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A PARADIGM FOR THE STRUCTURES OF CYCLIC ASPIRIN DERIVATIVES

2-(2-METHOXY-PHENOXY)-2-METHYL-4-OXO-1,3-BENZODIOXANE

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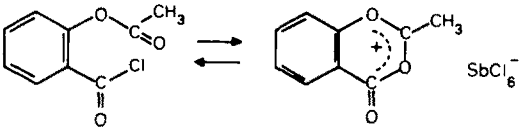
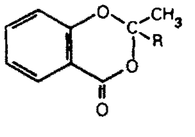
Abstract—Full characterization of the heterocyclic system of the title compound (3) was obtained by X-ray diffraction analysis. Crystals are orthorhombic, space group Pbca, with $Z = 8$ in a unit cell of dimensions $a = 9.968(3)$, $b = 23.808(4)$, $c = 11.668(2)$ Å; the structure was refined by full-matrix least-squares to $R_w = 0.036$ for 2055 independent reflections. The dioxane ring of the cyclic aspirin moiety exhibits a severely distorted half-boat conformation, with the phenoxy group axially oriented on the ring. With respect to the equatorial Me group the aromatic system of the guaiacol fragment is in a syn-clinal conformation favored by electrostatic interactions; relief from overcrowding is achieved mainly through angular deformations. Differences between the pertinent molecular dimensions of 3 and those of aspirin and salicylic acid are reported.

A number of unusual properties and reactions of acylsalicylic acid derivatives have long been explained[1-4] by assuming an equilibrium between the acylsalicylic acid derivative and a 6- or 7-membered cyclic intermediate. In the case of O-acetylsalicyloyl chloride (**1a**), the cyclic form (**1b**) was isolated (as the hexachloroantimonate salt) and studied by NMR spectroscopy in 1972.[5]



1a 1b

Later, it has been reported[6] that a solution of O-acetylsalicyloyl chloride and alcohol (or phenol), when heated in tetrahydrofuran in the presence of a base, yields the cyclic compound (**2**) as the main product. The series of compounds **2** can be referred to, for convenience, as the "cyclic aspirin derivatives".



R = alkoxy or phenoxy groups

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Members of this series are also the 1,3 - dialkanoyl - 2-(2 - methyl - 4 - oxo - 1,3 - benzodioxan - 2-yl)glicerides, synthesized and described by Paris *et al.*,[7] and the title compound **3**, a new[8] acetylsalicylic acid pro-drug which is endowed with the same pharmacological properties as the free acid. The use of drugs as carriers of other drugs to integrate their biological peculiarities and to improve their pharmacokinetics has been recently stressed.[7,9]

In compound **3**, which is characterized by a very good gastric tolerance and a tropism toward the bronchopulmonary district, the guaiacol moiety acts as a carrier of the cyclic aspirin. During the absorption stage of the drug, **3** splits in acetylsalicylic acid, salicylic acid, and guaiacol. So far, the structure proof of all cyclic aspirin derivatives rested primarily on their NMR spectra. To fully characterize the heterocyclic system of this class of substances, we have undertaken the X-ray diffraction analysis of **3**, and the results obtained are here described.

EXPERIMENTAL

Crystallographic measurements. Accurate unit-cell dimensions and intensity data were obtained from a crystal which had been ground to a sphere of approximate radius of 0.13 mm. The space group Pbca was indicated by the absences $0kl$ with k odd, $h0l$ with l odd, and $hk0$ with h odd. The density was measured by flotation in a dilute K_2HgI_4 soln. The sample was mounted on a computer-controlled diffractometer (Enraf Nonius CAD-4) using graphite-monochromatized Mo K_α radiation. Intensities were collected by the variable-rate ω-scan technique to a maximum 2ϑ value of 50°. No decay was observed during the data collection, monitored by the periodic measurement of three standard reflections. Out of 2416 measured reflections, 361 with net intensity less than zero were given zero weight; all other reflections were assigned variances, $\sigma^2(I)$, based on counting statistics plus the additional term $(0.025 \text{ scan count})^2$. The data were corrected for Lorentz and polarization factors but not for absorption.

Crystal data. $C_{16}H_{14}O_5$, $M = 286.3$, Orthorhombic, $a =$

9.968(3), $b = 23.808(4)$, $c = 11.668(2)$ Å, $U = 2769(1)$ Å^3, $Z = 8$, $D_c = 1.373$, $D_m = 1.37$ g cm^{-3}, $F(000) = 1200$. Mo K$_\alpha$ radiation, $\lambda = 0.7107$ Å; μ (Mo K$_\alpha$) = 1.11 cm^{-1}. Space group Pbca (No. 61).

Structure determination and refinement. The structure soln and refinement were accomplished by direct on-line processing of the diffraction data on the PDP-11 computer using the Enraf Nonius structure determination package which incorporates MULTAN.[10]

After preliminary refinement with isotropic thermal parameters for C and O atoms (derived from the E map corresponding to the soln with the highest figure of merit), a difference map revealed the positions of all 14 H atoms. The last cycles of least-squares refinement were carried out by simultaneously adjusting in a single matrix 247 parameters: coordinates for all the atoms, anisotropic b_{ij}'s for C and O atoms, isotropic B's for H atoms, a scale factor, and a secondary extinction coefficient [final value $2.1(4) \times 10^{-7}$]. Refinement was by minimization of the quantity $\Sigma\, w(|F_o| - |F_c|)^2$ with weights $w = 4\, F_o^2/\sigma^2\, (F_o^2)$. Atomic scattering factors were from ref. 11. The final values of the residuals are R = 0.069 [0.048 on the 1662 reflections having $F^2 > \sigma(F^2)$], and Rw = 0.036, and the goodness-of-fit, based on 2055 weighted reflections and 247 parameters, is 1.22. Table 1 reports the final positional parameters of the molecular structure. Lists of observed and calculated structure factors and thermal parameters are deposited with Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge CB2 1EW.

Precision and accuracy of the results. Crystals of the title compound were used to test the performances of two different diffractometers. So, besides the experimental data utilized on the present work, two more sets of data were collected, the first set

Table 1. Final positional parameters with estimated standard deviations in parentheses

Atom	x	y	z
C(1)	0.5635(2)	0.21677(6)	0.4703(1)
C(2)	0.4933(2)	0.22579(7)	0.3688(1)
C(3)	0.5134(2)	0.27539(7)	0.3090(1)
C(4)	0.6008(2)	0.31521(7)	0.3515(2)
C(5)	0.6696(2)	0.30625(7)	0.4511(2)
C(6)	0.6501(2)	0.25691(8)	0.5111(2)
C(7)	0.3495(2)	0.18753(9)	0.2249(2)
C(8)	0.6157(2)	0.12064(7)	0.5242(1)
C(9)	0.7581(2)	0.12785(8)	0.5602(2)
C(10)	0.5031(2)	0.07849(7)	0.3627(1)
C(11)	0.3981(2)	0.06489(6)	0.4451(1)
C(12)	0.2699(2)	0.05004(7)	0.4089(2)
C(13)	0.1757(2)	0.03492(8)	0.4890(2)
C(14)	0.2089(2)	0.03319(8)	0.6036(2)
C(15)	0.3350(2)	0.04856(7)	0.6413(2)
C(16)	0.4270(2)	0.06545(6)	0.5607(1)
O(1)	0.4056(1)	0.18469(5)	0.3374(1)
O(2)	0.6165(1)	0.10241(5)	0.4079(1)
O(3)	0.5544(1)	0.08124(5)	0.5964(1)
O(4)	0.5021(1)	0.06774(5)	0.2623(1)
O(5)	0.5344(1)	0.16913(4)	0.5359(1)
H(3)	0.467(2)	0.2814(6)	0.235(2)
H(4)	0.610(2)	0.3511(7)	0.311(1)
H(5)	0.727(2)	0.3345(8)	0.483(1)
H(6)	0.696(1)	0.2500(6)	0.582(1)
H(71)	0.299(2)	0.1512(8)	0.218(1)
H(72)	0.426(2)	0.1867(8)	0.168(2)
H(73)	0.295(2)	0.2224(8)	0.213(2)
H(91)	0.762(2)	0.1398(7)	0.641(1)
H(92)	0.808(2)	0.0919(7)	0.553(1)
H(93)	0.799(2)	0.1575(7)	0.514(1)
H(12)	0.248(2)	0.0529(7)	0.321(1)
H(13)	0.088(2)	0.0268(8)	0.465(1)
H(14)	0.141(2)	0.0225(7)	0.661(1)
H(15)	0.365(1)	0.0508(6)	0.719(1)

coming from the crystal previously described, mounted on a Syntex P1 diffractometer, and the second set from a larger crystal which had been ground to a sphere of approximate radius 0.17 mm, also mounted on the Syntex diffractometer. A detailed description of the different experimental conditions and an accurate statistical analysis of the final results will be published elsewhere, but it is worth noting here that the bond distances and angles derived from the three sets of data were in excellent agreement, the differences rarely exceeding twice the pooled standard deviation.

DISCUSSION

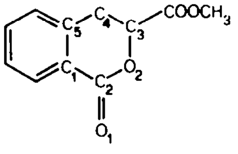
The atom numbering scheme adopted in the present structure analysis is reported in Fig. 1, which shows the molecular model as viewed along a principal axis of inertia. Molecular dimensions involving non-H atoms are given in Fig. 1 and in Table 2, while the equations of some least-squares planes are listed in Table 3. Distances and angles involving H atoms are in the usual range.

Inspection of the intermolecular contacts shows that none of them is less than the sum of van der Waals radii (C 1.7, O 1.4, H 1.2 Å), except for H(13)...H′(13) (at $-x$, $-y$, $1-z$), 2.32(4) Å. Therefore, it can be assumed that the conformation shown by the molecule in the crystal state is mainly, if not totally, dictated by intramolecular forces.

The benzene ring of the "cyclic aspirin" moiety is substantially planar, although some of the displacements from the least-squares plane passing through the six C atoms amount to more than six times the estimated standard deviations. Much larger are the deviations from the plane for the two heavy atoms directly bound to the ring, particularly for atom C(10), whose departure is 0.101(3) Å.

For the dioxane ring, which shows a distorted half-boat conformation with the "flap" at C(8) (see Fig. 2), the most representative plane is perhaps the one through the five atoms C(10), C(11), C(16), O(2) and O(3). The departures of the individual atoms from this plane, which makes a dihedral angle of 3.8° with that of the benzene ring, are given in Table 3. It will be seen that atoms C(10) and O(3) lie above the plane, and atoms O(2) and C(16) below, leading to the conclusion that the ring is also slightly twisted. The overall deformation of the system is clearly documented by the large difference between the values of the two torsion angles C(11)-C(16)-O(3)-C(8), 31.1(2)°, and C(11)-C(10)-O(2)-C(8), −10.4(2)°. As indicated by the value of the torsion angle O(4)-C(10)-O(2)-C(8), 173.9(2)°, the key factor in making one side of the ring much flatter than the other is the high tendency towards maximum overlap for the electrons of the O-C=O fragment. This requires a large displacement of the carbonyl atoms from the position that they would assume in an undistorted half-boat conformation; such a displacement can be measured by the dihedral angle, 15.6(2)°, between the benzene ring plane and that passing through the atoms C(11), C(10), O(2) and O(4).

A rather similar situation was found[12] in the corresponding fragment of the molecule of methyl 3,4-dihydroisocoumarin-3-carboxilate (4) where atoms C(2) and O(1) deviate by −0.083 and −0.344 Å, respectively, from the plane of the aromatic ring, atom C(4) lies in the plane, the torsion angle O(1)-C(2)-O(2)-C(3) is −166.5°, and the dihedral angle between the ring plane and that defined by atoms C(1), C(2), O(1) and O(2) is 10.9°.



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These values imply that in **4** too the half-boat conformation of the heterocycle is significantly distorted, the two torsion angles C(1)-C(5)-C(4)-C(3) and C(1)-C(2)-O(2)-C(3) being −28.5 and 18.6°, respectively.

The C(9) Me group of **3** adopts the equatorial position with the H atoms in a staggered conformation with respect to the three C(8)-O bonds. In the axially oriented phenoxy group, the conformation of the aromatic ring can be described by the two torsion angles C(9)-C(8)-O(5)-C(1), 64.3(2)°, and C(2)-C(1)-O(5)-C(8), 97.0(2)°. Using the notation proposed by Klyne and Prelog,[13] the value of the torsion angle around the C(8)-O(5) bond defines a syn-clinal conformation. Among the various possible orientations of the phenyl ring, characterized by different values of the rotation angle around the C(1)-O(5) bond, preference is given to the one that brings the

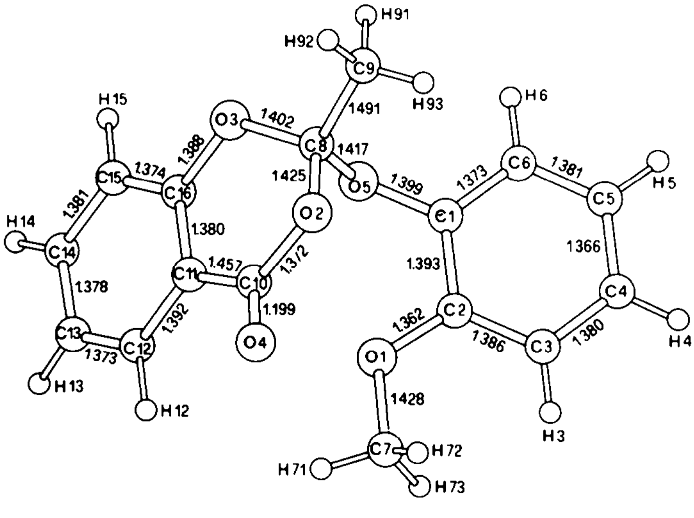

Fig 1. The molecule of **3** viewed along a principal axis of inertia. Numbering scheme and bond distances (Å) involving non-hydrogen atoms are shown. Estimated standard deviations are in the range 0.002–0.003 Å.

Table 2. Interatomic angles, torsion angles, and intramolecular contacts, with estimated standard deviations in parentheses

a) Bond angles (°)

C(2)-C(1)-C(6)	120.3(2)	C(11)-C(10)-O(2)	115.5(1)
C(2)-C(1)-O(5)	119.1(1)	C(11)-C(10)-O(4)	126.2(2)
C(6)-C(1)-O(5)	120.3(1)	O(2)-C(10)-O(4)	118.1(2)
C(1)-C(2)-C(3)	119.1(2)	C(10)-C(11)-C(12)	121.1(2)
C(1)-C(2)-O(1)	116.2(1)	C(10)-C(11)-C(16)	119.5(2)
C(3)-C(2)-O(1)	124.7(2)	C(12)-C(11)-C(16)	119.4(2)
C(2)-C(3)-C(4)	119.7(2)	C(11)-C(12)-C(13)	119.2(2)
C(3)-C(4)-C(5)	121.0(2)	C(12)-C(13)-C(14)	120.3(2)
C(4)-C(5)-C(6)	119.6(2)	C(13)-C(14)-C(15)	121.3(2)
C(1)-C(6)-C(5)	120.3(2)	C(14)-C(15)-C(16)	117.9(2)
C(9)-C(8)-O(2)	107.4(1)	C(11)-C(16)-C(15)	121.8(2)
C(9)-C(8)-O(3)	108.8(1)	C(11)-C(16)-O(3)	119.2(2)
C(9)-C(8)-O(5)	115.1(1)	C(15)-C(16)-O(3)	119.0(2)
O(2)-C(8)-O(3)	111.8(1)	C(2)-O(1)-C(7)	117.7(1)
O(2)-C(8)-O(5)	110.1(1)	C(8)-O(2)-C(10)	119.2(1)
O(3)-C(8)-O(5)	103.8(1)	C(8)-O(3)-C(16)	113.6(1)
		C(1)-O(5)-C(8)	119.3(1)

b) Selected torsion angles (°)

C(6)-C(1)-C(2)-O(1)	-177.4(2)	O(3)-C(8)-O(5)-C(1)	-177.0(1)
O(5)-C(1)-C(2)-C(3)	174.3(2)	O(2)-C(10)-C(11)-C(12)	168.3(2)
O(5)-C(1)-C(2)-O(1)	-4.0(2)	O(2)-C(10)-C(11)-C(16)	-13.2(2)
C(2)-C(1)-O(5)-C(8)	97.0(2)	O(4)-C(10)-C(11)-C(12)	-16.4(3)
C(1)-C(2)-O(1)-C(7)	-169.3(2)	O(4)-C(10)-C(11)-C(16)	162.1(2)
C(3)-C(2)-O(1)-C(7)	12.5(2)	C(11)-C(10)-O(2)-C(8)	-10.4(2)
O(1)-C(2)-C(3)-C(4)	177.2(2)	O(4)-C(10)-O(2)-C(8)	173.9(2)
C(9)-C(8)-O(2)-C(10)	162.8(1)	C(10)-C(11)-C(12)-C(13)	176.9(2)
O(3)-C(8)-O(2)-C(10)	43.6(2)	C(16)-C(11)-C(12)-C(13)	-1.6(3)
O(5)-C(8)-O(2)-C(10)	-71.3(2)	C(10)-C(11)-C(16)-C(15)	-174.6(2)
C(9)-C(8)-O(3)-C(16)	-171.5(1)	C(10)-C(11)-C(16)-O(3)	2.6(3)
O(2)-C(8)-O(3)-C(16)	-53.1(2)	C(12)-C(11)-C(16)-C(15)	3.9(3)
O(5)-C(8)-O(3)-C(16)	65.6(2)	C(12)-C(11)-C(16)-O(3)	-178.9(2)
C(9)-C(8)-O(5)-C(1)	64.3(2)	C(11)-C(16)-O(3)-C(8)	31.1(2)
O(2)-C(8)-O(5)-C(1)	-57.2(2)	C(15)-C(16)-O(3)-C(8)	-151.6(2)

c) Short intramolecular contacts (Å)

C(1)...C(9)	3.057(3)	C(3)...H(72)	2.81(2)
C(1)...O(2)	2.867(2)	C(3)...H(73)	2.75(2)
C(1)...H(93)	2.79(2)	C(6)...C(8)	3.266(2)
C(2)...C(8)	3.323(2)	C(6)...C(9)	3.306(3)
C(2)...H(72)	2.61(2)	C(6)...H(93)	2.79(2)
C(2)...H(73)	2.68(2)	C(7)...H(3)	2.53(2)
C(3)...C(7)	2.830(3)	C(10)...O(1)	2.725(2)

Table 3. Equations of least-squares planes in the form $Ax+By+Cz-D=0$, where x, y, z are fractional coordinates, and, in square brackets, displacements (Å) of relevant atoms from these planes

Plane A: C(11) → C(16)

$-3.0109\underline{x} + 22.6142\underline{y} + 0.9433\underline{z} - 0.7037 = 0$

[C(11) 0.015, C(12) -0.001, C(13) -0.018, C(14) 0.013, C(15) 0.009,
C(16) -0.019, O(3) -0.027, C(10) 0.101, O(4) 0.436, O(2) -0.141,
C(8) -0.665]

Plane B: C(10), C(11), C(16), O(2), O(3)

$-3.6252\underline{x} + 22.1063\underline{y} + 0.8714\underline{z} - 0.3422 = 0$

[C(10) 0.115, C(11) -0.037, C(16) -0.045, O(2) -0.042, O(3) 0.036,
C(12) -0.142, C(15) -0.045, C(8) -0.550, O(4) 0.436]

Plane C: C(10), C(11), O(2), O(4)

$-3.9990\underline{x} + 21.4420\underline{y} - 1.9501\underline{z} + 1.0617 = 0$

[C(10) -0.026, C(11) 0.007, O(2) 0.003, O(4) 0.005, C(16) 0.336,
C(8) -0.164]

Plane D: C(1) → C(6)

$7.4391\underline{x} - 10.1012\underline{y} - 5.9841\underline{z} + 0.8147 = 0$

[C(1) -0.003, C(2) 0.003, C(3) -0.004, C(4) 0.003, C(5) -0.003,
C(6) 0.003, O(1) 0.052, C(7) -0.175, O(5) 0.125, C(8) -1.039]

Dihedral angles (°): A∧B 3.8, A∧C 15.6, A∧D 47.9
B∧C 14.1, B∧D 45.3, C∧D 53.4

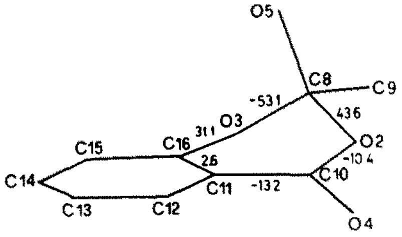

Fig. 2. A view of the "cyclic aspirin" moiety, showing the distorted half-boat conformation of the dioxane ring, for which torsion angles along the perimeter are reported. Puckering parameters (ref. 26) are: Q = 0.424, $\vartheta = 115.4°$, and $\Phi = 161.9°$.

electronegative atom O(1) in close contact with the partially positively charged atom C(10). In fact, the very short intramolecular distance between these two atoms, 2.725(3) Å, can be justified only in terms of electrostatic interaction.

The six C atoms of the aromatic ring of the guaiacol moiety are strictly coplanar, with a maximum deviation from the best plane of only 0.004 Å ($\sim 2\sigma$). The OMe group is not too far from coplanarity with the ring, the torsion angle C(3)–C(2)–O(1)–C(7) being 12.5(2)°. This arrangement results in close approach between atoms C(3) and C(7) [2.830(3) Å], which causes enlargement of the angle C(3)–C(2)–O(1) [124.7(2)°]. This, in turn, brings atoms O(1) and O(5) closer together, but the observed distance of 2.675(2) Å is still within the normally accepted range of allowed non-bonded contact distances.[14]

Relief from severe interactions between the guaiacol phenyl ring and the C(9) Me group is achieved mainly through a combination of two factors (i) bond angle deformations and (ii) bending of the phenyl ring. The angle C(1)–O(5)–C(8) is increased to 119.3(1)°, compared to values, in the range 114–117°, usually found[15–17] for the corresponding angle in phenoxy groups where the substituents at the O atom are, as in the present case, far from coplanar with the ring. The angle directly involving the Me group, O(5)–C(8)–C(9), is enlarged to 115.0(2)°, and this departure from the tetrahedral value is accompanied by a relevant closure of the O(3)–C(8)–O(5) angle, 103.8(1)°. The bending of the aromatic ring is apparent from the value of the displacement of atom O(5) from the aromatic plane, 0.125(2) Å. This deviation corresponds to a 5.1° angle between the O(5)–C(1) bond vector and the plane of the phenyl ring.

The formally single C–O bonds of the molecule, eight in number, are of two distinct types, according to the hybridisation state of the C atom. One of the four C(sp^3)–O bonds, C(8)–O(3), is significantly shorter than the other three, but its length, 1.402(2) Å, does not classify as unusual. Indeed, a large variety of values is found in heterocyclic-oxygen systems for the C(sp^3)–O distances, ranging, for example, from about 1.40 Å in 2-(*p*-chlorophenyl)-1,3-dioxane[18] to 1.462 Å in benzopyran derivatives.[19] The four C(sp^2)–O bond lengths of **3** are in the range 1.362(2)–1.399(2) Å, and the observed differences are clearly related to conjugative effects. The value of the C(10)–O(4) bond, which is formally double, is only slightly shorter than that in 4[12] [1.199(2) vs 1.208(6) Å], and compares well with values usually found in benzopyrone systems.

A detailed comparison of the pertinent bond distances and angles of the title compound with those of aspirin[20] and salicylic acid[21] is reported in Table 4. Bond length variations as well as angle deformations associated with the cyclisation process are all in the expected sense. Angle C(11)–C(10)–O(4) is a little greater than in **4**, 126.2(2) vs 125.1(6)°; similar values were found in many benzopyrone derivatives, e.g. coumarin[22] (125.6°), gnidicoumarin[23] (126.4 and 127.3°), and xanthotoxin[16] (126.0°).

Following the least-squares treatment of the anisotropic temperature factors proposed by Schomaker and Trueblood,[24] the tensors **T**, **L** and **S** were computed[25] for the two fragments of **3** which were expected to behave as rigid bodies in undergoing thermal libration. For the first fragment, that included atom O(1) and the ring C atoms of the guaiacol moiety, a very good agreement between observed and calculated U_{ij}'s was obtained, with a root-mean-square residue $\Delta U_{RMS} = \langle (U_{obs} - U_{calc})^2 \rangle^{1/2}$ of 0.0016, less than twice the value of σ_{RMS} (U_{obs}), 0.0009. The lengths of principal axes of the **L** tensor were 27, 20 and 15 (deg)^2, and the derived increase in the interatomic distances was about 0.008 A for all of them.

A little less satisfactory was the fit to a rigid-body model for the second fragment, which comprised atom C(10) and the aromatic ring of aspirin. While the ΔU_{ij}'s for most of the atoms rarely exceeded 3σ, atom C(16) showed a difference of eight standard deviations for U_{11}. No improvement was observed neither by replacing atom C(10) with atom O(3) into the fragment, nor by the inclusion of both atoms in the calculations. However, considering that ΔU_{RMS} was only slightly greater than $2\sigma_{RMS}$ (U_{obs}), 0.0024 vs 0.0011, this fragment too can be assumed to behave as a rigid body, at least to a first approximation. The librational motion is here more anisotropic than in the guaiacol moiety, the mean square rotational displacements amounting to 21, 12 and 9 (deg)^2. The implied corrections to the bond distances are in the range 0.005–0.007 Å.

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Table 4. Comparison of some molecular dimensions of **3** with those of aspirin[20] and salicylic acid[21]

	3	Aspirin*	Salicylic acid*
C(11)-C(16)	1.380(2) Å	1.400(5) Å	1.404(4) Å
C(16)-O(3)	1.388(2)	1.402(4)	1.357(4)
O(3)-C(8)	1.402(2)	1.364(4)	-
C(10)-C(11)	1.457(2)	1.498(5)	1.458(4)
C(10)-O(4)	1.199(2)	1.235(4)	1.234(4)
C(10)-O(2)	1.372(2)	1.287(4)	1.309(4)
C(15)-C(16)-O(3)	119.0(2)°	117.3(3)°	117.6(3)°
C(15)-C(16)-C(11)	121.8(2)	121.0(3)	119.6(3)
C(11)-C(16)-O(3)	119.2(2)	121.6(3)	122.8(3)
C(12)-C(11)-C(10)	121.1(2)	117.7(3)	121.2(3)
C(12)-C(11)-C(16)	119.4(2)	117.7(3)	118.6(3)
C(16)-C(11)-C(10)	119.6(2)	124.6(3)	120.4(3)
C(11)-C(10)-O(4)	126.2(2)	119.1(3)	122.8(3)
C(11)-C(10)-O(2)	115.5(2)	118.1(3)	116.0(3)
O(4)-C(10)-O(2)	118.1(2)	122.9(3)	121.2(3)
C(16)-O(3)-C(8)	113.6(1)	115.7(3)	-

* These are transposed to our crystallographic numbering system.

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