The X-Ray Crystal and Molecular Structure of Neohesperidin Dihydrochalcone Sweetener

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The molecular structure and absolute configuration of the sweetener neohesperidin dihydrochalcone have been determined by single-crystal X-ray analysis. The crystal structure consists of two crystallographically independent molecules which differ mainly in the orientation of the isovanillyl B-ring. The molecules are linked together by an intricate arrangement of intermolecular hydrogen bonds formed between the host and solvent water molecules. The relation between the X-ray-deduced structure of the sweetener and a hypothetical 'active' conformation is discussed.

Most of the known high-potency sweeteners were discovered fortuitously in the course of studies carried out for some other purpose. Despite substantial effort, the deliberate design and synthesis of new sweeteners has rarely been successful, except for compounds that are closely related in structure to an existing sweetener. This failure to understand the molecular basis of sweetness emphasizes the need to define the structures of known sweeteners as accurately as possible. We report here an X-ray crystallographic determination of the structure of neohesperidin dihydrochalcone† (1), a high-potency sweetener that can be prepared from either of the citrus bitter principles, neohesperidin (2) or naringin (3).[1]

(1)

(2) R = Me, R' = OH
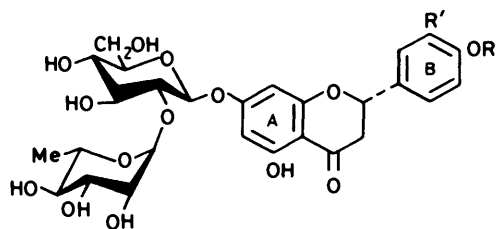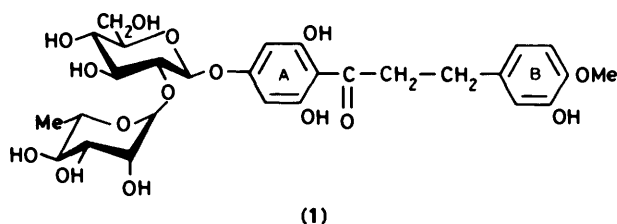
(3) R = R' = H

The X-ray results confirm the structure deduced from degradation and synthesis but show that the conformations existing in the crystal structure are different from that postulated as the 'active' conformation of dihydrochalcone sweeteners in solution.

† Systematic name (Chemical Abstracts): 1-[4-[[2-O-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-2,6-dihydroxyphenyl]-3-(3-hydroxy-4-methoxyphenyl)-1-propanone;3,5-dihydroxy-4-(3-hydroxy-4-methoxyhydrocinnamoyl)phenyl-2-O-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranoside.

Results and Discussion

The crystal structure of neohesperidin dihydrochalcone consists of two crystallographically independent molecules. The two molecular conformations, (A) and (B), with their atomic thermal motions and the numbering scheme used in the X-ray investigation are shown in Figures 1 and 2, respectively. The thermal ellipsoids on the Figures are drawn at the 50% probability level, and an arbitrary radius of 0.08 Å is assigned to the hydrogen atoms. The molecular structures and absolute configurations of conformations (A) and (B) are illustrated in the stereoscopic drawings, Figures 3 and 4 respectively. The final atomic co-ordinates and their estimated standard deviations (in parentheses) are listed in Table 1. The observed bond lengths and angles are reported in Tables 2 and 3, respectively. The gross structural features of these two molecules, (A) and (B), are closely similar. The entire neohesperidin dihydrochalcone molecule is roughly 'J-shaped' with the β-neohesperidosyl (2-O-α-L-rhamnosyl-β-D-glucosyl) residue forming the curved part of the 'J' and the hesperetin dihydrochalcone aglycone forming the linear segment. Both gyclosyl rings in the β-neohesperidosyl unit in (A) and (B) assume a chair conformation. Five chiral centres [C(4), C(5), C(12), C(14), and C(15)] have the R configuration, while the other five chiral centres [C(2), C(3), C(6), C(13), and C(17)] have the S configuration. The two aromatic rings of the hesperetin dihydrochalcone fragment in both molecules are essentially planar and have a maximum deviation of ±0.02(3) Å.

The similarity between the two independent molecules does not extend to the B-ring (the isovanillyl unit), primarily because the C(34)–C(35) single bond in molecule (B) has undergone a rotation which causes its B-ring to be turned through ca. 90°. A superimposition diagram of the two crystallographically independent molecules is shown in Figure 5.

The dihedral angle between the A- and B-rings is 38.6(4)° in molecule (A) and −59.8(5)° in molecule (B). The comparative dihedral angle data between the plane normals of all the ring units in the structure are given in Table 4. Other precise molecular conformational differences in conformers (A) and (B) are indicated by the values of the selected torsional angles listed in Table 5.

The two molecules of compound (1) in the crystal structure interact mutually with adjacent molecule units through an intricate arrangement of intermolecular hydrogen bondings formed mostly between the hydroxy groups of the host molecules and the solvent water molecules. The mode of molecular packing and hydrogen-bonding in the unit-cell is displayed in Figure 6. There are 11 water molecules occupying definite crystallographic positions in the asymmetric unit.
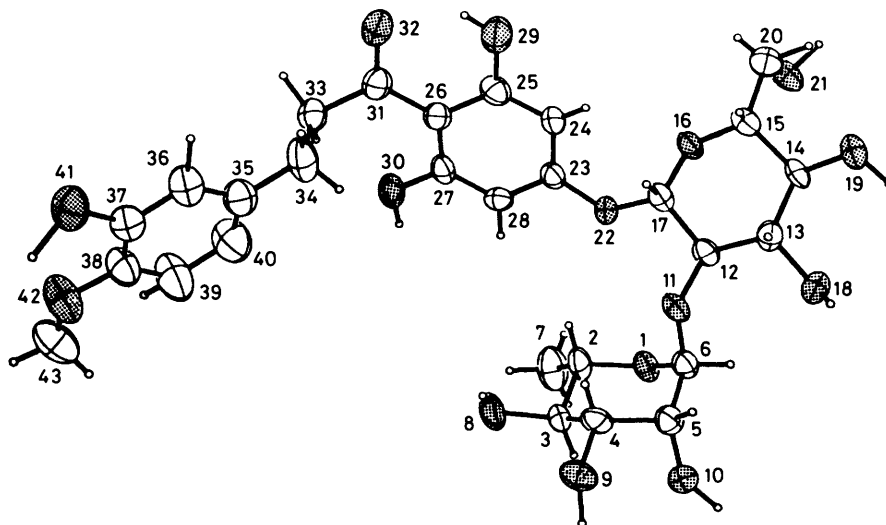
Figure 1. Conformer (A) of neohesperidin dihydrochalcone. The shaded areas represent oxygen atoms
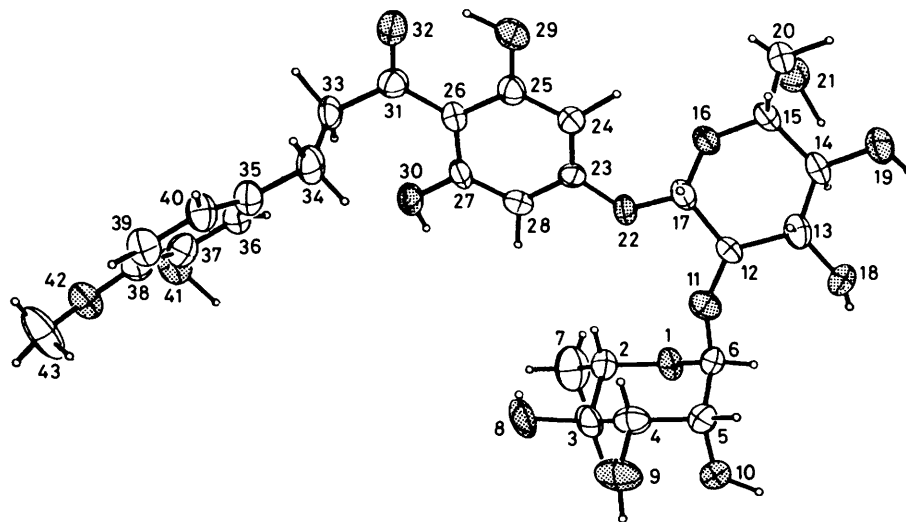

Figure 2. Conformer (B) of neohesperidin dihydrochalcone. The shaded areas represent oxygen atoms
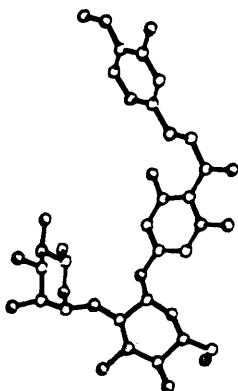

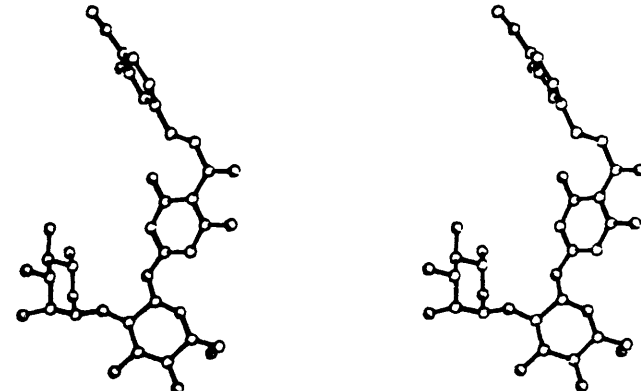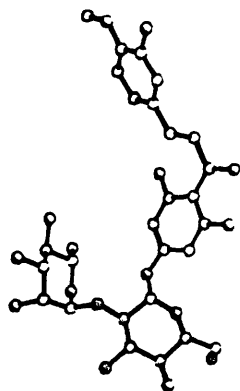**Figure 3.** Stereoscopic view of conformer (A) of neohesperidin dihydrochalcone

Figure 4. Stereoscopic view of conformer (B) of neohesperidin dihydrochalcone

Table 1. Atom co-ordinates ($\times 10^4$) for compound (1) conformers (A) and (B), with e.s.d.s in parentheses

Atom	(A) x	y	z	(B) x	y	z
O(1)	7 455(1)	3 174	5 413(1)	7 526(1)	7 660(4)	9 580(1)
C(2)	7 080(2)	3 342(7)	5 720(2)	7 923(2)	7 860(7)	9 285(2)
C(3)	6 720(2)	1 870(7)	5 735(2)	8 302(2)	6 405(7)	9 281(2)
C(4)	7 105(2)	446(7)	5 802(2)	7 921(2)	4 987(7)	9 211(2)
C(5)	7 504(2)	377(6)	5 485(2)	7 525(2)	4 866(7)	9 525(2)
C(6)	7 841(2)	1 887(6)	5 471(2)	7 163(2)	6 336(7)	9 517(1)
C(7)	6 697(3)	4 742(9)	5 584(2)	8 273(3)	9 310(8)	9 409(2)
O(8)	6 381(2)	2 054(5)	6 057(1)	8 652(2)	6 608(6)	8 970(1)
O(9)	6 780(2)	−945(4)	5 812(1)	8 258(2)	3 611(5)	9 196(1)
O(10)	7 144(1)	139(5)	5 100(1)	7 879(2)	4 719(5)	9 912(1)
O(11)	8 219(1)	1 983(4)	5 841(1)	6 789(1)	6 369(4)	9 149(1)
C(12)	8 693(2)	3 067(6)	5 849(1)	6 314(2)	7 427(7)	9 132(2)
C(13)	9 246(2)	2 209(6)	5 804(2)	5 757(2)	6 557(7)	9 194(2)
C(14)	9 769(2)	3 273(7)	5 867(2)	5 236(2)	7 586(7)	9 108(2)
C(15)	9 790(2)	4 197(7)	6 256(2)	5 190(2)	8 401(7)	8 702(2)
O(16)	9 247(1)	4 975(4)	6 254(1)	5 731(1)	9 150(5)	8 672(1)
C(17)	8 777(2)	3 913(7)	6 244(2)	6 205(2)	8 136(7)	8 707(2)
O(18)	9 180(2)	1 512(5)	5 408(1)	5 830(2)	5 979(5)	9 593(1)
O(19)	10 293(1)	2 370(5)	5 891(1)	4 710(2)	6 723(5)	9 116(1)
C(20)	10 269(3)	5 373(8)	6 338(2)	4 723(2)	9 604(8)	8 630(2)
O(21)	10 234(2)	6 446(5)	6 006(1)	4 787(2)	10 684(5)	8 955(1)
O(22)	8 282(1)	4 818(4)	6 281(1)	6 701(1)	9 063(4)	8 665(1)
C(23)	8 211(2)	5 197(6)	6 676(2)	6 769(2)	9 518(6)	8 281(1)
C(24)	8 649(2)	5 101(7)	7 003(2)	6 360(2)	9 375(7)	7 946(2)
C(25)	8 523(2)	5 440(7)	7 386(2)	6 499(2)	9 857(7)	7 573(2)
C(26)	7 958(2)	5 883(7)	7 449(2)	7 051(2)	10 478(7)	7 534(2)
C(27)	7 546(2)	6 074(6)	7 100(2)	7 461(2)	10 618(7)	7 900(2)
C(28)	7 663(2)	5 710(6)	6 719(2)	7 321(2)	10 137(6)	8 270(2)
O(29)	8 960(2)	5 260(6)	7 699(1)	6 084(2)	9 625(6)	7 245(1)
O(30)	7 011(1)	6 643(5)	7 144(1)	7 991(1)	11 223(5)	7 882(1)
C(31)	7 855(2)	6 071(7)	7 871(2)	7 170(2)	10 953(7)	7 131(2)
O(32)	8 273(2)	6 149(6)	8 155(1)	6 768(2)	10 944(6)	6 837(1)
C(33)	7 257(2)	6 026(7)	7 993(2)	7 769(2)	11 343(7)	7 047(2)
C(34)	7 067(3)	4 309(8)	7 992(2)	8 140(2)	9 883(7)	7 055(2)
C(35)	6 459(2)	4 128(8)	8 083(2)	8 751(2)	10 152(7)	6 979(2)
C(36)	6 378(3)	3 407(7)	8 449(2)	9 106(2)	11 304(7)	7 171(2)
C(37)	5 815(2)	3 191(7)	8 532(2)	9 682(3)	11 481(7)	7 113(2)
C(38)	5 350(3)	3 733(8)	8 276(2)	9 904(2)	10 437(7)	6 859(2)
C(39)	5 405(3)	4 475(11)	7 916(2)	9 570(2)	9 284(7)	6 665(2)
C(40)	5 989(3)	4 646(10)	7 836(2)	8 989(2)	9 146(7)	6 723(2)
O(41)	5 748(2)	2 556(5)	8 902(1)	10 003(2)	12 670(5)	7 302(1)
O(42)	4 815(2)	3 491(6)	8 395(1)	10 498(2)	10 669(5)	6 841(1)
C(43)	4 306(3)	4 027(10)	8 146(3)	10 787(3)	9 412(8)	6 671(3)
Ow(1)	6 401(2)	7 459(5)	6 428(1)			
Ow(2)	5 778(2)	8 470(6)	5 245(1)			
Ow(3)	8 584(2)	1 822(6)	8 606(1)			
Ow(4)	9 232(2)	2 960(7)	9 753(1)			
Ow(5)	9 438(2)	8 282(7)	5 507(2)			
Ow(6)	8 373(3)	7 128(8)	5 527(2)			
Ow(7)	6 285(4)	1 662(16)	9 656(2)			
Ow(8)	10 000	6 034(11)	5 000			
Ow(9)	5 000	404(13)	10 000			
Ow(10)	4 810(5)	3 702(21)	9 477(4)			
Ow(11)	5 376(5)	3 328(21)	9 807(4)			

Ow = O in water of crystallization.

Among these water molecules, two lie on the two-fold axis of symmetry at the special positions of $[0, 0.40, \frac{1}{2}]$ and $[\frac{1}{2}, 0.96, 0]$, and two are disordered with *ca.* 75% site of occupancy. The intermolecular distances that are less than 3.0 Å between two oxygen atoms in the structure are listed in Table 6, together with their symmetry transformations. Crystals of compound (1) are highly stable at room temperature, and no dehydration was observed during data collection. The stability of the hydrated crystals is presumably due to the large number of relatively

strong hydrogen bonds from solvent to host molecules and the compactness in structural arrangement.

In both conformers the hydrogen atom of the hydroxy group H–O(29) assumes the closest possible position to the carbonyl oxygen atom O(32); the observed distances between O(29) ··· O(32) in conformers (A) and (B) are 2.50(5) and 2.52(5) Å, respectively. This orientation is expected since it provides a more efficient and stable molecular packing in the crystal structure by enhancing the formation of intramolecular

Table 2. Bond lengths (Å) for comformers (A) and (B) of compound (1), with e.s.d.s in parentheses

	(A)	(B)		(A)	(B)
O(1)–C(2)	1.454(7)	1.460(7)	O(1)–C(6)	1.425(6)	1.418(7)
C(2)–C(3)	1.529(8)	1.538(9)	C(2)–C(7)	1.530(10)	1.518(10)
C(3)–C(4)	1.518(8)	1.510(9)	C(3)–O(8)	1.437(7)	1.426(7)
C(4)–C(5)	1.515(8)	1.503(9)	C(4)–O(9)	1.424(7)	1.430(8)
C(5)–C(6)	1.527(8)	1.522(8)	C(5)–O(10)	1.433(6)	1.425(7)
C(6)–O(11)	1.400(6)	1.390(6)	O(11)–C(12)	1.446(7)	1.429(7)
C(12)–C(13)	1.512(8)	1.542(8)	C(12)–C(17)	1.494(8)	1.529(8)
C(13)–C(14)	1.516(8)	1.494(8)	C(13)–O(18)	1.435(7)	1.406(7)
C(14)–C(15)	1.519(8)	1.514(8)	C(14)–O(19)	1.440(7)	1.438(7)
C(15)–O(16)	1.432(7)	1.434(7)	C(15)–C(20)	1.501(9)	1.497(9)
O(16)–C(17)	1.424(7)	1.400(7)	C(17)–O(22)	1.415(7)	1.429(7)
C(20)–O(21)	1.435(8)	1.421(8)	O(22)–C(23)	1.392(7)	1.374(7)
C(23)–C(24)	1.373(7)	1.354(7)	C(23)–C(28)	1.379(7)	1.399(7)
C(24)–C(25)	1.384(8)	1.397(8)	C(25)–C(26)	1.416(8)	1.418(8)
C(25)–O(29)	1.348(6)	1.356(6)	C(26)–C(27)	1.397(7)	1.431(7)
C(26)–C(31)	1.473(8)	1.472(8)	C(27)–C(28)	1.379(8)	1.389(8)
C(27)–O(30)	1.369(7)	1.351(7)	C(31)–O(32)	1.248(7)	1.244(6)
C(31)–C(33)	1.513(9)	1.503(8)	C(33)–C(34)	1.548(9)	1.528(9)
C(34)–C(35)	1.503(9)	1.503(9)	C(35)–C(36)	1.410(9)	1.384(8)
C(35)–C(40)	1.338(9)	1.393(9)	C(36)–C(37)	1.396(9)	1.394(9)
C(37)–C(38)	1.353(8)	1.393(9)	C(37)–O(41)	1.383(8)	1.364(8)
C(38)–C(39)	1.384(10)	1.363(9)	C(38)–O(42)	1.382(8)	1.409(7)
C(39)–C(40)	1.434(10)	1.403(8)	O(42)–C(43)	1.412(9)	1.439(8)

Table 3. Bond angles (°) of conformers (A) and (B) of compound (1), with e.s.d.s in parentheses

	(A)	(B)		(A)	(B)
C(2)–O(1)–C(6)	114.6(4)	115.0(4)	O(1)–C(2)–C(3)	109.5(4)	109.6(5)
O(1)–C(2)–C(7)	104.9(5)	106.5(5)	C(3)–C(2)–C(7)	111.8(5)	113.1(5)
C(2)–C(3)–C(4)	111.4(4)	109.9(4)	C(2)–C(3)–O(8)	107.5(5)	107.5(5)
C(4)–C(3)–O(8)	111.2(5)	112.2(5)	C(3)–C(4)–C(5)	110.0(5)	111.2(5)
C(3)–C(4)–O(9)	112.6(4)	111.6(5)	C(5)–C(4)–O(9)	111.7(5)	111.6(5)
C(4)–C(5)–C(6)	111.2(5)	109.3(5)	C(4)–C(5)–O(10)	107.0(4)	107.7(4)
C(6)–C(5)–O(10)	109.1(4)	109.2(4)	O(1)–C(6)–C(5)	110.9(4)	110.8(4)
O(1)–C(6)–O(11)	111.8(4)	112.9(4)	C(5)–C(6)–O(11)	106.2(4)	107.4(4)
C(6)–O(11)–C(12)	115.2(4)	115.0(4)	O(11)–C(12)–C(13)	109.8(4)	110.2(5)
O(11)–C(12)–C(17)	109.0(4)	107.9(4)	C(13)–C(12)–C(17)	109.4(4)	107.4(4)
C(12)–C(13)–C(14)	111.5(5)	111.0(5)	C(12)–C(13)–O(18)	109.1(4)	108.7(4)
C(14)–C(13)–O(18)	110.4(4)	111.5(5)	C(13)–C(14)–C(15)	110.7(4)	112.9(5)
C(13)–C(14)–O(19)	109.6(5)	110.8(5)	C(15)–C(14)–O(19)	108.9(4)	108.5(4)
C(14)–C(15)–O(16)	109.4(4)	109.5(4)	C(14)–C(15)–C(20)	115.6(5)	114.5(5)
O(16)–C(15)–C(20)	108.3(5)	107.4(5)	C(15)–O(16)–C(17)	111.8(4)	113.7(4)
C(12)–C(17)–O(16)	109.2(4)	110.0(4)	C(12)–C(17)–O(22)	110.7(4)	107.2(4)
O(16)–C(17)–O(22)	106.0(4)	106.2(5)	C(15)–C(20)–O(21)	110.4(5)	110.3(4)
C(17)–O(22)–C(23)	115.7(4)	117.7(4)	O(22)–C(23)–C(24)	123.6(5)	125.0(5)
O(22)–C(23)–C(28)	115.0(4)	112.1(4)	C(24)–C(23)–C(28)	121.4(5)	123.0(5)
C(23)–C(24)–C(25)	118.7(5)	118.4(5)	C(24)–C(25)–C(26)	122.0(4)	122.3(4)
C(24)–C(25)–O(29)	116.4(5)	115.9(5)	C(26)–C(25)–O(29)	121.5(5)	121.7(5)
C(25)–C(26)–C(27)	116.2(5)	116.5(5)	C(25)–C(26)–C(31)	117.9(4)	119.5(4)
C(27)–C(26)–C(31)	125.9(5)	123.9(5)	C(26)–C(27)–C(28)	122.0(5)	120.9(5)
C(26)–C(27)–O(30)	118.2(5)	119.1(5)	C(28)–C(27)–O(30)	119.8(4)	120.0(4)
C(23)–C(28)–C(27)	119.3(4)	118.8(4)	C(26)–C(31)–O(32)	120.3(5)	119.3(5)
C(26)–C(31)–C(33)	123.5(5)	123.1(4)	O(32)–C(31)–C(33)	116.0(5)	117.5(5)
C(31)–C(33)–C(34)	107.4(5)	110.5(5)	C(33)–C(34)–C(35)	112.1(5)	114.7(5)
C(34)–C(35)–C(36)	118.6(5)	123.0(5)	C(34)–C(35)–C(40)	123.1(6)	119.0(5)
C(36)–C(35)–C(40)	118.3(6)	117.8(5)	C(35)–C(36)–C(37)	119.1(5)	122.2(5)
C(36)–C(37)–C(38)	120.9(6)	118.0(5)	C(36)–C(37)–O(41)	118.0(5)	119.2(5)
C(38)–C(37)–O(41)	120.7(6)	122.7(5)	C(37)–C(38)–C(39)	122.2(6)	121.6(6)
C(37)–C(38)–O(42)	115.8(6)	113.2(5)	C(39)–C(38)–O(42)	122.0(5)	125.1(6)
C(38)–C(39)–C(40)	115.4(6)	119.2(6)	C(35)–C(40)–C(39)	124.0(7)	121.1(5)
C(38)–O(42)–C(43)	119.5(6)	115.6(5)			

hydrogen bonding between O(29) and O(32) to form a 6-membered chelate ring [O(29), C(25), C(26), C(31), O(32), and H(29)]. The slight distortion in the exocyclic angles at C(26), ∠C(27)–C(26)–C(31) [125.9(5)° for (A) and 123.9(5)° for (B)] being slightly larger and ∠C(25)–C(26)–C(31) [117.9(4)° for

(A) and 119.5(4)° for (B)] slightly smaller than trigonal, may be a result of this intramolecular hydrogen-bond formation. The analogous bond lengths and angles in both conformers are compatible with each other and are generally in good agreement with the literature values.[2] The thermal vibrational motions of

the atoms are within the normal accepted range except for the higher values of the solvent oxygen atoms, which are expected.

It has been suggested [3-5] that the 'active' conformation of dihydrochalcone (i.e., the conformation responsible for sweetness) is one in which the aglycone moiety (hesperetin dihydrochalcone) is bent or folded so that the planes of the A- and B-ring are approximately at right angles to each other. The basis for this suggestion is that this conformation resembles the bent (or axial) conformation of the sweetener phyllodulcin (4), a dihydroisocoumarin that bears some structural similarity to hesperetin dihydrochalchone. The axial conformer of phyllodulcin has been assumed to be the active form because it appears to contain the arrangement of proton donor and acceptor groups ('AH-B' groups) specified by Schallenberger[6]
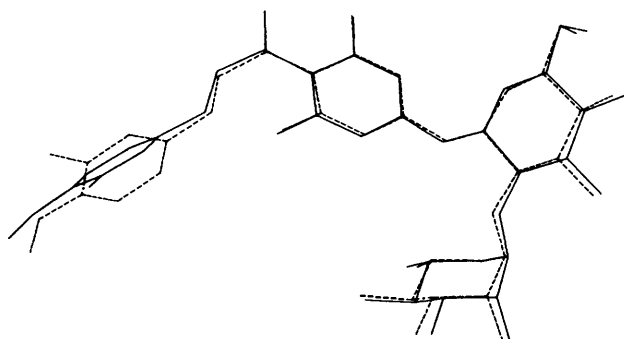
Table 4. Dihedral angles (°) between plane normals of compound (1) with e.s.d.s (mean) 0.5°

Plane	Definition	Planes	Angle in conformer (A)	(B)
A	C(23)—C(28)	A–B	38.6	– 59.8
B	C(35)—C(40)	A–C	– 45.6	40.6
C	C(12)—C(15), O(16), C(17)	A–D	83.1	– 85.4
D	O(1), C(2)—C(6)	B–C	– 77.0	84.9
		B–D	59.6	35.6
		C–D	51.5	54.3

Table 5. Selected torsional angles (°) of compound (1), with e.s.d.s (mean) 0.5°

	(A)	(B)
O(1)–C(6)–O(11)–C(12)	– 76.3	– 73.6
C(5)–C(6)–O(11)–C(12)	162.7	163.9
C(6)–O(11)–C(12)–C(13)	– 101.3	– 100.3
C(6)–O(11)–C(12)–C(17)	138.8	142.8
O(11)–C(12)–C(17)–O(22)	– 64.1	– 66.7
C(12)–C(17)–O(22)–C(23)	157.5	164.7
C(16)–C(17)–O(22)–C(23)	– 84.3	– 77.7
C(17)–C(22)–C(23)–C(24)	17.4	11.3
C(17)–C(22)–C(23)–C(28)	– 163.6	– 167.7
C(25)–C(26)–C(31)–C(33)	– 159.6	– 168.4
C(27)–C(26)–C(31)–C(33)	19.2	12.5
C(26)–C(31)–C(33)–C(34)	76.6	71.4
C(31)–C(33)–C(34)–C(35)	– 176.3	– 179.4
C(33)–C(34)–C(35)–C(36)	– 112.9	47.1
C(33)–C(34)–C(35)–C(40)	65.7	– 136.9

Figure 5. Superimposition of the two crystallographically independent molecules. Broken lines indicate conformer (A)
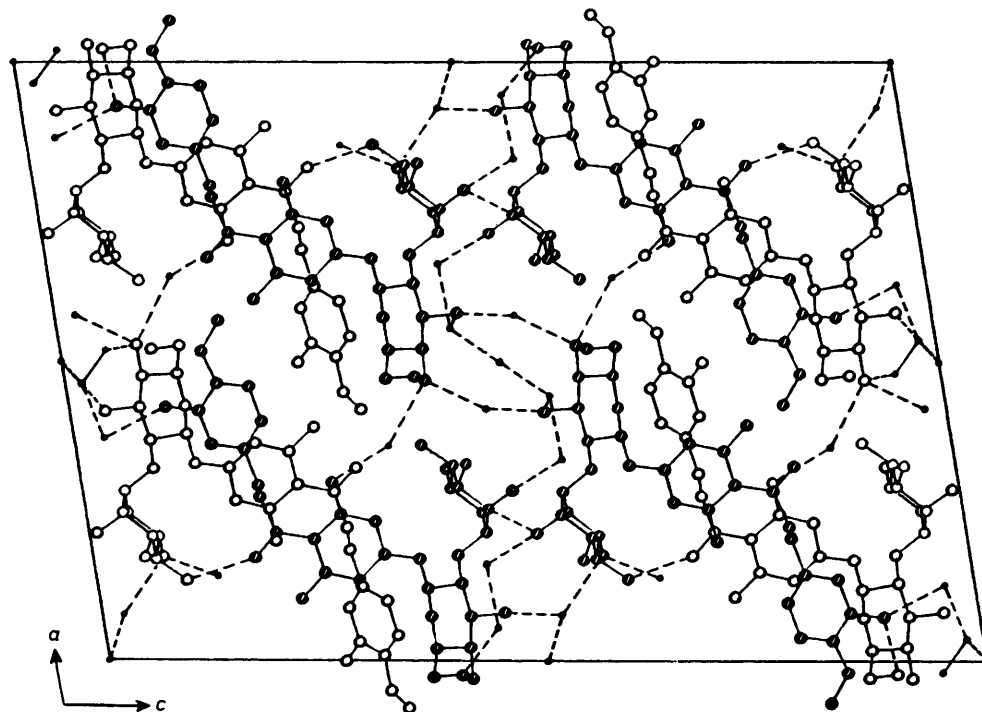

Figure 6. Molecular packing in the unit-cell, viewed along b, showing a single hydrogen-bonded layer. Broken lines indicate intermolecular hydrogen bonds. Shaded circles represent conformer (A), and smallest circles represent water oxygen atoms

and Kier[7-9] to be necessary for sweetness. In fact, the crystallographic data presented here show that the dihydrochalcone aglycone moiety exists in the solid state in a somewhat zig-zag but essentially linear or extended conformation rather than the postulated bent shape. Moreover, there is no evidence that the B-ring of phyllodulcin lies in the axial position; on the contrary, the n.m.r. spectrum [$J_{3,4a}$ 11.7 Hz, $(CD_3)_2CO$; 11 Hz, $CDCl_3$;[10] 10 Hz, CD_3OD[10]] indicates it is equatorial, as it is in

Table 6. Intermolecular distances (≤ 3.0 Å) between oxygen atoms, with e.s.d.s (mean) 0.009 Å

Atom	Distance (Å)	Atoms	Distance (Å)
Ow(1)···O(30A)*	2.671	Ow(6)···O(10A)^c	2.826
Ow(1)···O(9A)^a	2.733	Ow(7)···O(41A)	2.734
Ow(1)···O(19A)^b	2.901	Ow(7)···O(10B)^f	2.794
Ow(2)···O(9A)^a	2.810	Ow(7)···Ow(11)	2.673
Ow(2)···O(18A)^c	2.771	Ow(9)···Ow(11)	2.783
Ow(2)···O(19A)^b	2.756	Ow(10)···O(19B)	2.869
Ow(2)···Ow(8)^d	2.897	Ow(10)···Ow(11)^g	2.513
Ow(3)···O(9B)	2.702	Ow(11)···O(18B)	2.668
Ow(3)···O(19B)^d	2.893	Ow(11)···Ow(11)^g	2.329
Ow(3)···O(30B)^e	2.638	O(1A)···O(10A)^h	2.681
Ow(4)···O(9B)	2.755	O(1B)···O(10B)^f	2.726
Ow(4)···O(18B)^f	2.793	O(8A)···O(21A)^i	2.702
Ow(4)···O(19B)^d	2.765	O(8A)···O(32B)^a	2.784
Ow(4)···Ow(9)^f	2.806	O(8B)···O(21B)^b	2.770
Ow(5)···O(21A)	2.785	O(8B)···O(32A)	2.750
Ow(5)···O(18A)^a	2.864	O(21B)···O(41A)^a	2.790
Ow(5)···Ow(6)	2.685		

* A And B notations refer to atoms of conformers (A) and (B), respectively. Ow refers to water oxygen atom.

$^{a-i}$ Superscript refers to the symmetry transformations, as follows: ^{a} $x,1 + y,z$. ^{b} $x - \frac{1}{2},\frac{1}{2} + y,z$. ^{c} $\frac{3}{2} - x,\frac{1}{2} + y,1 - z$, ^{d} $\frac{1}{2} + x,y - \frac{1}{2},z$. ^{e} $x,y - 1,z$. ^{f} $\frac{3}{2} - x,y - \frac{1}{2},2 - z$. ^{g} $1 - x,y,2 - z$. ^{h} $\frac{3}{2} - x,\frac{1}{2} - y,1 - z$. ^{i} $\frac{1}{2} + x,\frac{1}{2} + y,z$.

(4)
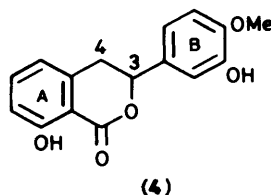
various synthetic dihydroisocoumarins that have been reported ($J_{3,4a}$ 12.0—12.1 Hz).[11] Thus, the crystallographic and n.m.r. data lend little support to the proposal that hesperetin dihydrochalcone and phyllodulcin have a bent conformation and, indeed, suggest that current views about the role of proton-donor and -acceptor groups in conferring sweetness require re-examination.

Experimental

Crystal Data.—For compound (1) $2(C_{28}H_{36}O_{15})\cdot 9H_2O\cdot\frac{1}{2}[2H_2O]$, $M = 1\,405.5$, monoclinic, space group $C2$, $a = 23.294(7)$, $b = 8.644(2)$, $c = 33.334(7)$ Å, $\beta = 99.06(2)°$, $V = 6\,628.2$ Å^3, $Z = 4$, $D_c = 1.41$ g cm^{-3}, $F(000) = 2\,992$, $\mu(\text{Cu-}K_\alpha) = 9.95$ cm^{-1}; crystals obtained from a solution of methanol–water (9:1) by slow evaporation, approximate specimen size $0.15 \times 0.30 \times 0.20$ mm.

Data Collection and Structure Refinement.—Intensity data were collected on a Nicolet R3 diffractometer with graphite-monochromatized Cu-K_α radiation ($\lambda = 1.5418$ Å) by the θ–2θ scan technique with variable scan speed (4—30° min^{-1}) at room temperature. The unit-cell dimensions were determined by least-squares fit to setting angles of 20 independent reflections measured on the diffractometer. Of the 4 767 independent reflections measured within the range $3° \leq 2\theta \leq 110°$m, 4 038 were considered as observed with $|F_o| \geq 4\sigma|F_o|$. During data collection two check reflections, monitored periodically for crystal and instrument stabilities, showed only statistical fluctuations. Intensity data were corrected for background, Lorentz, and polarization effects,[12] but not for absorption and

extinction. The crystal structure was solved by direct-methods program SHELXTL.[13] Atomic co-ordinates, thermal parameters, and scale factors were refined by a 'blocked-cascade' full-matrix least-squares procedure with the SHELXTL program package. The function minimized was $\Sigma\omega(|F_o| - |F_c|)^2$, where $\omega = [\sigma^2|F_o| + 0.001|F_o|^2]^{-1}$. Scattering factors were from 'International Tables for X-Ray Crystallography';[14] those of oxygen were corrected for anomalous dispersion. Positions of all hydrogen atoms were located on subsequent difference Fourier maps and included in the structure-factor calculation. Hydrogen positions relevant to the solvent water molecules were not determined. Least-squares refinement of all atomic parameters, with anisotropic temperature factors for non-hydrogen atoms and isotropic ones with no positional parameter constraint for hydrogen atoms, gave a discrepancy index $R = 0.052$ and R (weighted) $= 0.055$. At convergence, the average parameter shift is 0.12σ, and the final difference Fourier synthesis excursions are within ± 0.4 e Å^{-3}. The absolute configuration was determined by comparison of R-values for the two enantiomeric structures, yielding a ratio of R-values of 1.041. The structure with the lower R-value is considered to be the correct one.[15] Tables of anisotropic thermal parameters of non-hydrogen atoms, and positional parameters and thermal parameters of hydrogen atoms have been deposited as Supplementary Publication No. SUP 56472 (4 pp.).*

* For details of the Supplementary Publications Scheme, see Instructions for Authors (1986), in *J. Chem. Soc., Perkin Trans. 1*, 1986, Issue 1. Structure factors are available on request from the editorial office.

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