in order to establish the conformational details of the molecule in the solid state.



(I)

Experimental. Single crystals in the form of colourless needles elongated along [100] prepared in the Organic Chemistry Department of the University of Extremadura and kindly supplied by Professor J. A. Galbis Pérez. D_m by flotation method. Crystal 0·25 × 0·15 × 0·10 mm. Unit-cell parameters from 25 reflexions, $5 < \theta < 22°$. Enraf–Nonius CAD-4 diffractometer, graphite monochromator, $2 < \theta < 30°$ ($0 \le h \le 14$, $0 \le k \le 26$, $0 \le l \le 10$), ω–2θ scan mode. Two standard reflexions ($\bar{1}50$; 150), variation in intensity < 2% of mean value. 2438 independent reflexions measured, 770 unobserved [$I < 2\sigma(I)$]. Lorentz and polarization correction, no correction for absorption ($\mu R \sim 0{\cdot}12$) or extinction. Patterson function and heavy-atom method with initial set of phases based on Br and S atom positions. Full-matrix least-squares refinement on F, anisotropic. Difference Fourier synthesis revealed H-atom positions; isotropic temperature factor $B = 4{\cdot}0$ Å^2 for H atoms. Further least-squares refinement including positional parameters of H atoms and anomalous-dispersion correction for Br and S atomic scattering factors (*International Tables for*

* IUPAC name: 1-{6-acetoxy-3-(*p*-bromophenyl)-1-ethyl-2-thioxo-2,3,3a,5,6,6a-1*H*-furo[2,3-*d*]imidazol-5-yl}ethylene diacetate.

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