

angles are given in Table 2, and some least-squares planes are presented in Table 3. The average bond length in the benzene ring, 1.383 Å, is normal. The five-membered oxadiazolo ring (atoms 2 through 6) is planar (Table 3). In the heterocyclic six-membered ring (atoms 5–7 and 12–14), C(13) and C(14) deviate most notably and approximately equally on opposite sides of the best plane. The C(2)–N(6)–C(7)–C(8) torsion angle is 16.8 (2)° and C(5)–C(14)–C(13)–C(12) is 46.7 (2)°.

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2-Acetoxy-6-methylbenzoic Acid*

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Abstract. C₁₀H₁₀O₄, monoclinic, *P*2₁/*n*, *a* = 10.164 (2), *b* = 7.238 (2), *c* = 13.186 (3) Å, β = 96.74 (2)° at 299 K, *Z* = 4, *d*_c = 1.340 (1) Mg m⁻³; *R* = 0.041 for 1260 data having *F*_o² > 3σ(*F*_o²) measured by diffractometer. The crystal structure of 2-acetoxy-6-methylbenzoic acid (6-methylaspirin) has been determined. The molecule forms dimers with linear asymmetric hydrogen bonds of length 2.621 (2) Å. The carboxyl group is rotated 44.7 (2)° from the plane of the benzene ring. This rotation is significant when compared to aspirin, and is likely caused by steric interactions of the methyl group juxtaposed to the carboxyl.

Introduction. Considerable research has been devoted to understanding the efficiency of enzymatic catalysis. One school of thought ascribes a major part of this efficiency to the juxtaposition of functional groups (Kirby, 1980). In addition, the orientation of these

groups is also important, but just how important is a subject of controversy (Koshland, 1972; Wang, 1970; Gandour, 1978, 1981). Thus, studies of structure and dynamics on chemical models of enzymatic catalysts have the potential of providing information about geometry and its relationship to catalytic efficiency.

Studies of the pH dependence of hydrolysis rates of methyl-substituted 2-acyloxybenzoic acids (Gandour, Mani, Blanco, Wiseman & Williams, 1980) reveal that a 6-methyl substituent retards the rate in the neutral region; however, in the acid region there is an acceleration in the rate. An X-ray crystallographic analysis of the structure of 2-acetoxy-6-methylbenzoic acid (6-methylaspirin) has been performed to assist in explaining this novel pH-dependent steric effect. The combination of this report with the recent structure report on 2-acetoxy-3-methylbenzoic acid (Chiari, Fronczek, Davis & Gandour, 1981) reveals the marked structural changes to the catalyst (carboxyl group) and substrate (acetoxy group) of the model system brought about by methyl substitution.

6-Methylaspirin was prepared as described previously (Eliel, Rivard & Burgstahler, 1953). Crystals,

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m.p. 400.5–402 K uncor. (lit. m.p. 401.5–403 K, Eliel, Rivard & Burgstahler, 1953), suitable for diffraction studies were obtained by recrystallization from ethyl ether:petroleum ether.

Intensity data were obtained from a colorless crystal of dimensions 0.36 × 0.22 × 0.18 mm mounted in random orientation on an Enraf–Nonius CAD-4 automatic diffractometer. Cell dimensions were determined at 299 K by centering 25 reflections having $29^\circ < \theta < 36^\circ$. One quadrant of data having $4^\circ \leq 2\theta \leq 150^\circ$ was measured using graphite-monochromatized Cu $K\alpha$ radiation ($\lambda = 1.54184 \text{ \AA}$). The ω – 2θ scans were made at speeds varying from 0.370 to $10.0^\circ \text{ min}^{-1}$ in order to measure all significant data with approximately equal precision. Of the 1975 independent data thus measured, 1260 had $F_o^2 > 3\sigma(F_o^2)$, and were used in the refinement. Data were corrected for background, Lorentz, polarization and absorption effects. Absorption corrections ($\mu = 0.891 \text{ mm}^{-1}$) were applied using an empirical procedure based upon ψ scans for reflections near $\chi = 90^\circ$. The minimum relative transmission coefficient was 0.9238.

The structure was solved by routine application of direct methods by program *MULTAN* 78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978); all other computations were carried out using the *Enraf–Nonius Structure Determination Package* (Frenz & Okaya, 1980). Refinement was accomplished by full-matrix least squares based upon F with weights $w = |\sigma^2(F_o)|^{-1}$. H atoms were located by difference Fourier methods, the acid H appearing as a small peak of density 0.17 e \AA^{-3} . Non-H atoms were treated anisotropically, and H atoms were refined isotropically. Convergence was achieved with $R = 0.041$, $R_w = 0.059$ for observed data, $R = 0.075$ for all data, and a difference Fourier map using all data yielded 0.16 e \AA^{-3} as its largest residual.

Discussion. Positional parameters for heavy atoms are given in Table 1.* Bond distances are depicted in Fig. 1 and bond angles are given in Fig. 2.

Comparison of the crystal structures of 2-acetoxybenzoic acid (aspirin) (Wheatley, 1964) and 6-methylaspirin reveals a few noteworthy differences. As expected, methyl substitution at C(6) changes torsion angles involving the carboxyl substituent at C(1), and, to a lesser extent, the acetoxy group attached at C(2). As observed previously in 3-methylaspirin (Chiari, Fronczek, Davis & Gandour, 1981), the carboxyl group in 6-methylaspirin is

Table 1. *Fractional coordinates and isotropic or equivalent isotropic temperature factors, with e.s.d.'s in parentheses*

For non-H atoms $U_{eq} = (U_{11} U_{22} U_{33})^{1/3}$.

	x	y	z	U_{eq}/U (\AA^2)
O(1)	0.4965 (1)	0.1394 (2)	0.39904 (11)	0.070 (1)
O(2)	0.6506 (1)	0.1188 (2)	0.53208 (10)	0.062 (1)
O(3)	0.4666 (1)	0.5158 (2)	0.38245 (8)	0.050 (1)
O(4)	0.4255 (1)	0.4335 (3)	0.21837 (10)	0.077 (1)
C(1)	0.6739 (1)	0.3544 (2)	0.4118 (1)	0.042 (1)
C(2)	0.6027 (2)	0.5104 (2)	0.3763 (1)	0.044 (1)
C(3)	0.6635 (2)	0.6652 (3)	0.3430 (1)	0.057 (2)
C(4)	0.7999 (2)	0.6630 (3)	0.3431 (1)	0.066 (2)
C(5)	0.8712 (2)	0.5089 (3)	0.3764 (1)	0.059 (2)
C(6)	0.8124 (2)	0.3531 (3)	0.4123 (1)	0.049 (1)
C(7)	0.6003 (2)	0.1944 (2)	0.4483 (1)	0.046 (1)
C(8)	0.3849 (2)	0.4682 (3)	0.2977 (1)	0.055 (2)
C(9)	0.2445 (2)	0.4641 (4)	0.3190 (2)	0.072 (2)
C(10)	0.8964 (2)	0.1886 (3)	0.4477 (2)	0.067 (2)
H(3)	0.617 (2)	0.775 (3)	0.322 (1)	0.067 (6)
H(4)	0.839 (2)	0.776 (3)	0.309 (1)	0.076 (6)
H(5)	0.959 (2)	0.509 (3)	0.377 (2)	0.101 (9)
H(91)	0.189 (2)	0.420 (3)	0.262 (2)	0.091 (8)
H(92)	0.217 (3)	0.577 (4)	0.340 (2)	0.118 (9)
H(93)	0.242 (3)	0.382 (4)	0.374 (2)	0.132 (10)
H(101)	0.971 (2)	0.190 (4)	0.424 (2)	0.128 (10)
H(102)	0.854 (2)	0.090 (4)	0.422 (2)	0.104 (8)
H(103)	0.906 (2)	0.172 (3)	0.526 (2)	0.089 (8)
H(1AC)	0.585 (3)	0.016 (4)	0.554 (3)	0.168 (14)

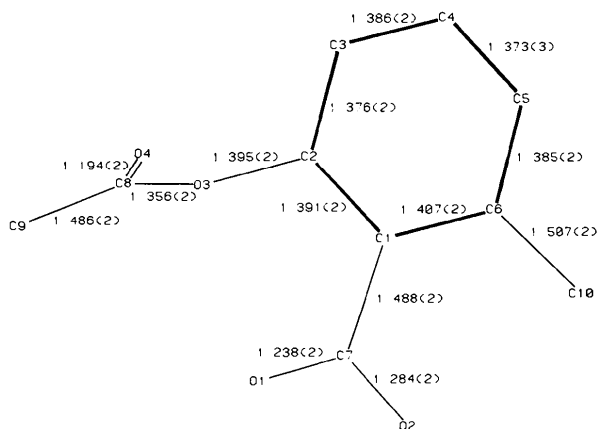


Fig. 1. Observed bond lengths (\AA).

positioned such that the shorter C–O bond, C(7)–O(1), is pointing toward the acetoxy group. The most significant difference is that the carboxyl and acetoxy groups are forced closer together; *i.e.* the C(7)–O(3) distance is 0.2 \AA shorter in 6-methylaspirin.

Selected torsion angles shown in Table 2 reveal conformational changes in the carboxyl and acetoxy groups caused by methyl substitution at C(6). The most dramatic change is the expected deviation of the carboxyl from coplanarity with the benzene ring. The

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36507 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. Selected torsion angles ($^{\circ}$)

	2-Acetoxybenzoic acid	2-Acetoxy-6-methylbenzoic acid
O(1)—C(7)—C(1)—C(2)	+178.2 (5)	+44.7 (2)
C(1)—C(2)—O(3)—C(8)	-85.5 (5)	-96.9 (3)
C(2)—O(3)—C(8)—C(9)	+178.1 (5)	+174.8 (3)
C(7)—C(1)—C(2)—O(3)	+3.0 (5)	+4.2 (3)

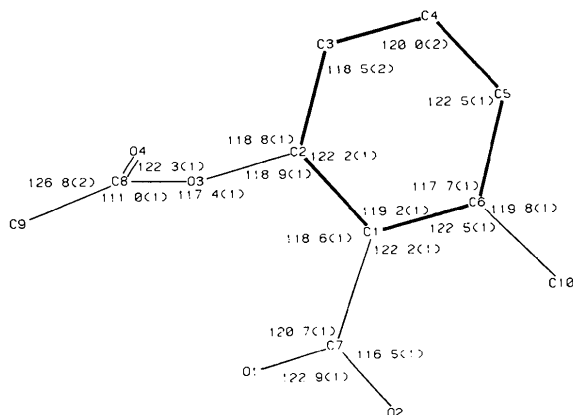
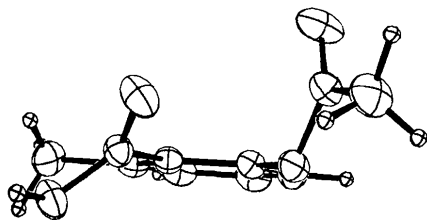
Fig. 2. Observed bond angles ($^{\circ}$).

Fig. 3. A view of 2-acetoxy-6-methylbenzoic acid which emphasizes the rotation of the carboxyl group out of the plane of the ring.

O(1)—C(7)—C(1)—C(2) angle is $44.7(2)^{\circ}$ in 6-methylaspirin and $178.2(5)^{\circ}$ in aspirin. Fig. 3 is a view of 6-methylaspirin which emphasizes the orientation of the carboxyl relative to the plane of the ring.

The acid dimer structure in 6-methylaspirin differs from aspirin in that O(1) is positioned closer to the acetoxy than O(2). However, the intermolecular O...O distances are virtually the same in the two structures — $2.621(2)$ Å in 6-methylaspirin and $2.645(3)$ Å in aspirin. Similar results have been reported for 3-methylaspirin (Chiari, Fronczek, Davis & Gandour, 1981).

The acetoxy group is nearly orthogonal to the ring in both 6-methylaspirin and aspirin. Comparison of the C(1)—C(2)—O(3)—C(8) angle reveals that the acetoxy group is skewed slightly away from the carboxyl in 6-methylaspirin but towards the carboxyl in aspirin.

There is also a slight but real twist in the ester backbone, C(2)—O(3)—C(8)—C(9), present in 6-methylaspirin. However, there is no pyramidalization about C(8), ruling out any significant interaction between O(1) and C(8). In fact, the O(1)...C(8) distance is $2.895(2)$ Å in 6-methylaspirin, slightly shorter than a comparable distance in aspirin, $2.943(3)$ Å [for aspirin it is the O(2)...C(8) distance].

All these structural changes are a result of the compression of distance between the carboxyl and acetoxy groups. The C(7)—O(3) distance in 6-methylaspirin is $2.781(2)$ Å whereas for aspirin the value is $2.988(4)$ Å. The atoms of nearest contact between the two groups are O(1) and O(3) [$2.747(2)$ Å] in 6-methylaspirin and O(2) and O(3) [$2.674(4)$ Å] in aspirin. Atoms C(7) and C(10) lie in the plane of the benzene ring and O(3) is slightly out of plane. A similar situation exists in aspirin [see Table 2, C(7)—C(1)—C(2)—O(3)]; but in 3-methylaspirin O(3) is noticeably (0.17 Å) out of plane (Chiari, Fronczek, Davis & Gandour, 1981). Thus, in 6-methylaspirin, rotation of the carboxyl out of the plane of the ring is the principal method by which contact between the two functional groups is minimized.

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