Data collection

Syntex $P2_1$ diffractometer
ω scans
Absorption correction: not applied
(T_{min} = 0.97, T_{max} = 1.00)
2727 measured reflections
2433 independent reflections
1563 observed reflections [$|F| > 4\sigma(F)$]
R_{int} = 0.032
θ_{max} = 26.5°
$h = 0 \rightarrow 12$
$k = 0 \rightarrow 13$
$l = -16 \rightarrow 16$
3 standard reflections monitored every 100 reflections
intensity variation: 2%

Refinement

Refinement on F
R = 0.062
wR = 0.053
S = 2.64
1563 reflections
201 parameters
All H-atom parameters refined
$w = 1/\sigma^2(F)$
$(\Delta/\sigma)_{max}$ = 0.098
$\Delta\rho_{max}$ = 0.31 e Å^{-3}
$\Delta\rho_{min}$ = 0.25 e Å^{-3}
Extinction correction: none
Atomic scattering factors from *Xtal*2.6 (Hall & Stewart, 1989)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
Si1	0.1173 (1)	0.1432 (1)	−0.03306 (8)	0.0303 (5)
C1	0.2176 (5)	0.1231 (7)	−0.1314 (4)	0.055 (3)
C2	0.1444 (6)	0.3170 (5)	0.0302 (5)	0.057 (3)
B1	0.2904 (5)	−0.0456 (5)	0.2955 (4)	0.041 (3)
B2	0.3156 (4)	0.0563 (5)	0.1914 (4)	0.038 (2)
B3	0.1392 (5)	0.0168 (5)	0.1931 (3)	0.032 (2)
B4	0.1432 (5)	−0.1563 (5)	0.2395 (3)	0.037 (2)
B5	0.3185 (5)	−0.2216 (5)	0.2666 (4)	0.042 (2)
B6	0.4242 (5)	−0.0903 (5)	0.2346 (4)	0.041 (3)
C7	0.1847 (3)	0.0064 (4)	0.0760 (2)	0.027 (2)
C8	0.0829 (3)	−0.1196 (3)	0.1056 (3)	0.027 (2)
B9	0.1831 (5)	−0.2674 (5)	0.1464 (4)	0.040 (2)
B10	0.3573 (5)	−0.2278 (5)	0.1414 (3)	0.040 (2)
B11	0.3556 (5)	−0.0553 (5)	0.0967 (4)	0.038 (2)
B12	0.2046 (4)	−0.1646 (5)	0.0399 (3)	0.037 (2)

Table 2. *Selected geometric parameters* (Å, °)

Si1—C1	1.853 (6)	C7—B11	1.718 (6)
Si1—C2	1.847 (5)	C7—B12	1.738 (6)
Si1—C7	1.907 (3)	C8—B3	1.718 (5)
Si1—C8^i	1.914 (3)	C8—B4	1.709 (5)
C7—B2	1.726 (5)	C8—B9	1.717 (6)
C7—B3	1.725 (6)	C8—B12	1.725 (6)
C7—C8	1.688 (5)		
Si1—C7—B2	117.4 (2)	Si1^i—C8—B3	119.6 (2)
Si1—C7—B3	120.2 (2)	Si1^i—C8—B4	117.8 (3)
Si1—C7—C8	125.0 (2)	Si1^i—C8—C7	124.0 (2)
Si1—C7—B11	117.0 (3)	Si1^i—C8—B9	117.3 (2)
Si1—C7—B12	119.4 (2)	Si1^i—C8—B12	118.8 (2)
B3—C7—C8	60.4 (2)	B3—C8—C7	60.9 (2)
C8—C7—B12	60.4 (2)	C7—C8—B12	61.2 (2)

Symmetry code: (i) $-x, -y, -z$.

Data were neither corrected for the intensity variation in the standard reflection nor for the minor variation caused by absorption. Cell refinement, data collection and reduction: Syntex $P2_1$. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1986). Program(s) used to refine structure: *Xtal*2.6 (Hall & Stewart, 1989). Molecular graphics: *Xtal*, *ORTEP* (Johnson, 1976). Software used to prepare material for publication: *Xtal BONDLA* and *ATABLE*.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71631 (16 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: AB1091]

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Structural Studies on the Antimuscarinic Agents Spiro-DAMP and Hydroxy-DAMP, and Comparison with Related Compounds

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Abstract

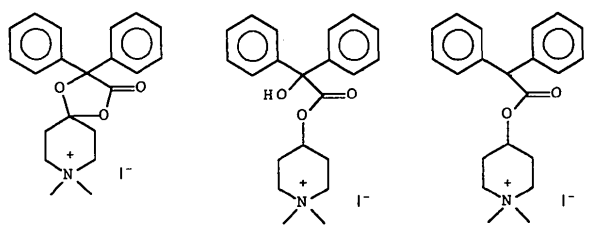
Compound (I), 8,8-dimethyl-3,3-diphenyl-1,4-dioxa-8-azoniaspiro[4.5]decan-2-one iodide, spiro-DAMP, has the ester moiety enclosed in a rigid dioxolane ring, giving rise to a spiro piperidine derivative. Compound (II), 4-(2-hydroxy-2,2-diphenylacetoxy)-1,1-dimethylpiperidinium iodide, hydroxy-DAMP, shows the ester substituent in an equatorial position

with respect to the piperidine ring, compared to an axial position in (I). Consequently, the topology of both polar and hydrophobic groups in the two derivatives is quite different. Comparisons are made with related antimuscarinic compounds, such as 4-DAMP, azaprophen and (−)-atropine.

Comment

Part of the current interest in the development of compounds acting as muscarinic antagonists stems from their possible use as probes for the chemical and spatial requirements of the receptor site. Three muscarinic receptor subtypes are presently pharmacologically defined (M_1, M_2, M_3) and, despite extensive efforts, the relative spatial locations of the commonly recognized ligand-binding groups (quaternary ammonium head, intermediate polar group, lipophilic moiety) are still uncertain.

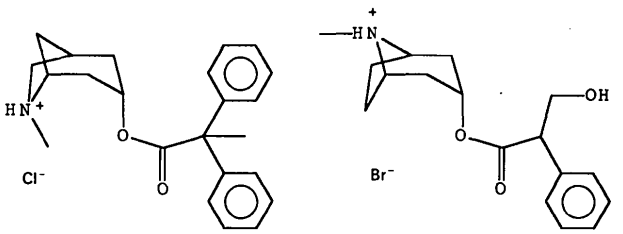
Spiro-DAMP (I) is a rather rigid molecule that shows high antagonistic activity at muscarinic receptors (Tumiatti *et al.*, 1992) and, considering both its conformational rigidity and receptor affinity, one might think that the locations of the functional groups in this molecule are almost ideal for binding to the muscarinic receptor site.



(I) (II) (III)

Abramson, Barlow, Franks & Pearson (1974) have synthesized and tested hydroxy-DAMP (II), a flexible molecule structurally similar to 4-DAMP (III), a well known M_3-selective muscarinic antagonist (Barlow, Berry, Glenton, Nikolaou & Soh, 1976). There are no rotation restrictions in the intermediate chain of hydroxy-DAMP, except for those occurring as a result of the greater volume of the OH group with respect to H.

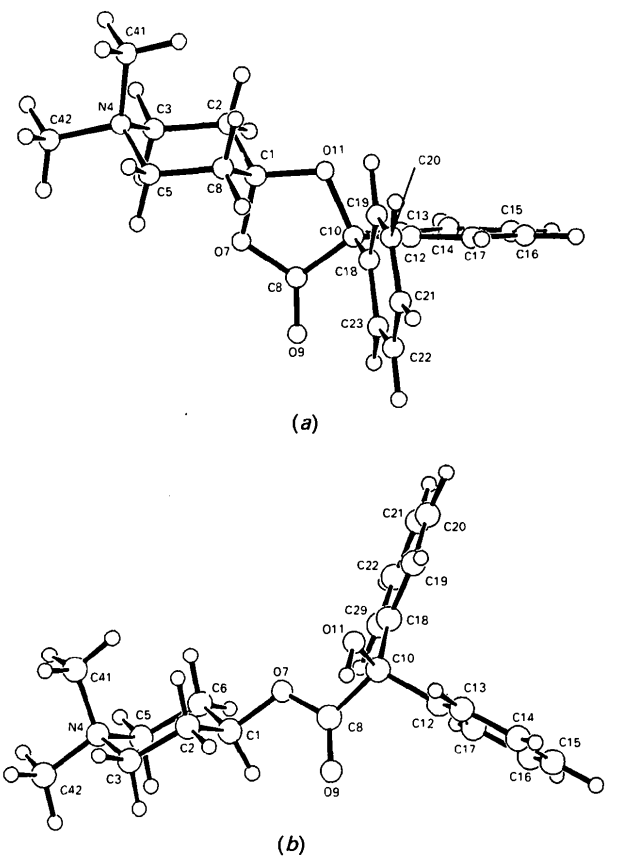
To our knowledge, compounds in which the key functional groups of the muscarinic antagonists are linked together by a frame of chemical bonds, as in spiro-DAMP, have not been reported previously. As a first step towards the understanding of the three-dimensional structure–activity relationships of these compounds, we report here the crystal structures of both spiro-DAMP and hydroxy-DAMP, and compare them with the known crystal structure of 4-DAMP [(III); Barlow, Howard, Johnson & Sanders, 1987], azaprophen [(IV); Karle, Karle & Chiang, 1990] and (−)-atropine [(V); Kussäther & Haase, 1972], *i.e.* compounds where the quaternary function is enclosed in a cyclic moiety.



(IV) (V)

Fig. 1 shows a plot of each compound, together with the atom labelling. The crystal packing of both compounds is determined by a network of hydrogen bonds. In both molecules the piperidine ring retains its chair conformation, as observed in the related compound 4-DAMP (III).

In the spiro derivative (I), the five-membered dioxolane ring displays a slight puckering with the



(*a*) (*b*)

Fig. 1. Molecular structures of (*a*) spiro-DAMP (I), and (*b*) hydroxy-DAMP (II), together with their crystallographic numbering systems. H atoms bear the same numbering as the corresponding C or O atoms to which they are bound.

atom O(11) 0.29 (1) Å above the least-squares plane passing through the remaining four atoms, giving rise to an envelope conformation. With respect to the piperidine, this last ring is approximately perpendicular [the acute angle between the two best planes is 85°] and the acyl substituent O(7) of the spiro junction is in an axial position. The two phenyl rings lie almost perpendicular to one another [86 (1)°] and the C(12)–C(17) ring is approximately coplanar to the piperidine [the angle between these two moieties is 22 (1)°]. Interestingly, in the rigid compound (I), only the carbonyl O atom O(9) is involved in hydrogen bonding, while the other two O atoms, O(7) and O(11), are clearly unfavoured for such contacts. O(9) actually takes part as an acceptor in the two hydrogen-bond interactions, one intramolecular with C(23)—H(23) [$D\cdots A$ 3.09 (1) Å, D—H$\cdots A$ 116°] and one intermolecular (symmetry $\frac{1}{2}-x$, $y-\frac{1}{2}$, z) with C(6)—H(62) [$D\cdots A$ 3.11 (1) Å, D—H$\cdots A$ 128°].

For compound (II), its overall geometry does not differ very much from that of the strictly related analogue 4-DAMP (III). As in (III), the ester substituent is in an equatorial position with respect to the piperidine ring. The insertion of a hydroxy group causes the addition of an electron-donor group, O(11). This donor group is involved in one interionic interaction, with an O(11)···I distance of 3.43 (1) Å and an O—H···I angle of 146°. O(7) is involved in one intramolecular contact, with C(23)···O(7) 2.87 (1) Å and a D—H$\cdots A$ angle of 101°. Alternatively, the carbonyl O atom, O(9), takes part in two intramolecular interactions, with C(2)—H(21) [C···O distance of 3.45 (1) Å, angle 148°], and C(41)—H(411) [C···O 3.52 (1) Å; angle 173°]. Finally, an interionic contact must be mentioned between C(20) and the I atom which is 3.91 (1) Å in length.

Considering the structures of Fig. 1, it appears that, as a result of the different spatial orientation of the ester groups, the three main binding functions (pharmacophoric groups, *i.e.* the quaternary ammonium N atom, the intermediate ester group and the bulky hydrophobic moiety) do not occupy corresponding spatial regions in the two molecules. As a consequence, the identification of a common mode of binding to the receptor is not straightforward. The crystal structures of a number of highly active antimuscarinic agents are known, but none are as conformationally constrained as spiro-DAMP. In Table 4 we report some key interatomic distances of spiro-DAMP and hydroxy-DAMP, together with the corresponding distances of some muscarinic antagonists in which the quaternary N atom is part of a ring as in (I) and (II): 4-DAMP (Barlow, Howard, Johnson & Sanders, 1987), azaprophen (Karle, Karle & Chiang, 1990) and (−)-atropine (Kussäther & Haase, 1972).

$N\cdots C_{acetyl}$ is the distance between the cationic N atom and the di(tri)substituted acetyl C atom corresponding to C(10) of (I) and (II); it may give a broad idea of the localization of the lipophilic moiety, also referring to the acetyl C atom of the natural ligand, acetylcholine. $N\cdots O_{ester}$ and $N\cdots O_{carbonyl}$ are the distances from the cationic N atom to the ester O atom [O(7) in (I) and (II)] and to the carbonyl O atom [O(9) in (I) and (II)], respectively. These distances are representative of the spatial relationships between the polar groups of the molecules. $N\cdots C_{acetyl}$ distances in Table 4 are not homogeneous and, as expected, the constrained spiro-DAMP displays a shorter distance than that of the extended hydroxy-DAMP. 4-DAMP is quite similar to the hydroxy analogue, while for azaprophen the corresponding N···C distance resembles that of spiro-DAMP; atropine is between the two. Barlow, Holdup, Harris, Veale & Williams (1990) have recently proposed a model for a muscarinic receptor based on the X-ray structure of 4-DAMP, and have indicated that the N···C distance of 6.5 Å is the maximum acceptable for a positive interaction with the hydrophobic site. Data in Table 4 show that much shorter $N\cdots C_{acetyl}$ distances (5.2–5.3 Å) may lead to productive binding. This might imply the existence of two distinct hydrophobic pockets, or, more likely, the possibility that extended flexible molecules assume a different conformation on binding to the receptor.

The set of $N\cdots O_{carbonyl}$ distances in Table 4 is much more homogeneous and based on it one could suggest that perhaps two of the pharmacophoric points have a common distance in all five molecules. However, it seems unrealistic that the correspondence of two atoms alone can account for the very high receptor affinity shared by all these antagonists. The distances from N to the second ester O atom ($N\cdots O_{ester}$) vary on a wider range and are not correlated with the aforementioned $N\cdots O_{carbonyl}$ distances. It is not definitely clear which role each of the two ester O atoms plays in the binding of antimuscarinics, but recent papers (Carrol *et al.*, 1992; Karle, Karle & Chiang, 1990) point to the involvement of the carbonyl O atom in a hydrogen bond.

In the last column of Table 4, distances are reported between the cationic N atom and the O(11) atoms of spiro-DAMP and hydroxy-DAMP, and the hydroxyl group of atropine. It is likely that these functions participate with additional interactions in the process of binding, having the capability of forming hydrogen bonds either as acceptors (all) or as donors (hydroxyl groups).

In conclusion, it seems impossible to hypothesize on the binding of the five ligands in the present conformation to a common site modelled on three pharmacophoric points: cationic N, carbonyl O and the hydrophobic moiety. The five antimuscarinic

agents cannot be superimposed to obtain a common pharmacophoric model, unless one admits that the conformation of the flexible compounds bound to the receptor differs somewhat from that in the crystal. The similarity of conformation in the solid state and on the receptor may be approached by molecules where the conformational freedom is restrained, as in spiro-DAMP. This compound (given the high affinity) may display a mutual localization of key groups close to the ideal one and can be used as a template on which to 'probe' conformations of other molecules. Azaprophen, as far as the three pharmacophoric points and the set of distances of Table 4 are considered, has a conformation in the solid state that can be close to the active one. Following this reasoning, 4-DAMP, hydroxy-DAMP and atropine cannot bind while retaining their crystal conformation: rotation around the ester bonds and/or 'flipping' of the piperidine ring seem necessary in order to achieve a conformation superimposable to that of spiro-DAMP. Preliminary molecular-modelling studies reveal that for all these compounds energetically accessible conformations exist which are compatible with a common pharmacophore. Work is in progress towards the definition and testing of a comprehensive muscarinic-antagonist receptor model.

Experimental

Compound (I)

Crystal data

$C_{21}H_{24}NO_3^+.I^-$
M_r = 465.3
Orthorhombic
Pbca
a = 18.145 (1) Å
b = 10.364 (4) Å
c = 21.596 (4) Å
V = 4061 (1) Å^3
Z = 8
D_x = 1.52 Mg m^{-3}
Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 25 reflections
θ = 7-11°
μ = 1.58 mm^{-1}
T = 293 K
Prismatic
0.35 × 0.28 × 0.15 mm
Transparent yellow
Crystal source: grown from methanol

Data collection

Enraf-Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
4016 measured reflections
2696 independent reflections
1359 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.01
θ_{max} = 25°
h = 0 → 12
k = 0 → 21
l = 0 → 25
3 standard reflections
frequency: 160 min
intensity variation: none

Refinement

Refinement on F
R = 0.039
wR = 0.042
S = 1.04
1359 reflections
178 parameters
H atoms refined with riding models
w = 0.8542/[$\sigma^2(F_o)$ + 0.00192(F_o^2)]
$(\Delta/\sigma)_{max}$ = 0.01
$\Delta\rho_{max}$ = 0.4 e Å^{-3}
$\Delta\rho_{min}$ = 0.35 e Å^{-3}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Compound (II)

Crystal data

$C_{21}H_{26}NO_3^+.I^-$
M_r = 467.3
Monoclinic
$P2_1/a$
a = 9.681 (2) Å
b = 22.465 (6) Å
c = 10.463 (5) Å
β = 113.9 (2)°
V = 2080 (1) Å^3
Z = 4
D_x = 1.49 Mg m^{-3}
Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 25 reflections
θ = 7-11°
μ = 1.54 mm^{-1}
T = 293 K
Plate
0.3 × 0.2 × 0.05 mm
Transparent yellow
Crystal source: grown from methanol

Data collection

Enraf-Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
3029 measured reflections
2884 independent reflections
1556 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.01
θ_{max} = 25°
h = −11 → 11
k = 0 → 26
l = 0 → 12
3 standard reflections
frequency: 160 min
intensity variation: none

Refinement

Refinement on F
R = 0.043
wR = 0.046
S = 1.5
1556 reflections
188 parameters
H atoms refined with riding models
w = 1.1/[$\sigma^2(F_o)$ + 0.0004(F_o)^2]
$(\Delta/\sigma)_{max}$ = 0.07
$\Delta\rho_{max}$ = 0.5 e Å^{-3}
$\Delta\rho_{min}$ = 0.45 e Å^{-3}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2) *for compound* (I)

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
I(1)	0.38134 (4)	0.16373 (7)	0.32416 (4)	0.0669 (5)
C(1)	0.3800 (4)	0.7629 (7)	0.2055 (4)	0.043 (5)
C(2)	0.4177 (5)	0.8008 (7)	0.2648 (4)	0.045 (6)
C(3)	0.3805 (6)	0.7369 (8)	0.3191 (4)	0.052 (6)
N(4)	0.3768 (4)	0.5915 (6)	0.3142 (3)	0.040 (4)
C(5)	0.3413 (5)	0.5545 (8)	0.2534 (4)	0.043 (5)
C(6)	0.3793 (4)	0.6167 (7)	0.1998 (4)	0.046 (5)
O(7)	0.3052 (3)	0.8105 (6)	0.2058 (3)	0.048 (4)
C(8)	0.2911 (5)	0.8735 (9)	0.1530 (4)	0.041 (6)
O(9)	0.2323 (3)	0.9222 (6)	0.1424 (3)	0.052 (4)
C(10)	0.3598 (4)	0.8730 (8)	0.1115 (4)	0.037 (5)
O(11)	0.4149 (3)	0.8260 (6)	0.1549 (2)	0.038 (3)

C(12)	0.3807 (5)	1.0085 (8)	0.0921 (3)	0.040 (2)
C(13)	0.3752 (5)	1.1082 (9)	0.1328 (4)	0.054 (2)
C(14)	0.3980 (6)	1.2291 (11)	0.1193 (5)	0.075 (3)
C(15)	0.4229 (6)	1.2513 (13)	0.0608 (5)	0.079 (3)
C(16)	0.4297 (7)	1.1539 (10)	0.0168 (6)	0.081 (3)
C(17)	0.4080 (5)	1.0342 (9)	0.0353 (4)	0.059 (3)
C(18)	0.3478 (5)	0.7772 (8)	0.0585 (4)	0.040 (2)
C(19)	0.4006 (5)	0.6859 (9)	0.0432 (4)	0.053 (3)
C(20)	0.3889 (6)	0.5988 (11)	−0.0054 (5)	0.059 (3)
C(21)	0.3268 (6)	0.6068 (11)	−0.0389 (5)	0.069 (3)
C(22)	0.2735 (6)	0.6971 (10)	−0.0248 (5)	0.068 (3)
C(23)	0.2838 (5)	0.7831 (10)	0.0234 (4)	0.055 (3)
C(41)	0.4529 (5)	0.5353 (8)	0.3211 (4)	0.056 (6)
C(42)	0.3302 (6)	0.5408 (10)	0.3652 (5)	0.058 (7)

Table 2. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2) *for compound* (II)

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
I	0.21210 (8)	0.09557 (4)	0.90892 (8)	0.0445 (4)
C(1)	0.4343 (11)	0.3046 (5)	1.1449 (10)	0.040 (7)
C(2)	0.3012 (12)	0.2942 (5)	1.0055 (11)	0.039 (7)
C(3)	0.2941 (13)	0.3441 (4)	0.9045 (11)	0.039 (7)
N(4)	0.2819 (8)	0.4051 (4)	0.9637 (8)	0.035 (4)
C(5)	0.4122 (11)	0.4137 (5)	1.1039 (10)	0.040 (7)
C(6)	0.4208 (12)	0.3649 (5)	1.2070 (11)	0.040 (7)
O(7)	0.4266 (8)	0.2600 (3)	1.2443 (8)	0.052 (5)
C(8)	0.4969 (11)	0.2078 (4)	1.2496 (11)	0.032 (6)
O(9)	0.5704 (9)	0.1986 (3)	1.1845 (8)	0.065 (6)
C(10)	0.4587 (11)	0.1620 (4)	1.3386 (11)	0.034 (6)
O(11)	0.3130 (7)	0.1391 (3)	1.2495 (7)	0.042 (5)
C(41)	0.1313 (11)	0.4120 (6)	0.9741 (13)	0.051 (8)
C(42)	0.2917 (13)	0.4512 (5)	0.8637 (12)	0.045 (7)
C(12)	0.5787 (9)	0.1131 (4)	1.3811 (9)	0.034 (3)
C(13)	0.5451 (16)	0.0566 (4)	1.3196 (14)	0.088 (5)
C(14)	0.6549 (15)	0.0118 (7)	1.3592 (17)	0.121 (6)
C(15)	0.7968 (16)	0.0222 (5)	1.4670 (15)	0.091 (5)
C(16)	0.8371 (12)	0.0796 (4)	1.5213 (12)	0.063 (4)
C(17)	0.7261 (9)	0.1240 (5)	1.4788 (11)	0.052 (3)
C(18)	0.4455 (10)	0.1860 (4)	1.4663 (10)	0.034 (3)
C(19)	0.3587 (11)	0.1532 (5)	1.5206 (10)	0.047 (3)
C(20)	0.3503 (14)	0.1711 (5)	1.6454 (11)	0.070 (4)
C(21)	0.4254 (13)	0.2225 (5)	1.7143 (13)	0.068 (4)
C(22)	0.5110 (13)	0.2549 (5)	1.6580 (13)	0.054 (3)
C(23)	0.5208 (12)	0.2364 (5)	1.5370 (11)	0.044 (3)

Table 3. *Selected bond distances* (Å) *and angles* (°) *for compounds* (I) *and* (II)

	(I)	(II)
C(1)—C(2)	1.51 (1)	1.52 (1)
C(1)—C(6)	1.52 (1)	1.53 (1)
C(2)—C(3)	1.50 (1)	1.52 (1)
C(3)—N(4)	1.51 (1)	1.53 (1)
N(4)—C(5)	1.51 (1)	1.51 (1)
N(4)—C(41)	1.51 (1)	1.51 (1)
N(4)—C(42)	1.49 (1)	1.50 (1)
C(5)—C(6)	1.49 (1)	1.52 (1)
C(1)—O(7)	1.44 (1)	1.47 (1)
O(7)—C(8)	1.34 (1)	1.35 (1)
C(8)—O(9)	1.20 (1)	1.18 (1)
C(8)—C(10)	1.54 (1)	1.53 (1)
C(1)—O(11)	1.42 (1)	-
C(10)—O(11)	1.46 (1)	1.44 (1)
C(10)—C(12)	1.51 (1)	1.53 (1)
C(10)—C(18)	1.53 (1)	1.49 (1)
C(2)—C(1)—C(6)	109.5 (6)	111.0 (9)
C(2)—C(1)—O(7)	109.5 (6)	107.9 (8)
C(6)—C(1)—O(7)	109.5 (6)	105.4 (8)
C(2)—C(1)—O(11)	109.3 (6)	-
C(6)—C(1)—O(11)	113.6 (6)	-
O(7)—C(1)—O(11)	105.4 (6)	-
C(1)—C(2)—C(3)	110.1 (7)	109.5 (9)
C(2)—C(3)—N(4)	113.9 (7)	111.7 (8)
C(3)—N(4)—C(5)	109.4 (6)	109.6 (8)
N(4)—C(5)—C(6)	111.5 (6)	112.5 (8)
C(1)—C(6)—C(5)	111.8 (7)	-
C(1)—O(7)—C(8)	110.0 (6)	117.0 (8)
O(7)—C(8)—O(9)	122.4 (8)	122.6 (9)
O(7)—C(8)—C(10)	109.9 (7)	111.7 (8)
O(9)—C(8)—C(10)	127.7 (9)	125 (1)
C(8)—C(10)—O(11)	100.6 (6)	105.3 (8)
C(8)—C(10)—C(12)	111.2 (7)	108.6 (8)
C(8)—C(10)—C(18)	108.8 (7)	115.5 (8)
O(11)—C(10)—C(12)	108.5 (6)	112.2 (8)
O(11)—C(10)—C(18)	111.3 (7)	107.0 (8)
C(12)—C(10)—C(18)	115.5 (7)	109.2 (8)
C(1)—O(11)—C(10)	110.0 (5)	-

Table 4. *Interatomic distances* (Å) *between cationic* N *and relevant atoms in the antimuscarinic molecules*

E.s.d.'s, where available, are within 0.01 Å.

	N···C_{acetyl}	N···O_{ester}	N···$O_{carbonyl}$	N···O
Spiro-DAMP (I)	5.26	3.51	5.69	4.27[a]
Hydroxy-DAMP (II)	6.54	4.23	5.43	6.64[a]
4-DAMP (III)	6.48	4.22	5.44	-
Azaprophen (IV)	5.23	3.27	5.41	-
(−)-Atropine (V)	5.93	3.74	5.30	8.11[b]

Notes: (*a*) Distance between cationic N and O(11) atoms; (*b*) Distance between cationic N and hydroxyl O atoms.

Both structures were solved by direct methods (*SHELXS*86; Sheldrick, 1990) and refined by full-matrix least-squares methods (*SHELX*76; Sheldrick, 1976). The majority of the H atoms, including the hydroxyl H atom in compound (II), were found in difference Fourier maps; the others were positioned at geometrically calculated positions and refined isotropically using riding models with adequate bond and angle constraints. Thermal vibrations were treated anisotropically for all non-H atoms, except for the phenyl rings. In compound (II), phenyl rings have been refined while applying a constraint of 1.400 Å to the C—C distances. Programs *PLATON* (Spek, 1990) and *SCHAKAL* (Keller, 1988) were used for geometrical calculations and graphics.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71652 (44 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: NA1044]

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Flavocommelin Octaacetate

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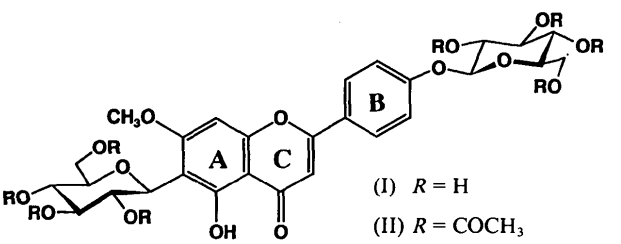
Abstract

Flavocommelin, 6-β-D-glucopyranosyl-2-[4-(β-D-glucopyranosyloxy)phenyl]-5-hydroxy-7-methoxy-4*H*-1-benzopyran-4-one, is a flavonoid component of a blue pigment, commelin, which is isolated from the petals of *Commelina communis*. The crystal structure of the octaacetate derivative, 5-hydroxy-7-methoxy-6-(3,4,5,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-[4-(3,4,5,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-phenyl]-4*H*-1-benzopyran-4-one, $C_{44}H_{48}O_{23}$, has been determined by X-ray diffraction. In the crystal, the molecules are arranged parallel to each other according to the periodicity of the crystal lattice. However, intermolecular stacking of the flavanone skeletons is not observed. This suggests that the hydrophilicity of the glucose moieties is one of the important factors governing the self association.

Comment

The mechanism of the color variation and stabilization of anthocyanins has been investigated previously (Goto & Kondo, 1991). The crystal structure of commelin has been determined and revealed that the pigment is a metal-complex anthocyanin (Kondo *et al.*, 1992). In the pigment there exists hydrophobic stacking of the aromatic rings of the anthocyanin and flavone molecules. One of the components, flavocommelin (I), also shows self association in condensed aqueous solutions (Goto, Yoshida, Yoshikane & Kondo, 1990). Because the crystallization of (I) is difficult, the acetate derivative, (II), was prepared.



(I) R = H

(II) R = $COCH_3$

There are many reports of crystal structures of flavone compounds, but none of them have a sugar moiety except aciculatin (Krause & Eggleston, 1991). In the crystal of aciculatin (monoclinic, space group $I2$, $Z = 8$), the aromatic rings are stacked: two independent flavone molecules lie separately on 2_1 screw axes with the flavanone skeletons almost perpendicular to the screw axes. The cell parameter b [7.371 (2) Å] is, therefore, roughly four times the van der Waals radius of the aromatic C atom (1.77 Å).

The molecular structure of the title compound is shown in Fig. 1. The C22–C23–C25–O4 plane of the hexopyranosyl ring of the glucose moiety connected by the O–glucopyranosyloxy bond is inclined at 30.1 (3)° to the phenyl ring *B*, while the C17–C18–C20–O3 plane of the other glucopyranosyl connected by the C–glucopyranosyl bond is almost perpendicular to the benzene ring *A* [84.4 (2)°], as a result of steric interactions. The phenyl ring *B* not only rotates around the C1—C10 bond but is also slightly bent with respect to the pyran plane, *C*. This bending is measured by the shift, *S*, of the center of ring *B* from the plane of ring *C* [$S = 0.25$ (2) Å]. Similar bending is also observed in other flavone crystals, as shown in Table 3. The *A*, *B* and *C* rings are essentially planar. The bending between the *B* and *C* rings must be a result of the crystal packing. Six of the 18 flavone molecules, whose deformations were calculated based on the crystal structure data, have *S*