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# Structural Studies of Analgesics and Their Interactions. VII. Stereoisomerism and Disorder in the Structure of Oxyphenbutazone Monohydrate

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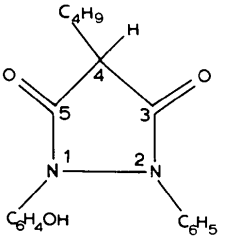
## Abstract

Oxyphenbutazone, $C_{19}H_{20}N_2O_3$, a metabolite and perhaps the active form of phenylbutazone, is a widely used non-narcotic analgesic and anti-inflammatory pyrazolidinedione derivative. The monohydrate of the compound crystallizes in the triclinic space group $P\bar{1}$ with two molecules in a unit cell of dimensions $a$ = 9·491 (4), $b$ = 10·261 (5), $c$ = 11·036 (3) Å and $\alpha$ = 72·2 (1), $\beta$ = 64·3 (1), $\gamma$ = 73·0 (1)°. The structure was solved by direct methods and refined to an $R$ value of 0·107 for 1498 observed reflections. The butyl group in the molecule is disordered. The hydroxyl group occupies two sites with unequal occupancies. On account of the asymmetry at the two N atoms and one of the C atoms in the central five-membered ring, the molecule can exist in eight isomeric states, of which four are sterically unfavourable. The disorder in the position of the hydroxyl group can be readily explained on the basis of the existence, with unequal abundances, of all four sterically favourable isomers. The bond lengths and angles in the molecule are similar to those in phenylbutazone. The crystal structure is stabilized by van der Waals interactions, and O—H···O hydrogen bonds involving the carbonyl and the hydroxyl groups as well as a water molecule.

## Introduction

Several pyrazolone and pyrazolidinedione derivatives are extensively used as non-narcotic anti-inflammatory analgesics. Like other structurally different anti-inflammatory analgesics, these drugs are believed to act through the inhibition of prostaglandin biosynthesis. As part of a programme of X-ray studies on such analgesics and their interactions, we have analysed the crystal structures of a number of analgesic pyrazolone derivatives and a crystalline complex of one of them (Krishna Murthy, Vijayan & Brehm, 1979, and references therein). We have also reported the structure determination of an analgesic pyrazolidinedione derivative, phenylbutazone, and its crystalline complex with piperazine (Singh & Vijayan, 1977). The X-ray analysis of 4-butyl-1-(4-hydroxyphenyl)-2-phenyl-3,5-pyrazolidinedione (*A*), a hydroxy derivative of phenylbutazone, is reported here. The compound, generally known as oxyphenbutazone, has pharmacological effects similar to those of phenylbutazone. Oxyphenbutazone is a metabolite of phenylbutazone and it has been suggested that the latter is converted into the former before it reaches the site of action (Curtis-Prior, 1976).




(*A*)

## Experimental

The compound was extracted from oxyphenbutazone tablets with the trade name Suganril, marketed by Suhrid Geigy Ltd, India. Crystals were grown from an aqueous methanol solution by slow evaporation. The space group and the unit-cell dimensions (given in the *Abstract*) were determined from X-ray diffraction photographs. The density measured by flotation in an aqueous potassium iodide solution agreed well with that calculated for two oxyphenbutazone molecules and two water molecules in the unit cell [$D_m$ = 1·249 (5), $D_c$ = 1·250 Mg m$^{-3}$].

The intensity data were collected on a CAD-4 four-circle diffractometer using graphite-monochromatized Cu $K\alpha$ radiation from a crystal with dimensions 0·38 × 0·30 × 0·45 mm up to a maximum Bragg angle of 60°. Of the 2458 independent reflections in this range, the intensities of 1498 had $I > 3\sigma(I)$

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and were used for structure determination and refinement. The data were corrected for Lorentz and polarization factors, but not for absorption.

## Structure analysis

The structure was determined by the use of *MULTAN* (Germain, Main & Woolfson, 1971) followed by conventional Fourier techniques and refined, first isotropically and then anisotropically, to an $R$ value ($R = \sum||F_o| - |F_c||/\sum|F_o|$) of 0·131 using a modified version of the block-diagonal SFLS programme written by Professor R. Shiono.

### *Disorder*

An examination of bond lengths, bond angles and temperature factors at this stage of refinement revealed two disturbing features. First, the bond lengths and angles in the butyl group deviated substantially from standard values, indicating probable disorder. Secondly, the hydroxyl O atom attached to one of the phenyl rings (referred to hereafter as phenyl ring 1) had a temperature factor higher than what one would normally expect. Difference Fourier maps phased on appropriate sets of atoms indicated the existence of two conformers, with equal occupancy factors, of the butyl group. They also showed that the hydroxyl group was disordered with two alternative positions. The position corresponding to an O atom attached to phenyl ring 1 was estimated to have an occupancy factor of 0·73. The second position with an occupancy factor of 0·27 corresponded to an O atom attached to the other phenyl ring in the molecule. These conclusions were confirmed by subsequent structure factor least-squares calculations.

In the subsequent refinement of the structure, the bond lengths in the disordered butyl group were manually constrained to lie between 1·48 and 1·58 Å; the bond angles in it were similarly constrained to lie between 104 and 116°. No constraints were imposed on the dimensions involving the other atoms. The positions of all the H atoms belonging to the oxyphenbutazone molecule were determined from geometrical considerations. The H atoms belonging to the water molecule were located from a difference Fourier map. These atoms were assigned the same isotropic temperature factors as those of the heavier atoms to which they are attached. They were included in the structure factor calculations in the final SFLS cycles, but their positional and thermal parameters were not refined. The refinement was terminated at $R = 0{\cdot}107$ when all the least-squares shifts (other than those in the positional parameters of the atoms in the disordered butyl group) were lower than the corresponding standard deviations. The weighting function used in the final calculations had the form $1/F_o$. The form factors were taken from *International Tables for X-ray Crystallography* (1974). The final positional parameters of the non-hydrogen atoms are given in Table 1.*

Table 1. *Coordinates* ($\times 10^3$) *and equivalent isotropic thermal parameters* ($\times 10$) (*Hamilton*, 1959) *of the non-hydrogen atoms*

The estimated standard deviations are given in parentheses. The positional parameters of C(9) through C(11′) were constrained during the final stages of refinement such that the bond lengths and angles in the disordered butyl group had acceptable values (see text). The standard deviations of these parameters are therefore not given.

| | $x$ | $y$ | $z$ | $B$ (Å$^2$) |
|---|---|---|---|---|
| N(1) | 780 (1) | 330 (1) | 488 (1) | 52 (7) |
| N(2) | 916 (1) | 295 (1) | 525 (1) | 52 (7) |
| C(3) | 1033 (2) | 364 (1) | 428 (2) | 50 (8) |
| C(4) | 981 (2) | 437 (1) | 306 (2) | 60 (9) |
| C(5) | 821 (2) | 404 (1) | 355 (2) | 55 (9) |
| O(6) | 1153 (1) | 364 (1) | 439 (1) | 66 (7) |
| O(7) | 735 (1) | 433 (1) | 289 (1) | 71 (7) |
| C(8) | 1100 (3) | 398 (2) | 169 (2) | 84 (13) |
| C(9) | 1110 | 241 | 185 | 106 (32) |
| C(9′) | 1125 | 249 | 164 | 72 (25) |
| C(10) | 1215 | 193 | 45 | 98 (40) |
| C(10′) | 1252 | 235 | 21 | 109 (40) |
| C(11) | 1380 | 221 | 11 | 172 (71) |
| C(11′) | 1315 | 80 | 20 | 181 (54) |
| C(12) | 676 (2) | 234 (1) | 544 (2) | 53 (8) |
| C(13) | 735 (2) | 89 (2) | 551 (2) | 68 (11) |
| C(14) | 629 (2) | 0 (2) | 607 (2) | 66 (11) |
| C(15) | 472 (2) | 46 (2) | 656 (2) | 66 (10) |
| C(16) | 413 (2) | 189 (2) | 644 (2) | 77 (12) |
| C(17) | 522 (2) | 279 (2) | 589 (2) | 71 (11) |
| O(18) | 366 (2) | −42 (2) | 720 (2) | 74 (10) |
| O(18′) | 792 (6) | 190 (5) | 1085 (4) | 73 (28) |
| C(19) | 886 (2) | 264 (1) | 668 (2) | 56 (9) |
| C(20) | 747 (2) | 328 (2) | 759 (2) | 63 (10) |
| C(21) | 729 (3) | 300 (2) | 898 (2) | 83 (13) |
| C(22) | 844 (3) | 207 (2) | 940 (2) | 97 (13) |
| C(23) | 980 (3) | 144 (2) | 849 (2) | 80 (12) |
| C(24) | 1002 (2) | 169 (2) | 713 (2) | 64 (10) |
| *W*(25) | 507 (2) | 325 (1) | 261 (1) | 89 (10) |

## Discussion

### *Molecular geometry*

The bond lengths and valency angles in the structure are given in Fig. 1. Fig. 2 shows a perspective view of the molecule. The bond lengths and angles in the

* Lists of structure factors, thermal parameters and H atom positional parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35678 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

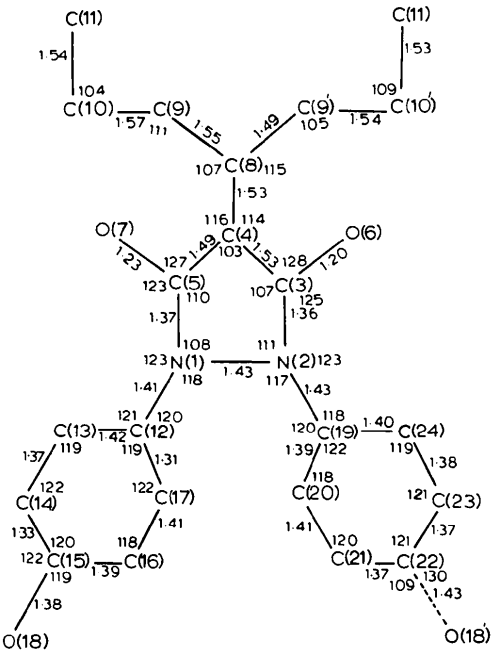


Fig. 1. Bond lengths (Å) and bond angles (°). The estimated standard deviations vary between 0·02 and 0·03 Å for all bond lengths except C(22)–O(18′) for which $\sigma$ is 0·05 Å. The estimated standard deviations for bond angles vary between 1·2 and 3°.

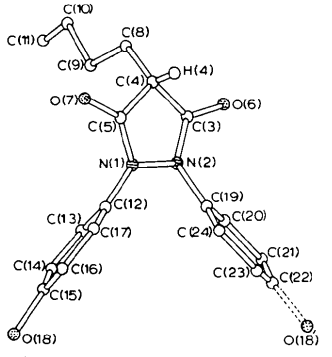


Fig. 2. A perspective view of the molecule. Only one H atom [H(4)] is indicated.

molecule are similar to those observed in the structure of phenylbutazone (Singh & Vijayan, 1977) and do not merit special comment. The two hetero N atoms are pyramidal. Phenyl ring 1 attached to N(1) lies on the same side of the five-membered ring as does the butyl group whereas phenyl ring 2 attached to N(2) lies on the opposite side. Some of the dihedral angles which define the conformation of the molecule are given in Table 2. The corresponding angles in the two crystallographically independent molecules in the structure of phenylbutazone are also given for comparison. The orientations of the two six-membered rings with respect to the five-membered ring are substantially different in phenylbutazone. In oxyphenbutazone also the orientations are different, but to a lesser extent.

Table 2. *Some dihedral angles* (°) *in the molecule*

The corresponding values in phenylbutazone are also given for comparison.

| | Oxyphenbutazone | Phenylbutazone molecule *A* | Phenylbutazone molecule *B* |
|---|---|---|---|
| N(2)–N(1)–C(12)–C(13) | −43 (2) | −40 (2) | −37 (2) |
| N(1)–N(2)–C(19)–C(20) | −32 (2) | −13 (2) | −14 (2) |
| C(4)–C(3)–N(2)–C(19) | −154 (2) | −147 (2) | −143 (2) |
| C(4)–C(5)–N(1)–C(12) | −152 (2) | −148 (2) | −147 (2) |
| C(12)–N(1)–N(2)–C(19) | −56 (2) | −67 (2) | −65 (2) |
| Angle between five-membered ring and phenyl ring 1 | 64 | 66 | 61 |
| Angle between five-membered ring and phenyl ring 2 | 53 | 40 | 42 |

## *Stereoisomerism and disorder*

As noted earlier, the two hetero N atoms are pyramidal in phenylbutazone and oxyphenbutazone. These N atoms can therefore be formally considered as asymmetric centres. In addition, C(4) also is an asymmetric centre in oxyphenbutazone on account of the substitution of a hydroxyl group at one of the phenyl rings. Rapid inversion can take place in solution at the N atoms if the energy barrier, resulting from steric factors, to such inversion is small. As noted when dealing with the struture of the phenylbutazone–piperazine complex (Singh & Vijayan, 1977), C(4) can be easily deprotonated. Therefore, rapid exchange between the two isomers resulting from the asymmetry of C(4) is likely to take place in solution. The different stereoisomers of the molecule might thus exist in a state of dynamic equilibrium in solution. In the solid state, however, it may be possible to observe the isomers individually.

With three asymmetric centres, the oxyphenbutazone molecule can exist in the eight isomeric states illustrated in Fig. 3. Of these, the first four can be considered to be sterically unfavourable as the hydroxyphenyl and the phenyl rings are on the same side of the five-membered ring. Of the rest, (V) and (VIII) are optical isomers; so are (VI) and (VII). The

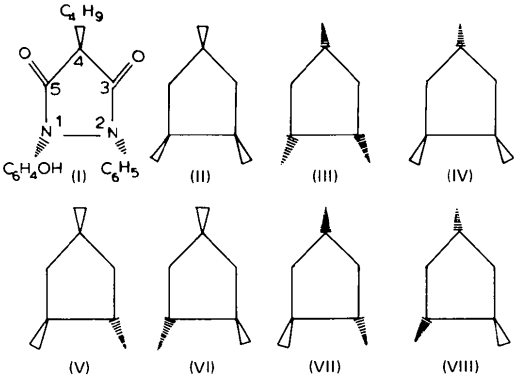


Fig. 3. The eight possible isomeric forms of the molecule.

butyl group and the hydroxyphenyl group are on the same side of the five-membered ring in (V) and (VIII) whereas the butyl group and the phenyl ring are on the same side in (VI) and (VII). The observed disorder of the hydroxyl group in the structure can be readily explained on the basis of the existence of these four isomers.

In the triclinic cell, there are two molecular sites which are related to each other by a centre of symmetry. (V) and (VII) coexist in one of the sites [(VII) is rotated by ~180° about an axis passing through C(4) and the mid-point of N(1)–N(2) before being superposed on (V)]. Judged by the observed occupancy factors of O(18) and O(18′), the occupancy factors of (V) and (VII) are 0·73 and 0·27 respectively. Likewise, (VIII) and (VI) coexist at the other site with occupancy factors of 0·73 and 0·27 respectively. Thus, all the four sterically favourable isomers are present in the crystal structure. However, two of these isomers in which the hydroxyphenyl group is on the same side of the five-membered ring as the butyl group are more abundant than those in which the phenyl and the butyl groups are on the same side.

From the relative occupancies of O(18) and O(18′) and with a Boltzmann distribution, the energy difference between the two sets of isomers is about 2·5 kJ $mol^{-1}$. This difference could have arisen from differences either in crystal forces or intramolecular interactions. O(18) and O(18′) have nearly the same environment. Both are hydrogen-bonded, as proton donors, to the crystallographically independent lone water molecule in the structure. As will be seen later, the O···O distance and the O–H···O angle have comparable values in both these hydrogen bonds. The main geometrical difference between the two hydrogen bonds at the receptor end pertains to the deviation of the donor group from the acceptor plane defined by the two lone pairs (of electrons) of the water O atom. The positions of the two water H atoms being known, this plane could be easily defined. O(18) and the attached H atom deviate from this plane by 0·09 (2) and 0·08 Å

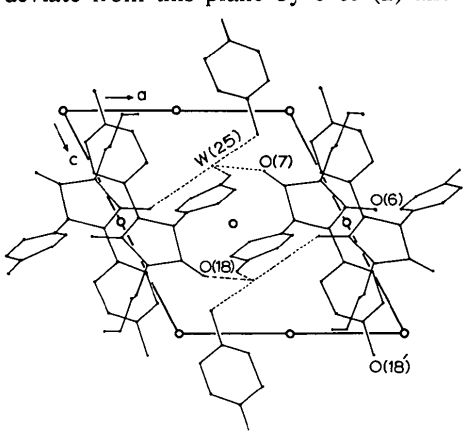


Fig. 4. Crystal structure as viewed along the *b* axis. Only atoms involved in hydrogen bonding are numbered.

Table 3. *Hydrogen-bond parameters*

| *A*–H···*B* | *A*···*B* | ∠(H–*A*···*B*) |
|---|---|---|
| O(18)–H(O18)···*W*(25)[a] | 2·77 (2) Å | 1° |
| O(18′)–H(O18′)···*W*(25)[b] | 2·81 (4) | 13 |
| *W*(25)–H1(*W*25)···O(7)[c] | 2·86 (2) | 34 |
| *W*(25)–H2(*W*25)···O(6)[d] | 3·05 (2) | 13 |

Symmetry code

(*a*) $1-x, -y, 1-z$ (*c*) $x,y,z$
(*b*) $x, y, 1+z$ (*d*) $x-1, y, z$

respectively, whereas the corresponding values of −1·85 (5) and −1·18 Å for O(18′) and H(O18′) respectively are substantially larger. The hydrogen bond formed by O(18) is thus stronger than that formed by O(18′) (Mitra, 1978). No means, however, currently exist for quantitatively evaluating the energy difference between the two hydrogen bonds. It is possible that the switch of the hydroxyl group from one six-membered ring to the other also contributes to the energy difference between the two sets of stereoisomers.

It may be noted that C(4) is not an asymmetric centre in phenylbutazone. Therefore, that molecule can exist in only two sterically favourable isomeric forms [(V) = (VII), (VI) = (VIII)]. Both these isomers exist with equal abundance in the centrosymmetric crystals of phenylbutazone (Singh & Vijayan, 1977).

### *Crystal structure and hydrogen bonding*

The crystal structure, shown in Fig. 4, is stabilized by van der Waals interactions and O–H···O hydrogen bonds. All the hydrogen bonds, the parameters of which are given in Table 3, involve the water molecule as donor or acceptor. The two carbonyl groups in the oxyphenbutazone molecule act as acceptors for a proton each from the water molecule which in turn is an acceptor in its hydrogen bond with the hydroxyl group.

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