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Hydrogen-bond motifs in *N*-monosubstituted derivatives of barbituric acid: 5-allyl-5-isopropyl-1-methylbarbituric acid (enallylpropymal) and 1,5-di(but-2-enyl)-5-ethylbarbituric acid

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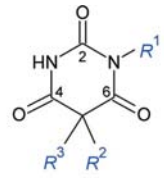
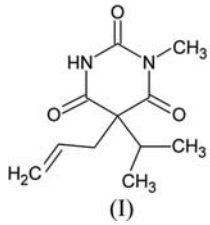
Both title structures exhibit essentially planar barbiturate rings. The crystal structure of enallylpropymal (5-allyl-5-isopropyl-1-methylbarbituric acid), $C_{11}H_{16}N_2O_3$, is composed of centrosymmetric N—H···O hydrogen-bonded dimers, while 1,5-di(but-2-enyl)-5-ethylbarbituric acid, $C_{14}H_{20}N_2O_3$, forms N—H···O hydrogen-bonded helical chains. Each of the ten known crystal structures of closely related *N*-monosubstituted derivatives of barbituric acid displays one of the fundamental N—H···O hydrogen-bonded motifs of the two title structures, *i.e.* either a dimer or a chain.

Comment

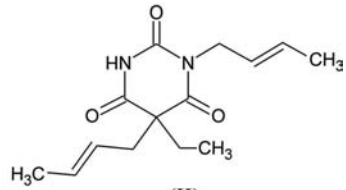
Barbituric acid derivatives are sedative, anaesthetic, anxiolytic, hypnotic and anticonvulsant agents, which have largely been replaced in pharmaceutical use by other drugs of lower abuse liability. However, barbiturates remain a very interesting class of compounds because of their multiple crystalline forms (Brandstätter-Kuhnert & Aepkers, 1962) and their hydrogen-bonding capabilities. The rigid barbiturate ring determines the geometric configuration of the potential hydrogen-bond donor and acceptor sites in the molecule (NH and carbonyl groups, see scheme). This in turn limits the geometric diversity of the hydrogen-bond patterns that can be formed. Subsequently, the observed patterns in the subset of compounds with R^1 = H are all based on a small number of standard motifs (Gelbrich *et al.*, 2007; Zencirci *et al.*, 2009). The number of feasible motifs should be even smaller for the related *N*-monosubstituted derivatives (R^1 = alkyl), to which the two title compounds belong, simply because they have only one hydrogen-bond-donor functionality.

Enallylpropymal [systematic name: 1-methyl-5-(propan-2-yl)-5-(prop-2-en-1-yl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione, and also known as narconumal], (I), was marketed as a potent sedative and hypnotic drug (Demole, 1937). Brandstätter-Kuhnert & Aepkers (1962) have studied its solid-state behaviour and found evidence for the existence of only one crystalline form. It has a melting point of 331–334 K, which is remarkably low in comparison to the other *N*-monosubstituted derivatives of barbituric acid listed in the same paper. The thermomicroscopic and DSC (differential scanning calorimetry) data obtained for our crystals of (I) are consistent with the data reported by Brandstätter-Kuhnert & Aepkers (1962).





(I)



(II)

The asymmetric unit of (I) contains one formula unit (see Fig. 1*a*). The barbiturate ring is essentially planar so that the r.m.s. deviation of the six fitted atoms from the mean plane is just 0.02 Å. The analogous parameter is 0.05 Å for the C10—C8—C5—C11—C12 fragment, which involves adjacent sections of the isopropyl and allyl substituents. These two essentially planar molecular fragments lie almost perpendicular to one another and form an angle of 88.7 (1)°.

Two molecules of (I) are joined together by two N—H···O hydrogen bonds to give a centrosymmetric dimer with a central $R_2^2(8)$ ring (Bernstein *et al.*, 1995). This motif is present in many barbiturates with two NH hydrogen-bond-donor groups (*i.e.* R^1 = H; Zencirci *et al.*, 2009). Neighbouring hydrogen-bonded dimers in the crystal structure of (I) are related to one another by translational symmetry. They assemble in such a way that the isopropyl and allyl groups of adjacent dimers align themselves in an approximately antiparallel fashion (see Fig. 2). Furthermore, an (allyl)C—H···O6(x + 1, y, z) interaction links the dimers into double-stranded chains which propagate parallel to the *a* axis (see Fig. 2 and Table 1).

Crystals of (II) {systematic name: 1,5-di[(2*E*)-but-2-en-1-yl]-5-ethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione} were identified as an unexpected by-product in a commercial sample of 5-(but-2-enyl)-5-ethylbarbituric acid, kalypnon (Boehringer und Söhne), obtained by our laboratory some 40 years ago. Kalypnon (also known as kalipnon, crotylbarbital, crotarbital, mepertan, barotal) was used for the treatment of insomnia during the 1960s.

The barbiturate ring of (II) is essentially planar, with the r.m.s. deviation of the six fitted atoms from the mean plane

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being just 0.04 Å (Fig. 1*b*). The analogous deviation for the C12—C11—C5—C15—C16 set of atoms, involving ring atom C5 and adjacent fragments of the crotyl and ethyl substituents, is 0.03 Å. Similar to the structure of (I), the barbiturate ring and the C_5-plane at C5 are almost perpendicular to one another and form an angle of 89.8 (2)°. The 1- and 5-substituted *trans*-crotyl groups lie on opposite sides of the plane through the barbiturate ring, so that the associated anticlinal N1—C7—C8—C9 and C5—C11—C12—C13 torsion angles are of the opposite sign.

The molecules of (II) are linked to one another by one N—H···O hydrogen bond (Table 2). The helical chains resulting from this interaction lie parallel to the *b* axis (see Fig. 3). Furthermore, chains that are adjacent to one another along the *a* axis are related by translational symmetry, while along the *c* axis there are centres of inversion between neighbouring chains. Two molecules belonging to neighbouring N—H···O-bonded chains are linked together *via* two (but-2-enyl)C—H···O4($-x+2, -y, -z+1$) contacts which are related by inversion symmetry (see Fig. 3 and Table 2). Altogether, N—H···O and C—H···O interactions result in a two-dimensional sheet of connected molecules that lies parallel to (101).

The crystal structures of eight *N*-monosubstituted barbituric acid derivatives with R^1 = alkyl (see scheme) are currently known [Cambridge Structural Database (CSD), Version 5.30, September 2009 update; Allen, 2002], in addition to those of (I) and (II) (see Table 3). A common feature of all these structures is the formation of a single N—H···O hydrogen bond in which the NH donor and one carbonyl acceptor site per molecule are employed. More precisely, only the carbonyl group in the 4-position (see scheme) is ever engaged in this interaction, whereas the carbonyl groups in the 2- and 6-positions are avoided, presumably because of their close proximity to the alkyl substitutent at N1.

Four of these previous examples concern the dimer motif of (I) (Brunner *et al.*, 2003; Dideberg *et al.*, 1975; Lewis *et al.*, 2005; Pyżalska *et al.*, 1980). The dimer is always centrosymmetric, with the exception of one structure of an enantiomerically pure chiral compound (Brunner *et al.*, 2003). The N—H···O-bonded chain motif is found in (II), where the chains exhibit a 2_1 symmetry, and in another four compounds (Gelbrich & Griesser, 2009; Nichol & Clegg, 2005; Wilhelm &

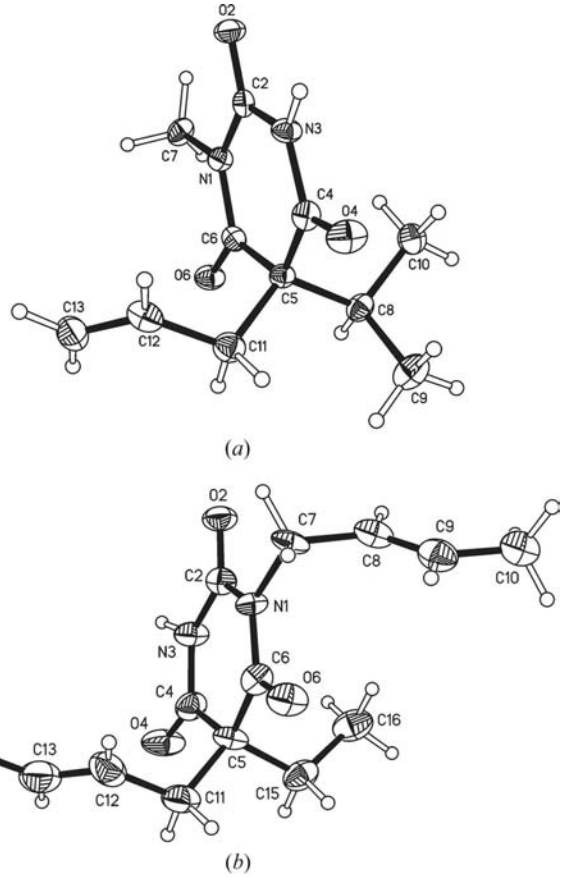

Figure 1
The molecular structures of (*a*) (I) and (*b*) (II), with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as spheres of arbitrary size.

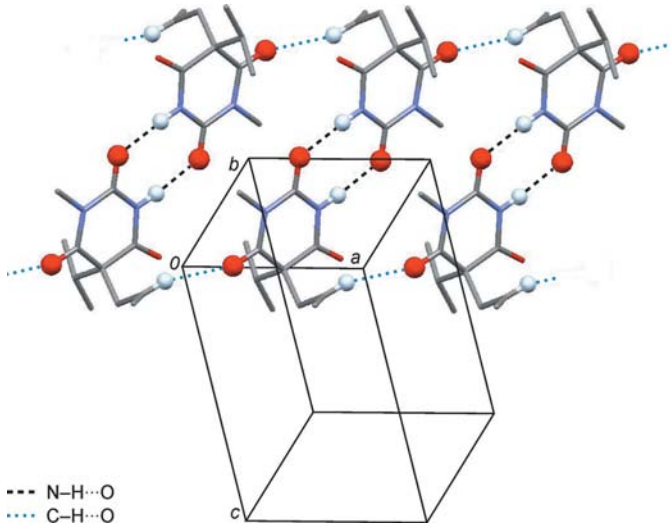

Figure 2
N—H···O-bonded dimers and C—H···O contacts in the crystal structure of (I). H and O atoms directly involved in these interactions are depicted as balls.

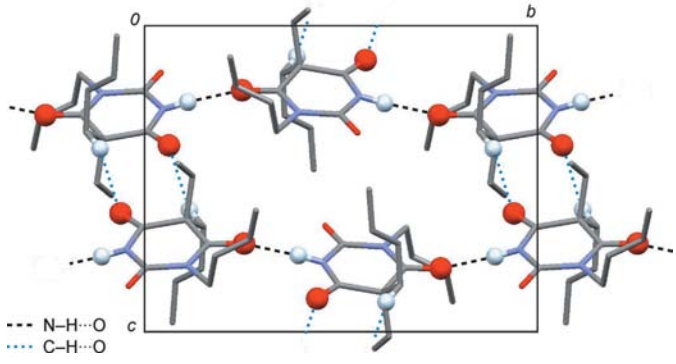

Figure 3
The packing of N—H···O-bonded chains and C—H···O contacts in the crystal structure of (II), viewed parallel to the *a* axis. H and O atoms directly involved in these interactions are depicted as balls.

Fischer, 1976; Wunderlich, 1973), where they show translational symmetry only. Consequently, the lattice vectors which correspond with the translation of these latter four hydrogen-bonded chains (see Table 3) are very similar in length (between 6.61 and 6.80 Å).

Experimental

Intergrown irregular-shaped crystals of (I) were obtained from a commercial sample of narconumal (F. Hoffmann–La Roche). Additional crystallization experiments did not produce any crystals of better quality. A commercial sample of kalypnon (Boehringer und Söhne) was found to contain small needle-shaped crystals of (II) which were clearly distinct from the rhombic crystals of the main product.

Compound (I)

Crystal data

$C_{11}H_{16}N_2O_3$
M_r = 224.26
Triclinic, $P\overline{1}$
a = 6.4160 (7) Å
b = 7.9559 (8) Å
c = 11.9569 (12) Å
α = 77.574 (7)°
β = 80.837 (7)°
γ = 75.518 (6)°
V = 573.51 (10) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 120 K
0.25 × 0.2 × 0.2 mm

Data collection

Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2007)
T_{min} = 0.977, T_{max} = 0.981
2000 measured reflections
2000 independent reflections
1386 reflections with $I > 2\sigma(I)$
R_{int} = 0

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.071
$wR(F^2)$ = 0.114
S = 1.18
2000 reflections
154 parameters
1 restraint
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.33 e Å^{-3}

Compound (II)

Crystal data

$C_{14}H_{20}N_2O_3$
M_r = 264.32
Monoclinic, $P2_1/n$
a = 10.2825 (11) Å
b = 13.2972 (16) Å
c = 10.3959 (10) Å
β = 92.999 (7)°
V = 1419.5 (3) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 120 K
0.1 × 0.03 × 0.02 mm

Data collection

Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2007)
T_{min} = 0.991, T_{max} = 1.000
11137 measured reflections
2440 independent reflections
1367 reflections with $I > 2\sigma(I)$
R_{int} = 0.147

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.080
$wR(F^2)$ = 0.127
S = 1.21
2440 reflections
180 parameters
1 restraint
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.33 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3···O2^{i}	0.88 (2)	1.99 (2)	2.866 (4)	174 (4)
C12—H12···O6^{ii}	0.95	2.51	3.424 (4)	163

Symmetry codes: (i) $-x+1, -y+2, -z$; (ii) $x+1, y, z$.

Table 2
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3···O6^{i}	0.88 (2)	1.92 (2)	2.798 (5)	176 (5)
C11—H11A···O4^{ii}	0.99	2.51	3.432 (6)	155

Symmetry codes: (i) $-x+\frac{3}{2}, y-\frac{1}{2}, -z+\frac{3}{2}$; (ii) $-x+2, -y, -z+1$.

Table 3
Hydrogen-bonding motifs in *N*-monosubstituted derivatives of barbituric acid (R^1 = alkyl, see scheme in *Comment*).

R^1	R^2	R^3	Symmetry	Reference
Dimer				
Methyl	Allyl	Isopropyl	Inversion	(I)
Methyl	Ethyl	Phenyl	Inversion	*a*
p-Bromophenyl	Allyl	Allyl	Inversion	*b*
Cyclohexyl	Allyl	Allyl	Inversion	*c*
Methyl	Allyl	(2*R*)-Hex-3-yn-2-yl	None	*d*
Chain				
But-2-enyl	But-2-enyl	Ethyl	2_1	(II)
2,3-Dibromopropyl	Ethyl	Ethyl	Translation (*b* axis)	*e*
Methyl	*β*-Bromoallyl	Isopropyl	Translation (*c* axis)	*f*
Methyl	Ethyl	Ethyl	Translation (*a* axis)	*g*
Methyl	Cyclohexen-1-yl	Methyl	Translation (*b* axis)	*h*

References: (*a*) Lewis *et al.* (2005); (*b*) Pyżalska *et al.* (1980); (*c*) Dideberg *et al.* (1975); (*d*) Brunner *et al.* (2003); (*e*) Gelbrich & Griesser (2009); (*f*) Wilhelm & Fischer (1976); (*g*) Wunderlich (1973); (*h*) Nichol & Clegg (2005).

The data collected for (I) were integrated for two separate non-merohedrally twinned components. The final BASF parameter for the minor component was 0.356 (3). The monoclinic lattice of (II) has a special geometry where the *a* and *c* axes are approximately equal in length, giving rise to imperfect pseudomerohedral twinning. The data integration was performed with a larger shoe box than usual in order to include the combined contributions from both twin components, and in the structure refinement the idealized pseudomerohedral twin matrix ($00\overline{1}/0\overline{1}0/\overline{1}00$) was applied. The final BASF parameter for the minor twin component was 0.272 (2). The data quality may also be affected by additional small nonmerohedral twin components that could not be modelled adequately. All H atoms were identified in a difference map. Methyl H atoms were idealized and included as rigid groups that were allowed to rotate but not tip (C—H = 0.98 Å) and refined with U_{iso}(H) = 1.5U_{eq}(C). H atoms bonded to secondary CH_2 (C—H = 0.99 Å) and aromatic C atoms (C—H = 0.95 Å) were positioned geometrically and refined with U_{iso}(H) = 1.2U_{eq}(C). H atoms attached to N atoms were refined with restrained distances [N—H = 0.88 (2) Å] and their U_{iso}(H) parameters were refined freely.

For both compounds, data collection: *COLLECT* (Hooft, 1998); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997). Data reduction: *EVALCCD* (Duisenberg *et al.*, 2003) for (I); *DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK* for (II). For both compounds, program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *XP* in *SHELXTL* (Sheldrick, 2008) and *Mercury* (Bruno *et al.*, 2002); software used to prepare material for publication: *publCIF* (Westrip, 2010).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ3168). Services for accessing these data are described at the back of the journal.

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