Table 3. *Torsion angle (°) comparison*

The atom numbering is according to garugambline-I.

| | (I) | (II) | Garuganin[a] |
|---|---|---|---|
| C(1)—C(2)—O(2)—C(20) | −163·5 (3) | −167·0 (3) | −184·4 (3) |
| C(6)—C(1)—O(1)—C(17) | −22·7 (3) | −23·7 (3) | 14·2 (3) |
| C(12)—C(13)—C(14)—C(19) | −88·4 (3) | −87·7 (3) | −82·6 (3) |
| C(12)—C(11)—O(11)—C(21) | 178·9 (3) | 178·7 (3) | −175·1 (3) |
| C(10)—C(11)—O(11)—C(21) | −0·4 (5) | −0·3 (4) | −3·0 (4) |
| C(7)—C(8)—C(9)—O(9) | −21·9 (4) | −19·7 (4) | −23·3 (4) |
| C(9)—C(8)—C(7)—C(5) | −83·4 (4) | −83·8 (3) | −78·4 (3) |
| C(8)—C(7)—C(5)—C(6) | 62·3 (3) | 59·6 (4) | 28·6 (4) |
| Ring *A* | | | |
| C(1)—C(2)—C(3)—C(4) | 1·8 (5) | 0·3 (4) | −0·5 (4) |
| C(2)—C(3)—C(4)—C(5) | −2·3 (5) | −2·0 (4) | 0·4 (4) |
| C(3)—C(4)—C(5)—C(6) | 0·5 (5) | 1·6 (4) | 0·1 (4) |
| C(4)—C(5)—C(6)—C(1) | 1·7 (4) | 0·6 (4) | −0·6 (4) |
| C(5)—C(6)—C(1)—C(2) | −2·3 (4) | −2·3 (4) | 0·5 (4) |
| C(6)—C(1)—C(2)—C(3) | 0·5 (4) | 1·8 (4) | −0·0 (4) |
| Ring *B* | | | |
| C(14)—C(15)—C(16)—C(17) | −0·7 (4) | 1·1 (4) | −0·3 (3) |
| C(15)—C(16)—C(17)—C(18) | −4·9 (4) | 4·2 (4) | −4·6 (3) |
| C(16)—C(17)—C(18)—C(19) | 5·1 (4) | −4·7 (4) | 4·6 (3) |
| C(17)—C(18)—C(19)—C(14) | 0·4 (4) | −0·2 (4) | 0·3 (3) |
| C(18)—C(19)—C(14)—C(15) | −5·8 (4) | 5·2 (4) | −5·0 (4) |
| C(19)—C(14)—C(15)—C(16) | 5·9 (4) | −5·6 (4) | 4·9 (3) |

Reference: (*a*) Pattabhi, Krishnaswamy & Gabe (1984).

The two aromatic groups *A* and *B* make dihedral angles of 79·6 (1) and 79·9 (1)° in (I) and (II) while the ansa bridge (see Fig. 2) plane makes angles of 57·7 (1), 53·8 (2), and 57·6 (1), 54·0 (1)° with rings *A*, *B* in (I) and (II) respectively. The corresponding values for garuganin-I are 95·3, 45·6, 57·2° (Pattabhi, Krishnaswamy & Gabe, 1984). The carbonyl group is perpendicular to ring *A* [87·9 (1)° in both structures] and approximately parallel to ring *B* [37·4 (2), 36·2 (1)° in (I) and (II)].

Table 2 shows that the bond angles C(12)—C(11)—O(11) and C(8)—C(9)—C(10) in both structures are significantly compressed, while the related angles C(12)—C(11)—C(10), C(11)—C(10)—C(9) are significantly expanded from the values expected at a C($sp^2$) centre. This tendency has been observed in garuganin-I (Pattabhi, Krishnaswamy & Gabe, 1984); in vinyl esters (Rappoport & Avramovitch, 1982), methyl (*E*)- and (*Z*)-β-chloro-α-cyano-*p*-nitrocinnamates (Strauss & Rappoport, 1982) and in *trans*-3-*p*-tolylthiocinnamic acid (Stephens, 1970). The bond C(9)—C(10) [1·462 (4) and 1·471 (3) Å in (I) and (II)] exhibits partial double bond character. Some relevant torsion angles observed in the present study have been compared (Table 3) with those in garuganin-I (Pattabhi, Krishnaswamy & Gabe, 1984), and are indicative of the conformational similarity of all three compounds. Indeed, the structural features of these macrocyclic diphenyl ethers, in comparison with ansamycin antibiotics, suggest that (I) and (II) may show antibiotic activity like garuganin-I (III). Biochemical studies to verify this possibility are being carried out.

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# Structure of Quercetin Dihydrate


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**Abstract.** 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-1-benzopyran-4-one, $C_{15}H_{10}O_7.2H_2O$, $M_r$ = 338·27, triclinic, $P\bar{1}$, $a$ = 14·976 (5), $b$ = 13·031 (5), $c$ = 3·7198 (4) Å, $\alpha$ = 85·69 (1), $\beta$ = 83·97 (2), $\gamma$ = 71·99 (3)°, $V$ = 685·8 (3) Å$^3$, $Z$ = 2, $D_m$ = 1·680 (7), $D_x$ = 1·638 Mg m$^{-3}$, $\lambda$(Cu $K\alpha$) = 1·54178 Å, $\mu$ =


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1·140 mm$^{-1}$, $F(000) = 352$, $T = 283$ K, final $R = 0·050$ for 2067 non-zero reflections. The dihedral angle between the benzopyran and phenyl rings is 8·01 (9)°, and there is an infinite stacking interaction between adjacent benzopyran rings and also between adjacent phenyl rings. All the hydroxyl groups of the quercetin molecule participate in hydrogen bonds to neighboring quercetin and/or water molecules.

**Introduction.** Quercetin, one of the natural flavonoids, is widely distributed in plants and is used as a yellow dyestuff. Quercetin and its glycosides (*e.g.* rutin, quercitrin *etc.*) are characterized as blood capillary stabilizers and exhibit some biological activities, such as acting as inhibitors of aldose reductase (Varma & Kinoshita, 1976) and of cyclic AMP phosphodiesterase (Ferrell, Chang Sing, Loew, King, Mansour & Mansour, 1979). In order to clarify the conformational properties of flavonoids and also to elucidate their structure–function relationships, we carried out an X-ray structure determination of quercetin and the results are compared with those of related compounds having a similar flavone skeleton.

**Experimental.** Quercetin, purchased from Nakarai Chemicals, Japan, crystallized from 1-propanol solution with a small amount of water; density by flotation in chloroform–ethylene dibromide mixture; crystal dimensions 0·8 × 0·1 × 0·02 mm; Rigaku automatic four-circle diffractometer (AFC-5R-300); $\omega$–$2\theta$-scan technique ($2\theta_{max} = 125°$); graphite-monochromatized Cu $K\alpha$ radiation; unit-cell dimensions by least-squares procedure based on the $2\theta$ values ($24 < 2\theta < 60°$) of 49 reflections; intensity fluctuation monitored periodically by three reflections ($00\bar{1}$, $1\bar{1}1$, $12\bar{1}$): <1·4%; 2189 unique reflections ($-17 \le h \le 17$, $-15 \le k \le 15$, $-4 \le l \le 0$); Lorentz and polarization corrections, but no absorption correction; structure solved by direct methods (*MULTAN*78; Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978); structure refined by full-matrix least squares with anisotropic temperature factors for all non-H atoms; all H atoms located from a difference Fourier map; the final refinement including H atoms with isotropic temperature factors reduced $R$ to 0·050 ($wR = 0·048$, $S = 1·719$) for 2067 observed reflections ($F_o \neq 0$) and 274 variables; function minimized $\sum w(|F_o| - k|F_c|)^2$, where $w = 1/\sigma^2(F_o)$ and $k$ is the scale factor; highest and lowest residuals in final difference Fourier map: 0·20 and −0·27 e Å$^{-3}$; $(\Delta/\sigma)_{max} = 0·15$ and $(\Delta/\sigma)_{av} = 0·02$ for non-H atoms; scattering factors from *International Tables for X-ray Crystallography* (1974); program system *UNICS* (1979) on the ACOS 930 computer of the Protein Engineering Research Center, Institute for Protein Research, Osaka University.

Table 1. *Atomic coordinates and thermal parameters of non-*H *atoms*

$B_{eq} = (4/3)\sum_i\sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

| | $x$ | $y$ | $z$ | $B_{eq}$(Å$^2$) |
|---|---|---|---|---|
| O(1) | 0·7890 (1) | 0·6788 (1) | 0·6053 (4) | 2·2 (1) |
| C(2) | 0·7060 (2) | 0·7539 (2) | 0·5231 (5) | 2·0 (1) |
| C(3) | 0·6226 (2) | 0·7330 (2) | 0·6150 (6) | 2·2 (1) |
| O(3) | 0·5394 (1) | 0·8067 (1) | 0·5405 (5) | 3·3 (1) |
| C(4) | 0·6194 (2) | 0·6340 (2) | 0·8014 (6) | 2·1 (1) |
| O(4) | 0·5411 (1) | 0·6167 (1) | 0·8932 (5) | 3·1 (1) |
| C(5) | 0·7138 (2) | 0·4555 (2) | 1·0514 (6) | 2·3 (1) |
| O(5) | 0·6337 (1) | 0·4308 (1) | 1·1609 (5) | 3·3 (1) |
| C(6) | 0·7994 (2) | 0·3830 (2) | 1·1108 (6) | 2·4 (1) |
| C(7) | 0·8814 (2) | 0·4111 (2) | 1·0059 (6) | 2·4 (1) |
| O(7) | 0·9671 (1) | 0·3411 (1) | 1·0716 (5) | 3·4 (1) |
| C(8) | 0·8787 (2) | 0·5104 (2) | 0·8373 (6) | 2·3 (1) |
| C(9) | 0·7912 (2) | 0·5810 (2) | 0·7730 (5) | 2·0 (1) |
| C(10) | 0·7074 (2) | 0·5575 (2) | 0·8740 (6) | 2·0 (1) |
| C(11) | 0·7218 (2) | 0·8520 (2) | 0·3456 (5) | 2·0 (1) |
| C(12) | 0·8120 (2) | 0·8638 (2) | 0·3169 (6) | 2·2 (1) |
| C(13) | 0·8277 (2) | 0·9573 (2) | 0·1637 (6) | 2·2 (1) |
| O(13) | 0·9153 (1) | 0·9716 (1) | 0·1317 (5) | 3·2 (1) |
| C(14) | 0·7537 (2) | 1·0404 (2) | 0·0313 (6) | 2·2 (1) |
| O(14) | 0·7727 (1) | 1·1321 (1) | −0·1160 (4) | 3·0 (1) |
| C(15) | 0·6648 (2) | 1·0289 (2) | 0·0562 (6) | 2·4 (1) |
| C(16) | 0·6481 (2) | 0·9363 (2) | 0·2121 (6) | 2·4 (1) |
| O(*W*1) | 0·0589 (1) | 0·8471 (1) | 0·5302 (5) | 3·3 (1) |
| O(*W*2) | 0·3890 (1) | 0·7346 (1) | 0·3643 (5) | 3·2 (1) |

**Discussion.** Final positional and thermal parameters are listed in Table 1.* Bond distances and angles are shown in Table 2 with average values for 13 reported flavone derivatives. The molecular conformation with atomic numbering is given in Fig. 1.

The benzopyran and phenyl rings are both essentially planar; the largest deviations from the least-squares planes are 0·022 (3) Å for C(3) and 0·005 (3) Å for C(12), respectively. The dihedral angle between the two rings is 8·01 (9)°, and that between the phenyl and pyrone rings is 1·00 (6)°. The bulky group at C(3) causes a larger torsion angle at C(3)—C(2)—C(11)—C(16); in the cases of 3-bromoflavone (Cantrell & Stalzer, 1982), 3-methoxyflavone (Wallet, Gaydou, Fadlane & Baldy, 1988), 14-bromo-3-hydroxyflavone and 14-bromo-5-hydroxyflavone [with no substitution at C(3)] (Hayashi, Kawai, Ohno, Iitaka & Akimoto, 1974), the torsion angles are 45·9, 37·2, 18·8 and 6·6°, respectively. This angle in quercetin, with the 3-hydroxyl group, is 6·7 (4)°. Similarly, when a bulky group is attached at C(12) or C(16), the torsion angle around the C(2)—C(11) bond also becomes larger (Kimura, Okuda, Taira, Shoji, Takemoto & Arichi, 1984). The bond lengths and angles of the flavone skeleton agree well with the averaged ones for the 13 flavone derivatives except for bond lengths

* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52290 (15 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Bond distances* (Å) *and angles* (°) *and the average values for* 13 *reported flavone derivatives*

| | | Average | | | Average |
|---|---|---|---|---|---|
| O(1)—C(2) | 1·371 (3) | 1·371 (10) | C(7)—O(7) | 1·359 (3) | |
| O(1)—C(9) | 1·368 (3) | 1·372 (19) | C(7)—C(8) | 1·386 (3) | 1·385 (21) |
| C(2)—C(3) | 1·362 (3) | 1·353 (18) | C(8)—C(9) | 1·381 (3) | 1·386 (14) |
| C(2)—C(11) | 1·469 (3) | 1·473 (16) | C(9)—C(10) | 1·390 (3) | 1·386 (14) |
| C(3)—O(3) | 1·358 (3) | | C(11)—C(12) | 1·397 (3) | 1·394 (14) |
| C(3)—C(4) | 1·431 (3) | 1·444 (12) | C(11)—C(16) | 1·398 (3) | 1·397 (18) |
| C(4)—O(4) | 1·269 (3) | 1·244 (13) | C(12)—C(13) | 1·383 (3) | 1·383 (13) |
| C(4)—C(10) | 1·423 (3) | 1·451 (22) | C(13)—O(13) | 1·373 (3) | |
| C(5)—O(5) | 1·352 (3) | | C(13)—C(14) | 1·392 (3) | 1·392 (18) |
| C(5)—C(6) | 1·365 (3) | 1·376 (14) | C(14)—O(14) | 1·374 (3) | |
| C(5)—C(10) | 1·418 (3) | 1·409 (23) | C(14)—C(15) | 1·378 (3) | 1·387 (25) |
| C(6)—C(7) | 1·396 (3) | 1·394 (13) | C(15)—C(16) | 1·380 (3) | 1·389 (18) |

| | | Average |
|---|---|---|
| C(2)—O(1)—C(9) | 121·7 (2) | 120·5 (13) |
| O(1)—C(2)—C(3) | 120·1 (2) | 120·8 (17) |
| O(1)—C(2)—C(11) | 111·5 (2) | 111·0 (15) |
| C(3)—C(2)—C(11) | 128·4 (2) | 128·1 (19) |
| C(2)—C(3)—O(3) | 121·1 (2) | |
| C(2)—C(3)—C(4) | 121·2 (2) | 122·2 (12) |
| O(3)—C(3)—C(4) | 117·6 (2) | |
| C(3)—C(4)—O(4) | 120·6 (2) | 122·5 (12) |
| C(3)—C(4)—C(10) | 116·7 (2) | 115·2 (12) |
| O(4)—C(4)—C(10) | 122·7 (2) | 122·3 (12) |
| O(5)—C(5)—C(6) | 120·2 (2) | |
| O(5)—C(5)—C(10) | 119·0 (2) | |
| C(6)—C(5)—C(10) | 120·8 (2) | 120·6 (08) |
| C(5)—C(6)—C(7) | 119·5 (2) | 119·6 (10) |
| C(6)—C(7)—O(7) | 120·3 (2) | |
| C(6)—C(7)—C(8) | 121·8 (2) | 121·8 (09) |
| O(7)—C(7)—C(8) | 117·8 (2) | |
| C(7)—C(8)—C(9) | 117·3 (2) | 118·0 (13) |
| O(1)—C(9)—C(8) | 117·1 (2) | 116·0 (12) |
| O(1)—C(9)—C(10) | 119·7 (2) | 121·3 (09) |
| C(8)—C(9)—C(10) | 123·2 (2) | 122·7 (15) |
| C(4)—C(10)—C(5) | 122·2 (2) | 122·2 (11) |
| C(4)—C(10)—C(9) | 120·5 (2) | 119·9 (09) |
| C(5)—C(10)—C(9) | 117·4 (2) | 117·9 (11) |
| C(2)—C(11)—C(12) | 119·7 (2) | 120·4 (16) |
| C(2)—C(11)—C(16) | 121·6 (2) | 120·1 (11) |
| C(12)—C(11)—C(16) | 118·6 (2) | 119·5 (16) |
| C(11)—C(12)—C(13) | 120·7 (2) | 120·1 (15) |
| C(12)—C(13)—O(13) | 122·2 (2) | |
| C(12)—C(13)—C(14) | 120·0 (2) | 120·5 (14) |
| O(13)—C(13)—C(14) | 117·8 (2) | |
| C(13)—C(14)—O(14) | 117·9 (2) | |
| C(13)—C(14)—C(15) | 119·5 (2) | 119·5 (16) |
| C(14)—C(15)—C(16) | 120·9 (2) | 120·4 (14) |
| C(11)—C(16)—C(15) | 120·2 (2) | 120·0 (15) |

References: Cantrell & Stalzer (1982); Castleden, Hall, Nimgirawath, Thadaniti & White (1985); Estrada, Conde, Márquez & Jiménez-Garay (1987); Hayashi, Kawai, Ohno, Iitaka & Akimoto (1974); Jurnak & Templeton (1975); Kimura, Okuda, Taira, Shoji, Takemoto & Arichi (1984); Lee, Lu & Zee (1974); Mariezcurrena (1978); Ting, Watson & Dominguez (1972); Vijayalakshmi, Rajan & Srinivasan (1986, 1987); Wallet, Gaydou, Fadlane & Baldy (1988).

C(4)—C(10) and C(4)—O(4), in which the former is shorter and the latter is longer than the averaged ones. This may be due to hydrogen-bond formation at the carbonyl group and also the substitution at C(5). In the 5-hydroxyflavone derivatives (Castleden, Hall, Nimgirawath, Thadaniti & White, 1985; Hayashi, Kawai, Ohno, Iitaka & Akimoto, 1974; Kimura, Okuda, Taira, Shoji, Takemoto & Arichi, 1984; Lee, Lu & Zee, 1974; Vijayalakshmi, Rajan & Srinivasan, 1986, 1987), the C(4)—C(10) bonds are shorter than those of unsubstituted derivatives (Wallet, Gaydou, Fadlane & Baldy, 1988; Hayashi, Kawai, Ohno, Iitaka & Akimoto, 1974; Cantrell & Stalzer, 1982), the C(4)—O(4) bonds are longer and angles C(3)—C(4)—C(10) are larger.

The stereo packing diagram of the molecules in the unit cell is illustrated in Fig. 2. All hydroxyl and carbonyl groups and water molecules participate in hydrogen bonds. Three hydroxyl groups at C(5), C(13) and C(14) positions act as both donors and acceptors of hydrogen bonds. The carbonyl group forms an intramolecular hydrogen bond with the hydroxyl group at C(5). The most pronounced feature in the crystal packing is the infinite stacking between adjacent benzopyran rings and also between adjacent phenyl rings with separation of about 3·4 Å. As shown by the unit-cell packing, the smaller the dihedral angle between the benzopyran and phenyl rings, the stronger the stacking interactions that occur between adjacent molecules. The dihedral angle may be affected by a substituent at the C(3) position as described above. We also performed an INDO calculation, rotating the phenyl ring around the C(2)—C(11) bond from 0 to 360°. The stable conformation of quercetin has the torsion angle C(3)—C(2)—C(11)—C(16) nearly 0 and 180°, but

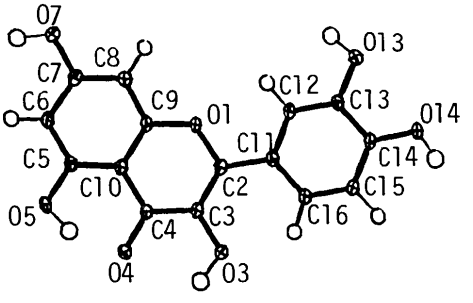


Fig. 1. An *ORTEP* (Johnson, 1976) plot of quercetin with atom labelling, ellipsoids at 30% probability.

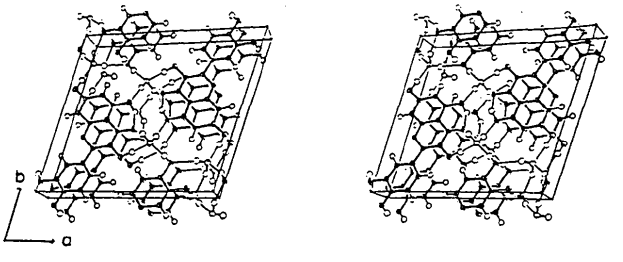


Fig. 2. Stereoscopic drawing of the molecular packing viewed along the *c* axis. Thin lines indicate hydrogen bonds.

the conformation with this angle nearly 90 or 270° is unstable and shows the highest energy level.

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# Structure of the Neuroleptic Drug 4-Amino-*N*-1-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(ethylsulfonyl)-2-methoxybenzamide (Amisulpride)

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**Abstract.** $C_{17}H_{27}N_3O_4S$, $M_r = 369{\cdot}48$, monoclinic, $P2_1/c$, $a = 13{\cdot}333\ (7)$, $b = 7{\cdot}946\ (4)$, $c = 17{\cdot}550\ (10)$ Å, $\beta = 96{\cdot}99\ (4)°$, $V = 1845\ (2)$ Å$^3$, $Z = 4$, $D_m = 1{\cdot}33$, $D_x = 1{\cdot}330$ Mg m$^{-3}$, graphite-monochromated Cu $K\alpha$ radiation, $\lambda = 1{\cdot}54178$ Å, $\mu = 1{\cdot}744$ mm$^{-1}$, $F(000) = 792$, $T = 293$ K. Final $R = 0{\cdot}038$ for 2405 unique observed reflections. The folded conformation of the molecule with the least-squares planes of the aromatic and the pyrrolidine rings almost perpendicular is essentially determined by intra- and intermolecular hydrogen bonds. In this way, two pseudorings are formed, one linking the amide H with the methoxy O, and a second one involving the 4-amino H and a sulfonyl O. An intermolecular hydrogen bond forces the planar amide group some 28° out of the plane of the aromatic ring.

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**Introduction.** Amisulpride belongs to the same class of neuroleptics as the widely reputed sulpiride. These drugs act by blocking the dopamine $D_2$ receptor (Kebabian & Calne, 1979). The present investigation is part of a study examining the structural requirements for doing so.

**Experimental.** Colorless crystals from a methanol–amyl acetate solution, $0{\cdot}6 \times 0{\cdot}2 \times 0{\cdot}2$ mm. Density measured by flotation in *n*-heptane/$CCl_4$, systematic absences from Weissenberg photographs. Siemens AED2 diffractometer, cell constants by least-squares refinement of the setting angles of 44 reflections with $35 < 2\theta < 55°$, $\omega/\theta$ scan, $[(\sin\theta)/\lambda]_{max} = 0{\cdot}5840$ Å$^{-1}$, $0 \le h \le 16$, $0 \le k \le 9$, $-21 \le l \le 21$. Intensities of four standard reflections (020, 400, 004, 100) monitored every hour showed only statistical fluctuations, 3530 reflections measured, 2405 observed reflections with $|F_o| > 6|\sigma(F_o)|$. Data reduction with Stoe &