Acta Cryst. (1986). C**42**, 626–628

Structure of (*R*,*S*)-Naringenin

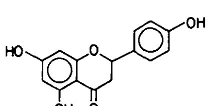
By Whanchul Shin and Myoung Soo Lah

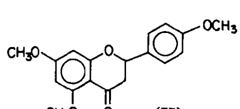
Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151, *Korea*

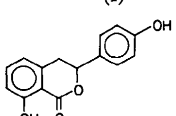
(*Received* 29 *July* 1985; *accepted* 29 *November* 1985)

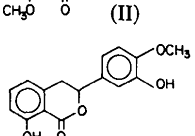
Abstract. 2,3-Dihydro-5,7-dihydroxy-2-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one, $C_{15}H_{12}O_5$, M_r = 272·25, monoclinic, $P2_1/c$, a = 4·965 (3), b = 15·449 (6), c = 16·845 (8) Å, β = 103·86 (8)°, V = 1254 (2) Å^3, Z = 4, D_x = 1·441 g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, μ = 8·17 cm^{-1}, F(000) = 568, T = 295 K, R = 0·054 for 1356 observed reflections. The hydroxyl O(5) and keto O(4) atoms form a strong intramolecular hydrogen bond, making a conjugated six-membered ring. The 4-hydroxyphenyl ring is bonded equatorially to the pyrone ring which adopts a slightly distorted sofa conformation, and is rotated so that it is approximately perpendicular to the mean plane of the benzopyrone ring. O(4′)—H···O(4) [2·711 (4) Å] and O(7)—H···O(4′) [2·805 (4) Å] hydrogen bonds make a two-dimensional hydrogen-bonding network.

Introduction. Most of the flavanoid compounds are known to be tasteless or bitter while their corresponding dihydrochalcones are very sweet (Horowitz & Gentili, 1969). In an effort to provide detailed structural information for a related compound, we have determined the crystal structure of racemic naringenin (I). Naturally occurring naringenin is optically active with an *R* configuration. The structure of naringenin will be compared with those of related compounds, especially 4′,5,7-trimethoxyflavanone (II) (TMF) (Marietzcurrena, 1978) and hydrangenol (III) (Schmalle, Jarchow, Hausen & Schultz, 1982), which is a structural analog of phyllodulcin (IV), an intensely sweet dihydroisocoumarin compound.


(I)


(II)


(III)


(IV)

Experimental. Colorless tabular crystals obtained from an aqueous solution at room temperature; density by flotation in petroleum ether/chloroform; crystal *ca* 0·2 × 0·3 × 0·5 mm; Rigaku AFC diffractometer, graphite-monochromated Cu $K\alpha$ radiation, $2\theta \le 120°$, ω–2θ scan, speed 4° min^{-1} in 2θ, ω-scan width $(1·4 + 0·6\tan\theta)°$, background measured for 12 s on either side of the peak; cell parameters by least-squares fit to observed 2θ values for 25 centered reflections with $22° \le 2\theta \le 48°$; intensity checks for three standard reflections showed little (±2·2%) variation; 1877 independent reflections (h −5 to 5, k 0 to 17, l 0 to 18), 1356 (72·2%) observed with $I \ge 3\sigma(I)$ and used in refinement; Lp corrections, no absorption or extinction correction. Structure solved by direct methods with *SHELX*76 (Sheldrick, 1976) and refined by full-matrix least squares on F with anisotropic thermal parameters; H atoms identified on a difference map and refined isotropically. $\sum w(|F_o| - |F_c|)^2$ minimized, with $w = k/[\sigma^2(F_o) + gF_o^2]$, $\sigma(F)$ from counting statistics, k and g optimized in the least-squares procedure (k = 2·26, g = 0·0011); wR = 0·060 for 1356 observed reflections, 229 variables, R = 0·073 for all data, S = 2·60, $(\Delta/\sigma)_{max}$ = 0·043 in final refinement cycle, max. and min. heights in final difference map 0·44 and −0·24 e Å^{-3}, respectively. All calculations performed with *SHELX*76 on a VAX 11/780.

Discussion. Final atomic parameters are in Table 1.* The molecule and numbering scheme are shown in Fig. 1. Bond lengths and angles are listed in Table 2.

The oxo 4-keto and 5-hydroxyl groups form a strong intramolecular hydrogen bond [O(4)···O(5) = 2·648 (5), O(5)—H(5) = 0·86 (4), H(5)···O(4) = 1·88 (5) Å, ∠O(5)—H···O(4) = 148 (4)°]. The C(4)—O(4) bond of 1·256 (4) Å is *ca* 0·03 Å longer than the normal carbonyl C—O bond of 1·23 Å and the C(9)—C(10) bond of 1·421 (4) Å is 0·03 Å longer than the benzene C—C bond length. These values indicate that the hydrogen-bonded six-membered ring is considerably conjugated. However, conjugation does not extend over the pyrone ring, judging from the C(2)—

* Lists of structure factors, anisotropic thermal parameters, coordinates of H atoms, bond lengths and angles involving the H atoms, dimensions of the phenyl ring and least-squares planes have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42686 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

0108-2701/86/050626-03$01.50

C(3) and C(3)—C(4) bond lengths of 1·508 (5) and 1·503 (5) Å, respectively. Bond lengths of the benzopyrone moiety in TMF show significant differences from those of naringenin due to the absence of the intramolecular hydrogen bond (see Table 2). The largest differences are in the C(9)—C(10) and C(5)—O(5) bonds. In TMF, the aromaticity of ring *A* is decreased and the π electrons tend to be localized in the C(5)—C(6), C(7)—C(8) and C(9)—C(10) bonds. The formation of the hydrogen-bonded six-membered ring has also been observed in phlorizin, containing a dihydrochalcone derivative of naringenin (Shin, 1985), 4′-bromo-5-hydroxyflavone (Hayashi, Kawai, Ohno, Iitaka & Akimoto, 1974) and hydrangenol (Schmalle, Jarchow, Hausen & Schultz, 1982).

The phenyl ring *C* is planar (maximum deviation 0·006 Å) with an average C—C bond length of 1·382 Å. Ring *A* is planar with a maximum deviation of 0·016 Å. O(1), C(4), O(4) and O(5) are displaced from plane *A* by 0·060, 0·036, 0·010 and −0·051 Å while C(2) and C(3) are displaced by −0·444 and 0·156 Å, respectively (e.s.d.'s for displacements from planes are ≃ 0·004 Å). The pyrone ring in naringenin adopts a slightly modified sofa conformation. Comparison of the torsion angles of the related compounds given in Table 3 indicates that the pyrone ring has a strong preference for the sofa conformation. The lactone ring in hydrangenol also adopts a sofa conformation. When the *A* rings of naringenin and hydrangenol are superimposed, all of the atoms in the *A* and *B* rings are fitted within 0·04 Å, except for the atoms at the O(1), C(2) and C(3) positions of naringenin which show deviations of 0·22 (2), 0·39 (2) and 0·37 (2) Å, respectively. However, the dihydropyran rings, devoid of the keto group at C(4), have half-chair conformations slightly distorted toward the sofa forms (Valente, Santarsiero & Schomaker, 1979). This difference in the conformation seems to be determined by the hybridization state of C(4), that is, the ring tends to be a sofa for sp^2 C(4) and a half-chair for sp^3 C(4).

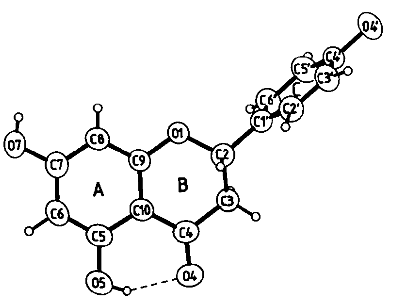


Fig. 1. *ORTEP* (Johnson, 1971) drawing of naringenin with the atomic numbering scheme.

Table 1. *Final positional (fractional* $\times 10^4$*) and equivalent isotropic thermal parameters* (Å^2) *with e.s.d.'s in parentheses*

$$U_{eq} = \tfrac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
O(1)	2139 (5)	4650 (1)	3465 (1)	0·047
C(2)	−349 (8)	4224 (2)	3583 (2)	0·057
C(3)	−1729 (11)	3701 (3)	2840 (2)	0·054
C(4)	−2154 (8)	4220 (2)	2065 (2)	0·048
C(5)	−297 (8)	5406 (2)	1328 (2)	0·051
C(6)	1649 (9)	6040 (2)	1315 (2)	0·053
C(7)	3620 (8)	6221 (2)	2029 (2)	0·047
C(8)	3754 (8)	5757 (2)	2749 (2)	0·046
C(9)	1860 (7)	5107 (2)	2753 (2)	0·041
C(10)	−245 (7)	4911 (2)	2042 (2)	0·045
O(4)	−4084 (8)	4024 (2)	1461 (2)	0·062
O(5)	−2285 (7)	5266 (2)	635 (2)	0·071
O(7)	5460 (6)	6871 (2)	2003 (2)	0·060
C(1′)	429 (8)	3696 (2)	4359 (2)	0·048
C(2′)	−821 (9)	3865 (2)	4989 (2)	0·055
C(3′)	−188 (9)	3381 (3)	5690 (2)	0·055
C(4′)	1728 (7)	2715 (2)	5787 (2)	0·043
C(5′)	3007 (9)	2528 (3)	5164 (2)	0·054
C(6′)	2321 (9)	3022 (3)	4452 (3)	0·058
O(4′)	2285 (7)	2272 (2)	6519 (2)	0·058

Table 2. *Bond lengths* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

O(1)—C(2)	1·454 (4) 1·428*	O(1)—C(9)	1·369 (3) 1·378*
C(2)—C(3)	1·508 (5) 1·496	C(2)—C(1′)	1·510 (4) 1·469
C(3)—C(4)	1·503 (5) 1·503	C(4)—C(10)	1·435 (4) 1·468
C(4)—O(4)	1·256 (4) 1·224	C(5)—C(6)	1·381 (5) 1·356
C(5)—C(10)	1·419 (4) 1·436	C(5)—O(5)	1·353 (4) 1·436
C(6)—C(7)	1·385 (5) 1·431	C(7)—C(8)	1·396 (4) 1·368
C(7)—O(7)	1·365 (4) 1·368	C(8)—C(9)	1·376 (4) 1·393
C(9)—C(10)	1·421 (4) 1·343	C(4′)—O(4′)	1·380 (4)
O(1)—C(2)—C(3)	111·2 (3)	O(1)—C(2)—C(1′)	108·2 (2)
O(1)—C(9)—C(8)	117·1 (3)	O(1)—C(9)—C(10)	121·9 (3)
C(2)—O(1)—C(9)	116·2 (2)	C(2)—C(3)—C(4)	112·1 (3)
C(2)—C(1′)—C(2′)	119·8 (3)	C(2)—C(1′)—C(6′)	122·0 (3)
C(3)—C(2)—C(1′)	113·6 (3)	C(3)—C(4)—C(10)	117·7 (3)
C(3)—C(4)—O(4)	119·8 (3)	C(4)—C(10)—C(5)	123·1 (3)
C(4)—C(10)—C(9)	119·5 (3)	C(5)—C(6)—C(7)	118·7 (3)
C(5)—C(10)—C(9)	117·4 (3)	C(6)—C(5)—C(10)	121·7 (3)
C(6)—C(5)—O(5)	117·9 (3)	C(6)—C(7)—C(8)	121·8 (3)
C(6)—C(7)—O(7)	117·3 (3)	C(7)—C(8)—C(9)	119·3 (3)
C(8)—C(7)—O(7)	120·8 (3)	C(8)—C(9)—C(10)	121·0 (3)
C(10)—C(4)—O(4)	122·5 (3)	C(10)—C(5)—O(5)	120·4 (3)
C(3′)—C(4′)—O(4′)	117·3 (3)	C(5′)—C(4′)—O(4′)	123·0 (3)

* Bond lengths of TMF for comparison. The average e.s.d. for TMF is 0·011 Å.

Table 3. *Comparison of torsion and dihedral angles* (°) *in related compounds*

	(*A*)	(*B*)	(*C*)	(*D*)	(*E*)	(*F*)	(*G*)
τ_1	49·8	−43·9	54·8	52·4	54·8	−53	−44
τ_2	−50·6	55·5	−55·0	−56·0	−51·6	56	61
τ_3	28·3	−26·8	−24·6	30·3	−19·3	−28	−44
τ_4	−3·1	−3·7	−6·2	−0·9	−9·5	0	15
τ_5	0·4	6·9	8·1	−5·4	2·7	0	0
τ_6	−24·8	22·9	23·0	−21·6	29·7	27	15
ψ	85·7	70·8	105·5	42·2	78·8		

ψ: dihedral angle between ring *A* and ring *C*.

τ_1: C(9)—O(1)—C(2)—C(3) τ_2: O(1)—C(2)—C(3)—C(4)
τ_3: C(2)—C(3)—C(4)—C(10) τ_4: C(3)—C(4)—C(10)—C(9)
τ_5: C(4)—C(10)—C(9)—O(1) τ_6: C(10)—C(9)—O(1)—C(2)

(*A*) This study (e.s.d.'s ≃0·4°). (*B*) TMF. (*C*) 4′-Bromoflavanone (Cantrell, Stalzer & Becker, 1974). (*D*) 3-Bromoflavanone (Cantrell & Hockstein, 1982). (*E*) Hydrangenol. (*F*), (*G*) Calculated angles (Bucourt & Hainaut, 1965) for sofa and half-chair forms of cyclohexene, respectively.

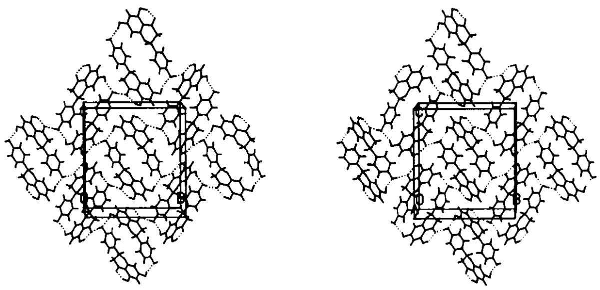


Fig. 2. *PLUTO* (Motherwell & Clegg, 1978) stereodrawing of the molecular packing. H bonding is represented by dotted lines.

The hydroxyphenyl ring is bonded equatorially to the pyrone ring. Although a pseudoaxial conformation has been suggested to be an active form for phyllodulcin (DuBois, Crosby, Stephenson & Wingard, 1977), this conformation has not been observed in the crystal structures of benzopyrone or dihydroisocoumarin derivatives. The *A* and *C* rings are nearly perpendicular to each other with a dihedral angle of 85·7°. Other flavanones also assume a similar conformation (see Table 3). However, the relative orientation of the phenyl and benzopyrone rings seems to be determined by crystal packing forces since, in solution, C(2′) and C(3′) are chemically and magnetically equivalent to C(6′) and C(5′) as determined by ^{13}C NMR studies of flavanones (Cotterill, Scheinmann & Stenhouse, 1977).

Two unique O—H···O hydrogen bonds make a two-dimensional hydrogen-bonded molecular layer through the formation of hydrogen-bonded dimers and hexamers (Fig. 2): O(7)···O(4′)(1 − *x*, 1 − *y*, 1 − *z*) = 2·805 (4), O(7)—H(7) = 0·83 (5), H(7)···O(4′) = 2·04 (5) Å, ∠O(7)—H···O(4′) = 154 (4)°; O(4′)···O(4)(1 + *x*, 0·5 − *y*, 0·5 + *z*) = 2·711 (4), O(4′)—H(4′) = 0·77 (4), H(4′)···O(4) = 1·95 (5) Å, ∠O(4′)—H···O(4) = 172 (5)°. There are only van der Waals interactions between these layers.

This work was supported by a research grant (No. 1984-46) from the Korea Research Foundation.

References

BUCOURT, R. & HAINAUT, D. (1965). *Bull. Soc. Chim. Fr.* pp. 4562–4567.

CANTRELL, J. S. & HOCKSTEIN, G. S. (1982). *Acta Cryst.* B**38**, 981–983.

CANTRELL, J. S., STALZER, R. A. & BECKER, T. L. (1974). *Acta Cryst.* B**30**, 154–161.

COTTERILL, P. J., SCHEINMANN, F. & STENHOUSE, I. A. (1977). *J. Chem. Soc. Perkin Trans.* 1, pp. 532–539.

DUBOIS, G. E., CROSBY, G. A., STEPHENSON, R. A. & WINGARD, R. E. (1977). *J. Agric. Food Chem.* **25**, 763–772.

HAYASHI, T., KAWAI, S., OHNO, T., IITAKA, Y. & AKIMOTO, T. (1974). *Chem. Pharm. Bull.* **22**, 1219–1226.

HOROWITZ, R. M. & GENTILI, B. (1969). *J. Agric. Food Chem.* **17**, 696–700.

JOHNSON, C. K. (1971). *ORTEP*. Report ORNL-3794, revised. Oak Ridge National Laboratory, Tennessee.

MARIETZCURRENA, R. A. (1978). *Acta Cryst.* B**34**, 2322–2324.

MOTHERWELL, W. D. S. & CLEGG, W. (1978). *PLUTO*. Program for plotting molecular and crystal structures. Univ. of Cambridge, England.

SCHMALLE, H. W., JARCHOW, O. H., HAUSEN, B. M. & SCHULTZ, K.-H. (1982). *Acta Cryst.* B**38**, 2938–2941.

SHELDRICK, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.

SHIN, W. (1985). *Bull. Korean Chem. Soc.* **6**, 7–11.

VALENTE, E. J., SANTARSIERO, B. D. & SCHOMAKER, V. (1979). *J. Org. Chem.* **44**, 798–802.

Acta Cryst. (1986). C**42**, 628–630

The Structure of a Reduction Product of the Cytotoxic Drug Nitracrine

BY GEORGE R. CLARK* AND SIMON HALL

Department of Chemistry, University of Auckland, Auckland, New Zealand

AND WILLIAM A. DENNY AND GEORGINA M. STEWART

Cancer Research Laboratory, University of Auckland School of Medicine, Auckland, New Zealand

(*Received* 23 *July* 1985; *accepted* 5 *December* 1985)

Abstract. 2,3-Dihydro-2,2-dimethyl-1-[3-(dimethylamino)propyl]-1*H*-pyrimidino[4,5,6-*de*]acridine dihydrochloride, $C_{21}H_{28}N_4^{2+}.2Cl^-$, $M_r = 407·11$, monoclinic, $P2_1/c$, $a = 15·351$ (1), $b = 12·108$ (1), $c = 11·559$ (2) Å, $\beta = 102·03$ (1)°, $V = 2101·4$ (7) Å^3, $Z = 4$, $D_m = 1·28$ (1), $D_x = 1·286$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0·71073$ Å, $\mu = 2·68$ cm^{-1}, $F(000) = 860$, $T = 293$ K, $R = 0·040$ for 1869 ($I > 2·5\sigma$) reflections. X-ray analysis shows that the nitracrine reduction product, 1-amino-9-(dimethylaminopropyl)acridine, has condensed with one mole of acetone across the primary and secondary amine functions, to form a pyrimidinoacridine ring system. The acridine nucleus suffers a concomitant buckling from planarity.

* To whom correspondence should be addressed.

0108-2701/86/050628-03$01.50