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# (±)-2-(2-Fluoro-4-biphenyl)propionic Acid (Flurbiprofen)

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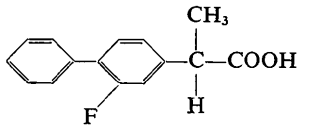
**Abstract.** $C_{15}H_{13}O_2F$, $P\bar{1}$, $a=9{\cdot}315$ (4), $b=12{\cdot}738$ (9), $c=5{\cdot}823$ (2) Å, $\alpha=83{\cdot}0$ (1), $\beta=107{\cdot}2$ (1), $\gamma=107{\cdot}0$ (1)°, $Z=2$, $d_{calc}=1{\cdot}29$ g cm$^{-3}$. The structure was solved by using a fragment of the molecule obtained in an $E$ map derived from the symbolic addition procedure as a partial structure for the tangent formula in space group $P1$.




(I)

**Experimental.** Flurbiprofen (I) is a non-steroidal anti-inflammatory agent which inhibits collagen-induced platelet aggregation. Its activity approaches that observed with prostaglandin $E_1$ (Nishizawa, Wynalda, Suydam & Molony, 1973). The crystals were provided by Dr E. Nishizawa of the Upjohn Company. 1953 independent reflections were collected from a small weakly scattering crystal ($\sim 0{\cdot}05\times 0{\cdot}08\times 0{\cdot}5$ mm). Data were collected on an automatic diffractometer with the $\theta$–$2\theta$ scanning technique (1·7° scan in $2\theta$ at a scanning speed of 2° min$^{-1}$) using Cu $K\alpha$ radiation ($\lambda=1{\cdot}54178$ Å, Ni filter). Unit-cell parameters were determined from a least-squares fit of the coordinates of 12 reflections which were individually centered on the diffractometer. During data collection three standard reflections were monitored after each 50 new reflections had been measured. The monitored data gave no indication of crystal deterioration.

The structure was solved by a combination of the symbolic addition procedure for centrosymmetric crystals and the tangent formula. One of the $E$ maps indicated by the symbolic addition procedure (Karle &

Table 1. *Fractional coordinates and thermal parameters with standard deviations*

The thermal parameters are of the form $T=\exp[-\frac{1}{4}(B_{11}h^2a^{*2}+B_{22}k^2b^{*2}+B_{33}l^2c^{*2}+2B_{12}hka^*b^*+2B_{13}hla^*c^*+2B_{23}klb^*c^*)]$. Standard deviations are based solely on least-squares parameters.

| | $x$ | $y$ | $z$ | $B_{11}$ | $B_{22}$ | $B_{33}$ | $B_{12}$ | $B_{13}$ | $B_{23}$ |
|---|---|---|---|---|---|---|---|---|---|
| F | 0·3742 (5) | 0·0444 (3) | 0·7635 (7) | 7·1 (3) | 5·4 (2) | 4·6 (2) | 1·9 (2) | 1·2 (2) | −1·2 (2) |
| O(1) | 0·0992 (6) | −0·4294 (4) | 0·3173 (10) | 5·3 (3) | 4·9 (3) | 5·9 (3) | −0·6 (2) | 1·8 (3) | −0·3 (2) |
| O(2) | 0·1776 (6) | −0·4309 (5) | 0·7119 (10) | 6·1 (3) | 6·8 (3) | 5·4 (3) | −0·5 (3) | 1·7 (3) | 0·7 (2) |
| C(1) | 0·3213 (8) | −0·0270 (5) | 0·5826 (12) | 3·6 (3) | 4·2 (3) | 4·1 (3) | 0·3 (3) | 1·5 (3) | −0·8 (3) |
| C(2) | 0·3570 (8) | −0·1267 (5) | 0·6348 (13) | 3·5 (3) | 3·7 (3) | 5·2 (4) | 0·8 (3) | 1·9 (3) | 0·2 (3) |
| C(3) | 0·3107 (7) | −0·1992 (5) | 0·4508 (13) | 3·7 (3) | 3·3 (3) | 5·4 (4) | 0·5 (3) | 2·1 (3) | −0·1 (3) |
| C(4) | 0·2273 (8) | −0·1714 (5) | 0·2233 (13) | 4·5 (3) | 3·9 (3) | 4·9 (4) | 0·5 (3) | 1·4 (3) | −1·0 (3) |
| C(5) | 0·1921 (8) | −0·0703 (5) | 0·1734 (13) | 4·7 (4) | 3·8 (3) | 4·8 (4) | 0·3 (3) | 1·8 (3) | −0·6 (3) |
| C(6) | 0·2400 (8) | 0·0046 (5) | 0·3579 (12) | 3·9 (3) | 3·6 (3) | 4·7 (4) | 0·6 (3) | 1·9 (3) | −0·4 (3) |
| C(7) | 0·2072 (8) | 0·1142 (5) | 0·3081 (13) | 4·1 (3) | 4·0 (3) | 4·7 (4) | 1·4 (3) | 1·2 (3) | −0·3 (3) |
| C(8) | 0·1315 (8) | 0·1490 (6) | 0·4500 (13) | 4·1 (3) | 5·5 (4) | 5·5 (4) | 2·1 (3) | 1·4 (3) | −0·8 (3) |
| C(9) | 0·1010 (10) | 0·2518 (7) | 0·3958 (16) | 7·1 (5) | 6·7 (5) | 6·3 (5) | 4·0 (4) | 1·8 (4) | −1·2 (4) |
| C(10) | 0·1423 (11) | 0·3177 (7) | 0·2074 (16) | 9·1 (6) | 5·5 (5) | 6·7 (5) | 4·3 (4) | 1·2 (4) | −0·5 (4) |
| C(11) | 0·2183 (10) | 0·2839 (6) | 0·0691 (15) | 7·3 (4) | 4·8 (4) | 5·8 (4) | 2·3 (4) | 1·4 (4) | 0·3 (3) |
| C(12) | 0·2490 (9) | 0·1812 (6) | 0·1164 (13) | 6·3 (4) | 4·1 (3) | 4·7 (4) | 1·7 (3) | 1·9 (3) | 0·1 (3) |
| C(13) | 0·3490 (8) | −0·3118 (5) | 0·5075 (14) | 4·2 (4) | 3·7 (3) | 6·1 (5) | 1·1 (3) | 1·7 (3) | −0·0 (3) |
| C(14) | 0·1958 (9) | −0·3971 (5) | 0·5020 (15) | 4·5 (4) | 3·3 (3) | 5·8 (4) | 1·4 (3) | 1·4 (3) | −0·0 (3) |
| C(15) | 0·4255 (9) | −0·3355 (6) | 0·3266 (15) | 5·8 (4) | 5·2 (4) | 9·4 (5) | 2·2 (3) | 3·7 (4) | −0·3 (4) |

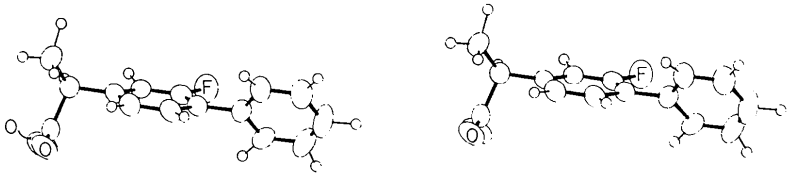



Fig. 1. Stereo configuration of the molecule drawn by program *ORTEP* (Johnson, 1965). The heavy atoms are shown at their final refined coordinates with anisotropic thermal parameters. The hydrogens are drawn at their difference map coordinates with arbitrary isotropic parameters.

Table 1 (*cont.*)

| | *x* | *y* | *z* |
|---|---|---|---|
| H(O) | −0·033 | −0·501 | 0·301 |
| H(C2) | 0·447 | −0·145 | 0·811 |
| H(C4) | 0·197 | −0·221 | 0·081 |
| H(C5) | 0·133 | −0·041 | −0·024 |
| H(C8) | 0·097 | 0·080 | 0·606 |
| H(C9) | 0·036 | 0·261 | 0·523 |
| H(C10) | 0·128 | 0·401 | 0·204 |
| H(C11) | 0·245 | 0·339 | −0·089 |
| H(C12) | 0·274 | 0·150 | −0·030 |
| H(C13) | 0·416 | −0·317 | 0·707 |
| H(C15) | 0·442 | −0·408 | 0·383 |
| H(C15) | 0·337 | −0·341 | 0·146 |
| H(C15) | 0·547 | −0·280 | 0·310 |

Karle, 1966), using space group $P\bar{1}$, contained a fragment which was consistent with the structural formula of this compound. However, use of this fragment (and its centrosymmetric mate) as a basis for phasing Fourier maps did not lead to improvements in the model. Thus, the centrosymmetric mate of the fragment was discarded, and the fragment alone was used to initiate the phasing of reflections in space group $P1$. The set of phases determined from this fragment was refined and expanded with the tangent formula in the usual way (Karle, 1968). Both molecules in the cell appeared as a result of this procedure, and, as expected, they were related by a center of symmetry not coincident with the origin. The contents of the cell were then shifted along $x$, $y$ and $z$ to place the inversion center at the origin of the cell, and refinement proceeded in $P\bar{1}$. The procedure employed in this structure solution is one which may be used when the orientation of a fragment is correct, but its position with respect to a proper origin in incorrect.

The structure was refined by full-matrix least-squares methods (Busing, Martin, Levy, Ellison, Hamilton, Ibers, Johnson & Thiessen, 1971). Hydrogen atoms, which were located in difference maps, were included in the final cycles of refinement as constants. The hydrogen atoms were assigned thermal parameters equal to the final isotropic value for the atom to which they were bonded. 48·9% of the data (955 reflections) had values of $F_o$ such that $|F_o| < 3{\cdot}0\sigma_{Fo}$ and these reflections were given zero weight for refinement purposes. Scattering factors used were those listed in *International Tables for X-ray Crystallography* (1962). The function minimized was $\sum w(|F_o| - |F_c|)^2$ where $w =$ weight and was calculated according to the procedure outlined by Gilardi (1973). Final $R$ values were $R =$ 6·2% and $R_w = 6{\cdot}7\%$ for the reflections included in the refinement and $R = 10{\cdot}2\%$ and $R_w = 8{\cdot}2\%$ for the full set of data. At the completion of the refinement, the standard deviation of an observation of unit weight was 1·05. The maximum observed shifts were $0{\cdot}2\sigma$ for the positional coordinates and $0{\cdot}5\sigma$ for the thermal parameters. Refined coordinates and thermal parameters for the non-hydrogen atoms, and the coordinates of the hydrogen atoms as determined from the difference map are listed in Table 1. A comparison of observed and calculated structure factors is available.*

**Discussion.** The configuration of the molecule is illustrated in Fig. 1. Biphenyl itself is planar in the solid state (Hargreaves & Rizvi, 1962; Trotter, 1961). In flurbiprofen both of the aromatic rings are planar but the presence of the fluorine atom on C(1) forces a rotation of the two planes about the C(6)–C(7) bond such that the C(1)–C(6)–C(7)–C(8) torsion angle is −54·4°. Bond distances and angles are shown in Fig. 2. The average C–H bond length is 1·12 Å. The molecular packing is influenced by the presence of an intermolecular hydrogen bond between the two oxygen atoms of the carboxyl group. The hydrogen bonds link the molecules into pairs across a center of symmetry. The

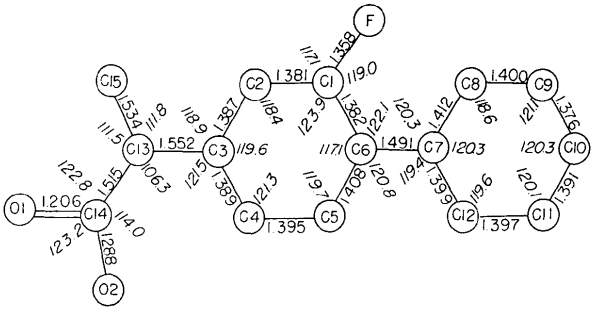



Fig. 2. Bond distances and angles. The numbering scheme does not correspond to the chemical numbering used to name the compound. Standard deviations are of the order of 0·009 Å for the bond lengths and 0·6° for the bond angles.

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30773 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

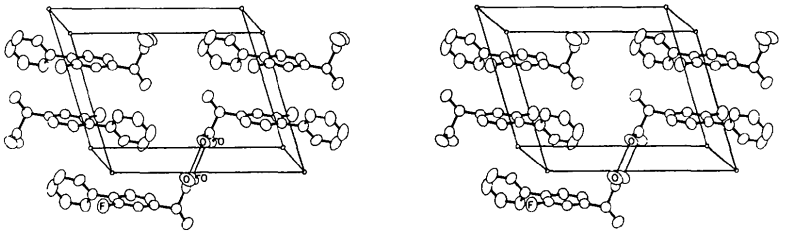


Fig. 3. Molecular packing for flurbiprofen. The view is seen looking down **c** with **b**→ and **a**↑. The O···O hydrogen bond is illustrated across the center of symmetry at $0, \frac{1}{2}, \frac{1}{2}$.

hydrogen atom was located approximately mid-way between the two oxygen atoms; O(1)···H = 1·29, O(2)···H = 1·36, O(1)···O(2) = 2·64 Å and O(1)···H···O(2) = 174·2°. The hydrogen bond, which is shown in Fig. 3, is the only intermolecular approach less than the van der Waals separations.

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# Chlormadinone Acetate (6-Chloro-17-hydroxypregna-4,6-diene-3,20-dione Acetate)


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**Abstract.** $C_{23}H_{29}ClO_4$, orthorhombic, $P2_12_12_1$, $a = 10{\cdot}925$ (6), $b = 12{\cdot}068$ (6), $c = 16{\cdot}179$ (9) Å, $\varrho_{obs} = 1{\cdot}26$, $\varrho_{calc} = 1{\cdot}261$ g cm$^{-3}$, $Z = 4$. Chlormadinone acetate is isomorphous with cyproterone acetate but has markedly different biological activity. The structures of cyproterone acetate (I) and chlormadinone acetate (II) are identical except in ring *A*.


Table 1. *Heavy-atom parameters and their standard deviations*

The values have been multiplied by $10^4$. The temperature factor is in the form:
$T = \exp[-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl)]$.

| | *x/a* | *y/b* | *z/c* | $b_{11}$ | $b_{22}$ | $b_{33}$ | $b_{12}$ | $b_{13}$ | $b_{23}$ |
|---|---|---|---|---|---|---|---|---|---|
| C(1) | 3745 (5) | 3130 (4) | 4139 (2) | 110 (6) | 70 (4) | 32 (2) | 6 (9) | 30 (6) | 1 (5) |
| C(2) | 3836 (5) | 4234 (4) | 3684 (3) | 138 (6) | 89 (4) | 30 (2) | 3 (10) | 23 (7) | 13 (5) |
| C(3) | 2877 (4) | 5051 (4) | 3939 (3) | 103 (6) | 78 (4) | 38 (2) | −33 (11) | −18 (6) | 13 (6) |
| C(4) | 2306 (4) | 4900 (4) | 4744 (2) | 75 (4) | 72 (4) | 35 (2) | −2 (9) | −6 (5) | 9 (5) |
| C(5) | 2633 (4) | 4091 (3) | 5278 (2) | 67 (4) | 52 (3) | 30 (2) | −23 (7) | −3 (5) | −5 (5) |
| C(6) | 2053 (4) | 3994 (3) | 6102 (2) | 79 (5) | 51 (3) | 34 (2) | −8 (8) | 3 (5) | −14 (5) |
| C(7) | 2246 (4) | 3165 (3) | 6622 (2) | 97 (5) | 54 (3) | 26 (2) | −17 (8) | 11 (5) | −4 (4) |
| C(8) | 3051 (4) | 2213 (3) | 6422 (2) | 77 (5) | 46 (3) | 27 (1) | 10 (7) | −1 (5) | −6 (4) |
| C(9) | 3289 (4) | 2125 (3) | 5480 (2) | 68 (4) | 57 (3) | 25 (1) | −4 (7) | 16 (5) | −6 (4) |
| C(10) | 3632 (4) | 3267 (3) | 5092 (2) | 78 (5) | 56 (3) | 29 (2) | −7 (8) | 0 (5) | 1 (4) |
| C(11) | 4154 (4) | 1174 (4) | 5289 (3) | 99 (5) | 62 (4) | 39 (2) | 14 (8) | 39 (6) | 3 (5) |
| C(12) | 3695 (4) | 51 (4) | 5620 (2) | 85 (5) | 61 (4) | 40 (2) | 19 (9) | 38 (5) | −9 (5) |
| C(13) | 3395 (4) | 125 (3) | 6545 (2) | 74 (4) | 50 (3) | 34 (2) | −1 (7) | 11 (5) | 6 (5) |
| C(14) | 2528 (4) | 1094 (3) | 6702 (2) | 63 (5) | 61 (3) | 25 (1) | −2 (8) | 2 (5) | −1 (4) |
| C(15) | 2123 (5) | 946 (3) | 7605 (2) | 107 (5) | 58 (4) | 32 (2) | 0 (9) | 12 (6) | −6 (5) |
| C(16) | 2038 (4) | −319 (3) | 7705 (2) | 103 (5) | 61 (4) | 33 (2) | 2 (8) | 28 (6) | 2 (4) |
| C(17) | 2637 (4) | −850 (3) | 6928 (2) | 82 (5) | 52 (3) | 35 (2) | 9 (8) | −15 (6) | −3 (4) |
| C(18) | 4601 (4) | 216 (4) | 7043 (3) | 80 (5) | 74 (4) | 58 (2) | 6 (9) | −12 (7) | 16 (6) |
| C(19) | 4834 (4) | 3715 (4) | 5458 (3) | 80 (5) | 75 (4) | 55 (2) | −29 (9) | −18 (7) | 21 (6) |
| C(20) | 3376 (4) | −1894 (4) | 7104 (3) | 91 (5) | 64 (4) | 43 (2) | −2 (8) | −3 (7) | 14 (5) |
| C(21) | 3692 (5) | −2667 (4) | 6408 (3) | 127 (7) | 74 (4) | 57 (3) | 57 (9) | 12 (8) | 13 (6) |
| O(23) | 3768 (3) | −2082 (3) | 7791 (2) | 139 (4) | 89 (3) | 49 (1) | 44 (7) | −41 (5) | 18 (4) |
| O(24) | 1714 (2) | −1105 (2) | 6302 (1) | 76 (3) | 53 (2) | 37 (1) | −1 (5) | −7 (4) | 9 (3) |
| C(25) | 919 (4) | −1936 (3) | 6464 (3) | 87 (5) | 47 (3) | 52 (2) | 2 (8) | −15 (7) | −2 (5) |
| C(26) | 111 (5) | −2157 (4) | 5732 (3) | 123 (7) | 73 (4) | 64 (3) | −21 (10) | −56 (8) | 6 (6) |
| O(27) | 896 (3) | −2446 (2) | 7100 (2) | 130 (4) | 65 (3) | 51 (1) | −41 (6) | −3 (5) | 21 (4) |
| O(28) | 2614 (3) | 5849 (3) | 3510 (2) | 161 (5) | 124 (4) | 49 (1) | 40 (8) | −1 (6) | 78 (5) |
| Cl(29) | 1073 (1) | 5066 (1) | 6403 (1) | 125 (1) | 60 (1) | 43 (1) | 36 (2) | 26 (1) | −10 (1) |