Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.034$
$wR(F^2) = 0.081$
$S = 0.748$
2199 reflections
166 parameters
H atoms riding with a fixed and unique $U_{\rm eq}$
$w = 1/[\sigma^2(F_o^2) + (0.042P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max} < 0.001$
$\Delta\rho_{\rm max} = 0.106$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.117$ e Å^{-3}
Extinction correction: *SHELXL*93
Extinction coefficient: 0.013 (2)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

C1—N10	1.322 (2)	N3—C4	1.363 (2)
C1—N2	1.374 (2)	C4—C5	1.407 (2)
N2—N3	1.313 (2)	C5—N10	1.355 (2)
N10—C1—N2	125.15 (15)	N3—C4—C9	118.5 (2)
N10—C1—C11	118.88 (14)	C5—C4—C9	120.7 (2)
N2—C1—C11	115.97 (13)	N10—C5—C4	119.85 (14)
N3—N2—C1	119.36 (13)	N10—C5—C6	120.73 (15)
N2—N3—C4	118.61 (14)	C4—C5—C6	119.4 (2)
N3—C4—C5	120.82 (15)	C1—N10—C5	116.20 (14)

Reflection intensities were evaluated by profile fitting of a 96-step peak scan among a 2θ shells procedure (Diamond, 1969) and then corrected for Lorentz–polarization effects. S.u.'s $\sigma(I)$ were estimated from counting statistics. The structure was solved by direct methods and completed by a combination of full-matrix least squares and Fourier map. All non-H atoms were refined anisotropically. H atoms were located at idealized positions and allowed to ride on their parent C atoms, with a common isotropic displacement parameter ($U_{\rm iso} = 0.07$ Å^2). The two methyl groups show disordered H atoms which have been treated in an ideal manner considering them in two positions rotated by 60° with respect to each other. All calculations were performed on a μ-VAX 3400 and on a AXP DecStation 3000/400.

Data collection: *P3/V* (Siemens, 1989). Cell refinement: *P3/V*. Data reduction: *SHELXTL-Plus* (Sheldrick, 1990*a*). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990*b*). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *XPW* (Siemens, 1996). Software used to prepare material for publication: *PARST*95 (Nardelli, 1995) and *SHELXL*93.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1306). Services for accessing these data are described at the back of the journal.

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Ambroxol Theophylline-7-acetate Salt Monohydrate†

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Abstract

In the title monohydrate salt of ambroxol (AMB) with theophylline-7-acetic acid (TAA), $C_{13}H_{19}Br_2N_2O^+.-C_9H_9N_4O_4^-.H_2O$, protonation of the secondary amino group of AMB takes place. An N^+—H···O^- hydrogen bond is established between the protonated N atom and an O atom of the carboxylate anion, the same atom as is involved in an N—H···O interaction with the aromatic amino group of the cation. The other O atom of the carboxylate anion participates in an N^+—H···O^- hydrogen bond with a symmetry-related salt molecule, giving rise to a dimeric arrangement. The water molecule is linked to a carbonyl O atom of TAA and the aromatic amino group of AMB, and connects the salt molecules in the crystal at the level of the OH group of AMB.

Comment

Ambroxol (AMB) is reported to form a 1:1 salt with theophylline-7-acetic acid (TAA) in aprotic solvents

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† Systematic name: [(2-amino-3,5-dibromophenyl)methyl](*trans*-4-hydroxycyclohexyl)ammonium 1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-7*H*-purine-7-acetate hydrate.

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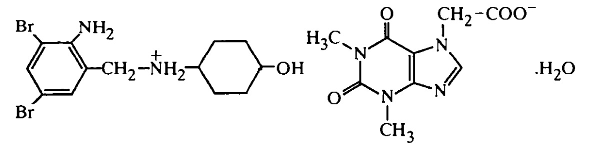

AMB TAA

which shows interesting secretolytic and bronchodilator activity (Massaroli, 1985). When recrystallized from aqueous solvents, the salt can separate as a monohydrate. In this compound, protonation of the secondary amino group of AMB takes place (Fig. 1). The AMB cation, with the aliphatic ring in a chair conformation and the aromatic ring and its substituents essentially coplanar (with the exception of C8 which is shifted from the plane by 0.18 Å), has an extended conformation as depicted by the C6—C8—N9—C10 torsion angle (Table 1). A similar value for the N27—C30—C31—O32 torsion angle describes the orientation of the carboxyl group of the acetate group of the TAA anion, whose theophylline moiety has intramolecular bond distances and angles similar to those found in other purine systems (Sutor, 1958; Shefter, 1969; Shefter & Sackam, 1971). There is a marked degree of puckering of the atoms comprising the purine nucleus as well as of its pyrimidine and imidazole portions, which are tilted about the C21—C22 bond by *ca* 3 Å as in the 5-chlorosalicylic acid–theophylline complex (Shefter, 1969).

According to Table 2, which shows the relevant geometries of the hydrogen bonds, an N—H···O hydrogen bond is established between the protonated N9 atom and the O32 atom of the carboxylate anion, which is also involved in an interaction (N7—H7*B*···O32) with the aromatic amino group of the cation. The O33 atom of the carboxylate anion is involved in an N—H···O hydrogen bond [N9···O33^{i}; symmetry code: (i) $1-x$, $1-y$, $1-z$] with a symmetry-related salt molecule, giving rise to a dimeric arrangement (Fig. 2).

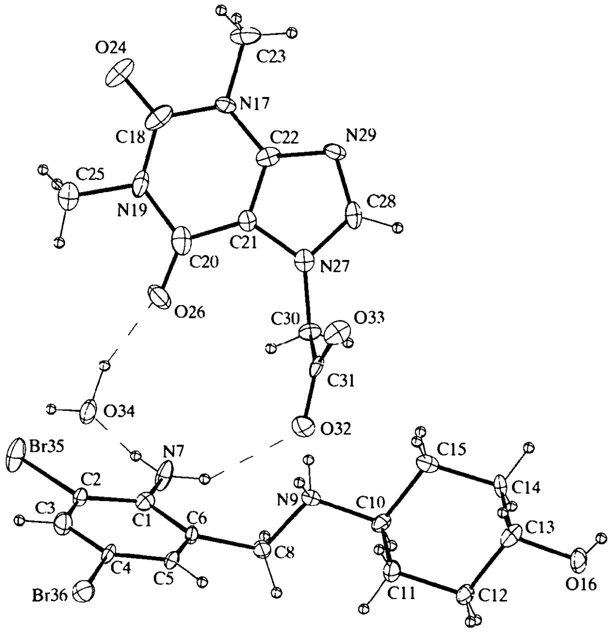

Fig. 1. *ORTEP*II (Johnson, 1976) plot of the title compound showing 30% probability displacement ellipsoids. Dashed lines indicate hydrogen bonds.

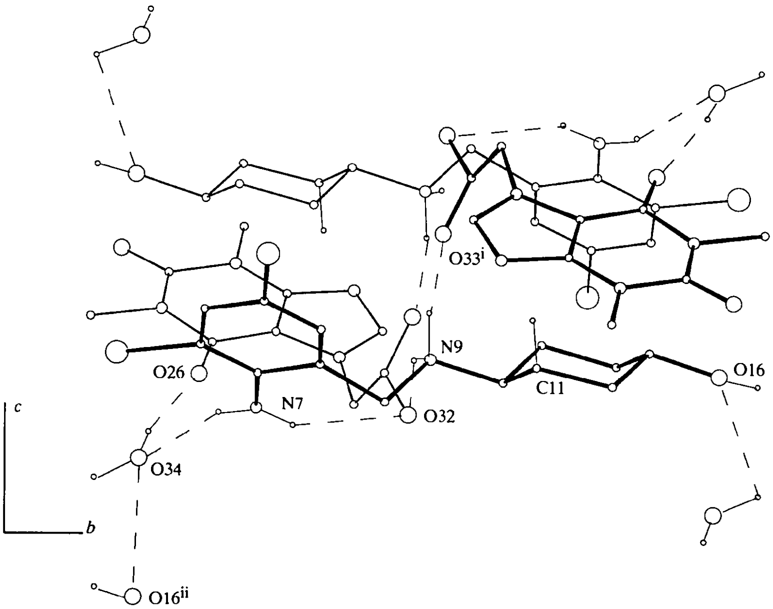

Fig. 2. Drawing of the hydrogen bonds (dotted lines) involving centrosymmetrically related molecules of the title compound (see Table 2 for symmetry codes).

Stacking interactions also occur between the phenyl ring of AMB and the purine ring of TAA, the distance between the best planes being *ca* 3.1 Å. The water molecule is linked to the carbonyl O26 atom of TAA through an O—H···O interaction (O34···O26) and to the aromatic amino group of AMB through an N—H···O interaction (N7···O34). As can be seen in Fig. 2, the water molecules connect the salt dimers in the crystal at the level of the O16^{ii} hydroxyl group of AMB through an O34···O16^{ii} interaction [symmetry code: (ii) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$].

Experimental

Single crystals of the title compound were obtained as colourless plates by crystallization of TAA (0.002 mol) and AMB (0.002 mol) from 20 ml of water.

Crystal data

$C_{13}H_{19}Br_2N_2O^+.C_9H_9N_4O_4^-.H_2O$
$M_r = 634.32$
Orthorhombic
Pbca
$a = 22.935\,(4)$ Å
$b = 27.125\,(3)$ Å
$c = 8.332\,(1)$ Å
$V = 5183\,(1)$ Å^3
$Z = 8$
$D_x = 1.626$ Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
$\lambda = 0.7107$ Å
Cell parameters from 40 reflections
$\theta = 2$–$22°$
$\mu = 3.18$ mm^{-1}
$T = 296\,(2)$ K
Prism
0.45 × 0.20 × 0.15 mm
Colourless

Data collection

Philips PW1100 diffractometer
ω–2θ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{min} = 0.525$, $T_{max} = 0.625$
9270 measured reflections
2513 independent reflections
1356 reflections with $I > 2\sigma(I)$
$R_{int} = 0.173$
$\theta_{max} = 22.03°$
$h = 0 \rightarrow 24$
$k = 0 \rightarrow 28$
$l = 0 \rightarrow 8$
3 standard reflections
frequency: 180 min
intensity decay: 1.3%

Refinement

Refinement on F^2
$R(F) = 0.086$
$wR(F^2) = 0.143$
$S = 1.317$
2507 reflections
328 parameters
H atoms constrained
$w = 1/[\sigma^2(F_o^2) + (0.0293P)^2 + 64.1637P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = -0.040$
$\Delta\rho_{max} = 0.66$ e Å^{-3}
$\Delta\rho_{min} = -0.52$ e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

C1—N7	1.37 (2)	C20—O26	1.21 (2)
C8—N9	1.50 (1)	C31—O32	1.22 (2)
N9—C10	1.51 (1)	C31—O33	1.25 (2)
C13—O16	1.45 (1)		
C2—C1—N7	122 (2)	N19—C20—O26	122 (2)
C6—C1—N7	122 (2)	C21—C20—O26	128 (2)
C8—N9—C10	113 (1)	N27—C30—C31	114 (1)
C12—C13—O16	108 (1)	C30—C31—O32	117 (2)
C14—C13—O16	111 (1)	C30—C31—O33	117 (1)
N19—C20—C21	110 (1)	O32—C31—O33	126 (2)
C6—C8—N9—C10	156 (1)	N27—C30—C31—O32	161 (1)

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N7—H7*A*···O34	0.86	2.35	3.16 (2)	159
N7—H7*A*···Br35	0.86	2.66	3.08 (1)	111
N7—H7*B*···O32	0.86	2.26	3.00 (2)	144
N9—H9*B*···O32	0.98	1.81	2.70 (2)	150
N9—H9*B*···O33	0.98	2.71	3.61 (2)	153
N9—H9*A*···O33^i	0.98	1.79	2.76 (2)	166
O16—H16···Br35^{ii}	0.82	2.54	3.33 (1)	164
O34—H34*A*···O26	0.98	1.87	2.78 (2)	155
O34—H34*B*···O16^{iii}	0.98	2.34	2.73 (2)	103

Symmetry codes: (i) $1-x, 1-y, 1-z$; (ii) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$; (iii) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$.

The lattice parameters were measured with the Philips *LAT* routine. Scan speed was 0.05° s^{-1} with a scan width of 2.0° (intensities negligible at $\theta = 22°$). H atoms were included at calculated positions and refined using a riding model, except for the atoms of the water molecule, H34*A* and H34*B*, which were placed in calculated positions corresponding to minima of the non-bonded potential energy profiles. The low accuracy of the structure refinement derives from the weak diffracting power of the crystals. Nevertheless, the final results can be considered satisfactory from the chemical point of view.

Program(s) used to solve structure: *MULTAN*80 (Main *et al.*, 1980). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *PARST* (Nardelli, 1983, 1991, 1995).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1242). Services for accessing these data are described at the back of the journal.

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6,7,8,9-Tetrahydro-4-trifluoromethyl-2*H*-pyrano[3,2-*g*]quinolin-2-one, (I), and 6,7,8,9-Tetrahydro-9-ethyl-4-trifluoromethyl-2*H*-pyrano[3,2-*g*]quinolin-2-one, (II)

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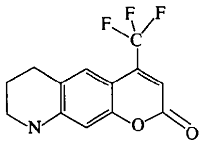
Abstract

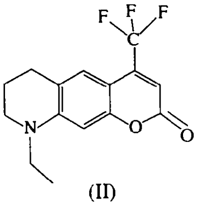
The title compound, $C_{13}H_{10}F_3NO_2$, (I), and its ethyl derivative, $C_{15}H_{14}F_3NO_2$, (II), are trifluoromethylcoumarin derivatives of the 6,7,8,9-tetrahydro-2*H*-pyrano[3,2-*g*]quinolin-2-one moiety. Compound (I) is stabilized by one C—F···H and two C—O···H intermolecular hydrogen bonds. Compound (II) crystallizes with two molecules in the asymmetric unit and is stabilized by van der Waals intermolecular interactions. The independent molecules in (II) are stacked in parallel layers in an alternating sequence, with the coumarin moieties forming an angle of 76.5 (4)° between adjacent parallel stacks.

Comment

Both title compounds are laser dyes and are also known as coumarin 340, (I), and coumarin 355, (II). Few examples of coumarin derivatives involving a fused piperazine ring system adjacent to the coumarin moiety which are used as laser dyes have been crystallized and structurally characterized.



(I)



(II)

Bond lengths and angles in the coumarin moiety of each compound are normal (Jasinski & Woudenberg, 1993). The asymmetric unit of compound (I) is shown in Fig. 1, while the two molecules, *A* and *B*, of compound (II) are shown in Fig. 2. In compound (II), one C atom in molecule *B* (C14*B*) is disordered and was included in the least-squares anisotropic refinement of the structure as C14*B*1 [occupancy 0.47 (2)] and C14*B*2 [occupancy 0.53 (2)]. H atoms on C13, C14 and C15 were included unrefined in the final least-squares refinement, with partial occupancies. The dihedral angle between the least-squares planes of the benzene and pyrone rings in both compounds are normal. Values for the torsion angles C8—C7—N16—C15 [177.6 (2) in (I), and −178.3 (4) for molecule *A* and −175.9 (4)° for molecule *B* in (II)] and C6—C7—N16—C15 [−1.3 (3) in

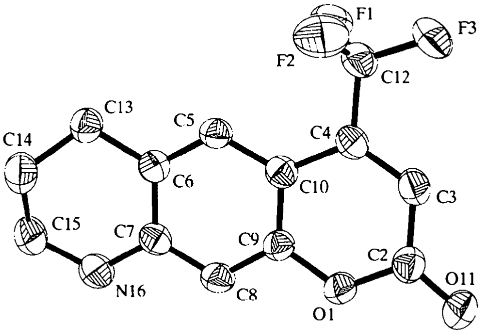


Fig. 1. *ORTEP*II (Johnson, 1976) drawing of (I) showing the atomic numbering scheme. Displacement ellipsoids are shown at the 50% probability level.

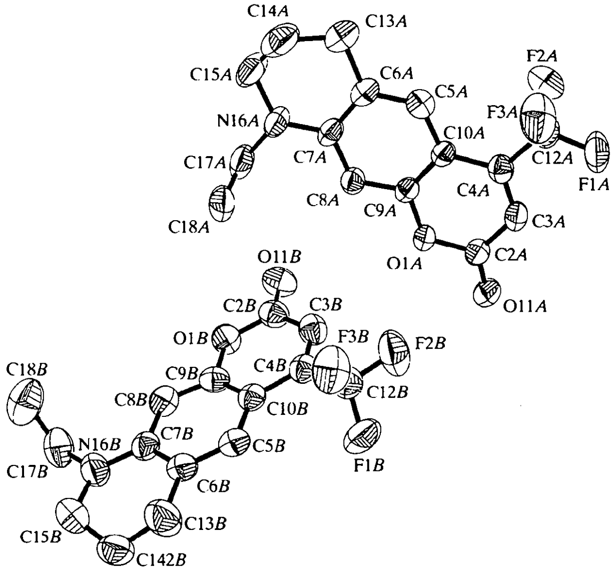


Fig. 2. *ORTEP*II (Johnson, 1976) drawing of (II) showing the atomic numbering schemes of molecules *A* and *B*. Displacement ellipsoids are shown at the 50% probability level.