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The Crystal and Molecular Structure of Apterin $C_{20}H_{24}O_{10}.H_2O$ (Vaginidiol Monoglucoside), 8-[2-(Glucosyloxy)isopropyl]-9-hydroxy-8,9-dihydroangelicin

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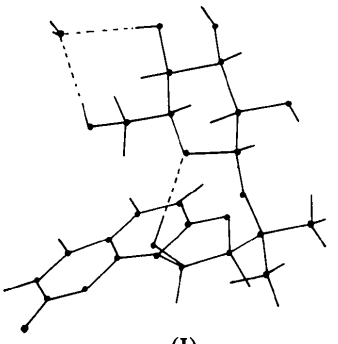
The structure of the monohydrate of the title compound has been determined from diffractometer data. The crystals are orthorhombic, space group $P2_12_12_1$, $Z = 4$, with $a = 8{\cdot}0438$ (13), $b = 10{\cdot}0211$ (19), $c = 25{\cdot}513$ (6) Å. The structure was solved with *MULTAN* and refined by the full-matrix least-squares method to a final R value of 0·054 for 1702 observed reflections. The bonding of the sugar molecule to the aglycone is similar to the arrangement found in cellobiose. The anomeric O atom of the sugar molecule forms the glycosidic bond, and the hetero-atom of the pyranose ring is acceptor of an intramolecular hydrogen bond from the hydroxy group of the dihydrofuran ring of the aglycone. The coumarin nucleus is almost planar, the dihydrofuran ring has a half-chair conformation, but three of the ring atoms are coplanar with the coumarin moiety, and this leads to pronounced shortening of C(13)–O(7), 1·355 (5) Å. The dimensions of the coumarin moiety and the β-glucose molecule are close to normal values. All the hydroxy groups of the sugar and the water molecule are engaged in hydrogen bonds with distances from 2·718 (5) to 2·933 (5) Å.

Introduction

The coumarin nucleus is the basis of various compounds possessing important pharmacological and physiological activities (Schofield, 1922). Plant extracts containing coumarins as main constituents have been applied against gastrointestinal diseases, typhus and paralysis (Butenandt & Marten, 1932), for the therapy of leucoderma (Jois, Manjunath & Rao, 1933; Stahman, Hubner & Link, 1941), as anticoagulants (Danek, 1964; Garden, Hayes & Thomson, 1956), and recently against psoriasis. The coumarin nucleus can also exert toxic effects. Photosensitization contact dermatitis is often caused by plants containing compounds related to furanocoumarins. After exposure to the appropriate furanocoumarin in the plant, followed by exposure to ultraviolet radiation, the characteristic sunburn-like rash develops. After healing, a white atrophic area remains on the skin for months or even years. For example, contact with *Heracleum mantegazzianum* leaves produces an erythematous blush within 24 h and a blister by 48 h.

Most interest has, however, been focused on the less polar furanocoumarins. Biochemical investigation of the formation of the furanocoumarins has likewise mainly been concerned with coumarins like xanthotoxin (methoxypsoralene) and pimpinellin, *i.e.* the less polar furanocoumarins.

In a search for more polar coumarins we isolated a compound from *Heracleum mantegazzianum* Somm. and Lev. (Fischer, Jasperse, Karlsen & Bærheim Svendsen, 1974). This compound was tentatively identified as 8-[2-(glucosyloxy)isopropyl]-9-hydroxy-8,9-dihydroangelicin (I). The same glucoside was reported to be present in *Zizia aptera* (Steck & Wetter, 1974) and given the same structure as reported by us (Fischer *et al.*, 1974). However, because of intramolecular hydrogen bonding, it is very difficult to elucidate the structure of this glucoside by the usual spectroscopic methods, and an X-ray diffraction study of the compound was therefore undertaken.



(I)

Experimental

Colourless, prismatic crystals of apterin were obtained by slow evaporation from a methanol solution. Preliminary diffraction data showed an orthorhombic primitive lattice with systematic absences of $h00$, $0k0$, and $00l$ when the non-zero index is odd. The space group is $P2_12_12_1$ (No. 19) with four general positions. The lattice constants were obtained by a least-squares fit of 26 measured 2θ values and e.s.d.'s given are based on this calculation. The density was measured by the flotation method. The crystal data are given in Table 1.

The crystal, 0·25 × 0·25 × 0·10 mm, used for data collection was mounted with the c axis approximately along the φ axis of a Syntex $P\bar{1}$ diffractometer. Intensity data were collected using the $\theta/2\theta$ scan technique with variable scan speed and graphite-monochromatized Mo $K\alpha$ radiation. Three selected reflections (319, 307, 036) were monitored periodically (every 50 reflections) to check for variations and hence ensure a common scale. 2185 reflections were measured. Reflections with $I < 2\sigma$ were considered unobserved, giving 1702 observed reflections. The data were corrected for Lorentz and polarization effects but not for absorption and extinction as this was considered unnecessary (μ = 1·40 cm^{-1}). The scattering factors for C and O were taken from Doyle & Turner (1968) whereas the values given by Stewart, Davidson & Simpson (1965) were used for H. All calculations were performed using computer programs written or modified for use on a CYBER-74 computer and are described elsewhere (Groth, 1973).

Table 1. *Crystal data*

$C_{20}H_{26}O_{11}$, 8-[2-(glucosyloxy)isopropyl]-9-hydroxy-8,9-dihydroangelicin, orthorhombic, $P2_12_12_1$, a = 8·0438 (13), b = 10·0211 (19), c = 25·5133 (56) Å, V = 2056·6 Å^3, Z = 4, D_x = 1·43 g cm^{-3}, D_c = 1·429 g cm^{-3}, $F(000)$ = 936, M_r = 442·4, μ = 1·40 cm^{-1} for Mo $K\alpha$ (λ = 0·71069 Å).

Structure determination and refinement

The structure was solved by direct methods using a multisolution tangent formula approach, *MULTAN* (Germain, Main & Woolfson, 1971). One set of phases with a figure of merit of 1·145 was immediately obvious (FOM for next best set is 0·953) and was used as input for the calculation of an E map. In this map 31 atomic positions could be located, 30 of which belonged to the same molecule. The last atom was found to be a water molecule of crystallization. There

Table 2. *Final positional parameters* ($\times 10^4$) *for the heavy atoms and corresponding estimated standard deviations*

	x	y	z
O(1)	7044 (5)	2999 (3)	4590 (1)
O(2)	8445 (5)	5402 (3)	4995 (2)
O(3)	6019 (6)	7520 (4)	4983 (2)
O(4)	4511 (6)	7784 (4)	3968 (1)
O(5)	5262 (5)	4192 (3)	4087 (3)
O(6)	1894 (6)	4993 (5)	3792 (2)
O(7)	7194 (5)	2446 (4)	3401 (1)
O(8)	4106 (5)	1548 (4)	4232 (1)
O(9)	2033 (5)	418 (4)	3211 (1)
O(10)	−390 (5)	−585 (4)	3183 (2)
O(11)	8990 (7)	2746 (5)	1045 (2)
C(1)	6864 (7)	4228 (5)	4332 (2)
C(2)	6822 (7)	5280 (5)	4769 (2)
C(3)	6288 (7)	6636 (5)	4553 (2)
C(4)	4739 (7)	6518 (5)	4227 (2)
C(5)	4892 (8)	5412 (5)	3815 (2)
C(6)	3327 (9)	5208 (6)	3495 (2)
C(7)	7866 (7)	1892 (5)	4324 (2)
C(8)	7720 (8)	774 (5)	4721 (2)
C(9)	9676 (8)	2241 (6)	4221 (2)
C(10)	7003 (8)	1437 (5)	3816 (2)
C(11)	5154 (7)	1024 (5)	3824 (2)
C(12)	4645 (8)	1470 (5)	3288 (2)
C(13)	5845 (9)	2310 (6)	3088 (2)
C(14)	5648 (10)	2949 (6)	2600 (3)
C(15)	4212 (10)	2711 (7)	2324 (2)
C(16)	2963 (10)	1874 (6)	2512 (2)
C(17)	1470 (10)	1544 (7)	2238 (2)
C(18)	355 (10)	721 (7)	2442 (3)
C(19)	561 (9)	147 (7)	2949 (3)
C(20)	3222 (8)	1264 (6)	3003 (2)

were no further peaks of similar electron density in the map.

The coordinates determined from this map were refined by the isotropic full-matrix least-squares method, minimizing the function $\sum w(F_o - F_c)^2$ where w is the inverse of the variance of F (*i.e.* $1/\sigma^2$). The isotropic refinement converged to $R = 0{\cdot}10$. Further refinement, introducing anisotropic thermal parameters for the atoms, gave $R = 0{\cdot}084$. A difference electron density map based on these results was then calculated and the positions of the 26 H atoms were obtained. Inclusion of the H atoms lowered the R value to 0·056. Isotropic thermal parameters for the hydrogen atoms were refined, and ranged from $B = 1{\cdot}4$–$9{\cdot}0$ (e.s.d.'s 1·0–5·7) Å^2.

Final positional parameters for the heavy atoms are given in Table 2 and, with isotropic thermal parameters, for the H atoms in Table 3.* The bond distances and angles determined are given in Fig. 1. Standard deviations in the bond lengths and angles are 0·005–0·008 Å and 0·4–0·7°, not including H atoms.

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33322 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 3. *Positional parameters* (× 10^3) *for the hydrogen atoms, and isotropic thermal parameters with estimated standard deviations in parentheses*

	x	y	z	B (Å^2)
H(18)	−72	44	221	6·3 (1·8)
H(17)	127	201	187	3·7 (1·3)
H(15)	405	323	195	6·4 (1·7)
H(14)	658	360	245	6·4 (1·8)
H(11)	501	0	391	1·4 (1·0)
H(10)	769	53	376	2·5 (1·1)
H(5)	584	571	356	5·1 (1·6)
H(4)	372	628	447	3·4 (1·3)
H(3)	726	702	431	1·9 (1·1)
H(2)	591	498	505	1·7 (1·1)
H(1)	782	444	406	4·0 (1·4)
H(161)	313	603	326	4·4 (1·4)
H(262)	350	439	326	3·9 (1·4)
H(81)	649	53	479	4·6 (1·6)
H(82)	826	103	508	4·6 (2·2)
H(83)	833	−9	459	4·6 (2·2)
H(91)	976	302	394	2·7 (1·2)
H(92)	1034	144	407	2·7 (1·8)
H(93)	1028	257	456	2·7 (1·8)
H(O4)	332	777	396	6·9 (2·1)
H(O6)	159	590	385	9·0 (5·7)
H(O8)	450	245	418	5·2 (2·0)
H(O11)	949	331	131	8·9 (3·7)
H(O21)	901	266	67	8·0 (3·5)
H(O2)	865	472	527	6·8 (2·7)
H(O3)	510	820	500	7·2 (2·7)

Discussion

The molecular structure

The glycoside is formed from one molecule of β-glucose and one molecule of vaginidiol. The bonding of the sugar molecule to the aglycone is similar to the arrangements found in cellobiose (Chu & Jeffrey, 1968). The anomeric O atom of the sugar molecule, O(1), forms the glycosidic bond. The pyranose hetero-atom O(5) is the acceptor of an intramolecular hydrogen bond of 2·834 Å from the hydroxy group, O(8)—H(8), of the dihydrofuran ring of the fused-ring system. A fairly short van der Waals contact of 2·923 Å between the hetero-atom of the sugar and O(7) of the furan ring is also present. This bonding situation leads to a fairly rigid molecular entity. Fig. 1 shows the molecule and the identity of the atoms.

The dimensions of the coumarin nucleus in this molecule are in agreement with those found in a number of other systems (Valente, Trager & Jensen, 1975; Shimizu, Kashino & Haisa, 1975; Shen & Bryan, 1975; Boles & Taylor, 1975; Boles, Taylor & Girven, 1975; Fayos, 1976). The C(17)—C(18) bond is, however, relatively short, 1·326 Å. Some of this shortening may be caused by thermal motion, which is found to be relatively pronounced for these two atoms. Part of the shortening could also be a result of resonance in the O(10)—C(19)—C(18)—C(17) system of the pyrone ring. The phenyl ring is planar. The ring plane also contains the lactone group O(10)—C(19)—O(9)—, and O(7) of the furan ring. The other half of the lactone ring, C(16)—C(17)—C(18)—C(19) and O(10), is also planar; the angle between the two planes is 3·4°. The equations of the planes, and the deviations of atoms from these planes are given in Table 4.

The angles in the coumarin nucleus are consistent with angles determined for the isolated coumarin molecule (Miasnikova, Davydova & Simonov, 1973; Gavuzzo, Mazza & Giglio, 1974). The dihydrofuran ring is definitely not planar. The conformation can best be described as a half chair with C(10) 0·231 Å above the phenyl-ring plane and C(11) 0·092 Å below it.

Table 4. *Equations of the best planes through* C(12), C(13), C(14), C(15), C(16) *and* C(20), *plane* I, *and through* O(10), C(19), C(18), C(17), *plane* II

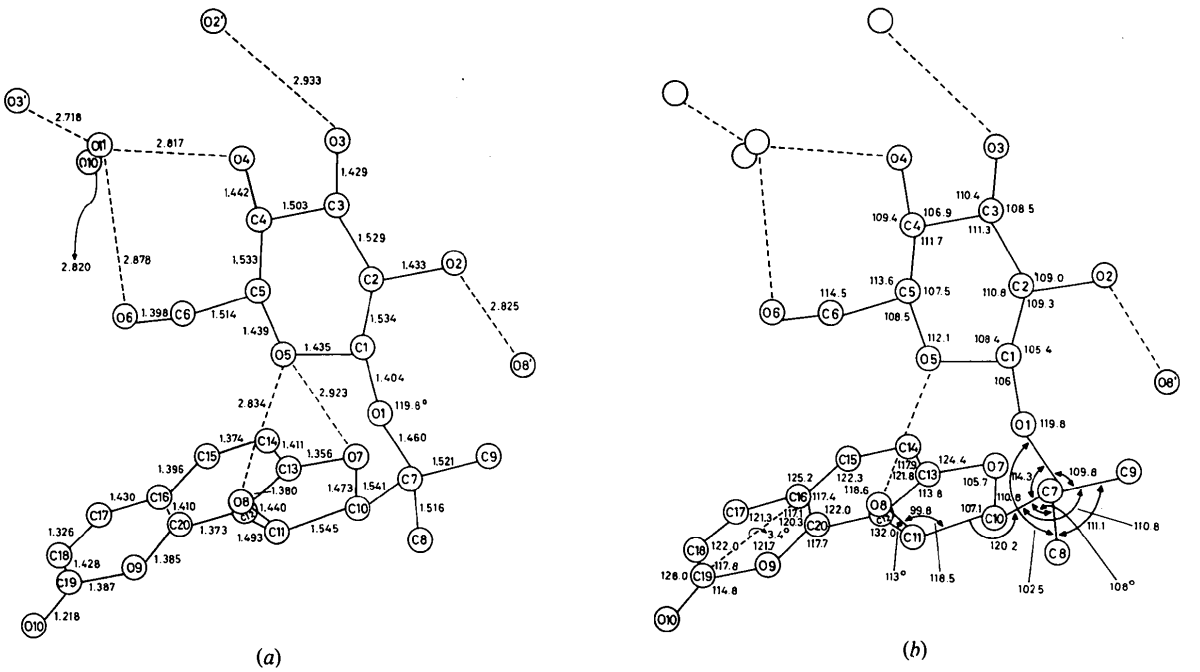
I: $(0{\cdot}0540a - 0{\cdot}0776b - 0{\cdot}0178c)R - 3{\cdot}338 = 0$
II: $(0{\cdot}0580a - 0{\cdot}0784b - 0{\cdot}0159c)R - 2{\cdot}970 = 0$

Deviations (Å × 10^3) of atoms from plane I

C(12)	2	C(15)	2	O(7)	1	O(10)	−31
C(13)	−4	C(16)	0	O(9)	0	C(17)	54
C(14)	−2	C(20)	−2	C(19)	1	C(18)	70

Deviations (Å × 10^3) of atoms from plane II

O(10)	−8	C(17)	−10	O(9)	80	C(12)	153
C(19)	13	C(16)	6	C(14)	76	C(13)	149
C(18)	9	C(15)	10	C(20)	76		



(*a*) (*b*)

Fig. 1. (*a*) Bond distances (Å) and (*b*) bond angles (°). The estimated standard deviations are 0·005–0·008 Å and 0·4–0·7°, not including hydrogen atoms.

The reported structure is in accordance with the previously proposed C(10) (*R*) (Cahn–Ingold–Prelog convention) of athamantin and suggests a common biogenetic pathway. The NMR coupling between the vicinal protons at C(10) and C(11) was 7 Hz and indicated a *cis* configuration. This has been a point of discussion for some time. The *cis* configuration was established by this structure elucidation.

The C(13)–O(7) bond is short, 1·356 Å, and the C(10)–O(7) bond long, 1·473 Å. The shortening can be explained as a result of delocalization because of the coplanarity with the phenyl ring. The different C–O bond lengths in the five-membered ring show a certain resemblance to those observed in γ-lactones, 1·340 and 1·475 Å (β-D-glucurono-γ-lactone; Kim, Jeffrey, Rosenstein & Corfield, 1967), 1·358 and 1·464 Å (D-galactono-γ-lactone; Jeffrey, Rosenstein & Vlasse, 1967), 1·346 and 1·472 Å (D-gulono-γ-lactone; Berman, Rosenstein & Southwick, 1971). The mean C–O distance is 1·41 Å in each case and is of normal value. The angles in the furan ring show some deviation from regularity and range from 99·9–113·8°, probably as a result of strain in the fused-ring system.

It is interesting to compare the dimensions of the ring system in this molecule with corresponding dimensions in the xanthotoxin (Stemple & Watson, 1972) and byak-angelicol (Fayos, 1976) molecules consisting of a coumarin nucleus fused to a furan ring at C(13) and C(14) positions, *i.e.* the furan ring is twisted 180° about C(13)–O(7) relative to the arrangement in this compound. In these cases the C–O bonds in the furan rings are found to be of equal lengths, 1·380 Å. In the rings, however, a C–C double bond joins the two C atoms which do not belong to the phenyl ring. The two C–C bonds in the present dihydrofuran ring are 1·493 and 1·545 Å and are of normal length for C(sp^3)–C(sp^2) and C(sp^3)–C(sp^3) bonds respectively. The C–OH bond length is 1·440 Å, also as expected. The C–C distances of the isopropyl group are 1·521 and 1·516 Å and are somewhat short, probably because of thermal effects. All six H atoms of the methyl groups have been located in a difference Fourier map. The H atoms of both methyl groups are staggered with respect to the bonds protruding from C(7), giving interhydrogen distances of about 2 Å.

The glycosidic linkage has bond lengths of 1·460 and 1·404 Å with a C–O–C angle of 119·8°. These values are as expected and compare well with 1·446, 1·397 Å and 116·1° determined for cellobiose. The dihedral angle C(1)–O(1)–C(7)–C(10) is −61° and C(1) is *gauche* to C(10). C(1) and C(8) are *trans* (177·4°) and C(1) and C(9) are *gauche* (64°). Furthermore, O(1) and O(7), and O(1) and C(11) are approximately *gauche* (+70 and −55° respectively).

The dimensions of the β-glucose molecule are as expected for the normal pyranose sugar conformation

(1*e*2*e*3*e*4*e*). The mean bond length is 1·523 Å and the mean C—O bond length is 1·435 Å. The C—O(1) glycosidic bond is shortened by 0·031 Å (5σ) in agreement with observations made on other β-pyranosides. The C(6)—O(6) bond is found to be fairly short, 1·398 Å, and again this is believed to be caused by thermal vibrations which are fairly large for O(6). The thermal vibrations for the terminal atoms in the glycoside are significantly larger than for the inner, more firmly bound atoms.

Hydrogen bonding

All the hydroxyl groups of the sugar and water molecules are engaged in hydrogen bonds with distances from 2·718 to 2·933 Å. O(2) and O(3) of the pyranose molecule act both as donors and acceptors, whereas O(4) and O(6) are donors only. The last two O atoms are both hydrogen bonded to the same water molecule. The water molecule is tetrahedrally surrounded, being hydrogen-bond donor to the carbonyl O of the coumarin moiety of one molecule and to O(3) of the sugar moiety of another glycoside molecule. The main role of the water molecules in the crystal structure of the glycoside is to connect the different molecules in the three-dimensional network. As pointed out earlier, O(5) is an acceptor of an intramolecular hydrogen bond from O(8), and O(8) is simultaneously an acceptor of an intermolecular hydrogen bond from O(2)′.

This intramolecular hydrogen bonding may explain the inefficiency of β-glucosidase, emulsin, in splitting off the carbohydrate moiety. Even after incubation with emulsin for two months, only traces of the aglycone could be detected. Internal hydrogen bonding between glucose and the coumarin part of the molecule prevents the enzymatic effect.

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