Short Note

Cocrystal of Codeine and Cyclopentobarbital

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Cocrystal of Codeine and Cyclopentobarbital

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Abstract: The two-component compound formed by codeine and cyclopentobarbital was produced by grinding techniques and by evaporation from alcoholic solutions. The cocrystal nature of this phase was established unequivocally by single crystal X-ray structure determination. The asymmetric unit contains one formula unit. In the cyclopentobarbital molecule, the cyclopentenyl ring is disordered over two positions related by a rotation of approximately 180° about its C–C bond to the pyrimidine ring. The two NH groups of the cyclopentobarbital molecule form N—H···N and N—H···O bonds to piperidine and hydroxyl groups, respectively, belonging to different codeine molecules. In addition, the hydroxyl and methoxy groups of neighboring codeine molecules are linked by O—H···O interactions, resulting H-bonded framework structure of codeine and cyclopentobarbital molecules. The cocrystal was also characterized by thermal analysis, X-ray powder diffraction and IR spectroscopy.

Keywords: barbiturate; co-crystal; crystal structure; hydrogen bonding; opiate; pharmaceuticals

1. Introduction

Codeine (I), (5a,6a)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol (Scheme 1), is a natural alkaloid of the opium poppy plant *Papaver somniferum*, first discovered in 1832 by Pierre Jean Robiquet [1]. Codeine is contained in the WHO model list of essential drugs [2]. With an annual production (2013) of about 361,000 kg, it is the most widely used narcotic drug in medical practice. Codeine is applied as an analgesic for the treatment of mild to moderate pain, as an antitussive (cough depressant) and as an antidiarrhoeal agent [3-5].

The List of Narcotic Drugs under International Control (Yellow List) not only contains the free base of codeine, but also 20 codeine multicomponent systems [6]. These are primarily salts with mineral acids (*e.g.* HCl, phosphate, sulphate) and common organic acids (glucuronic, salicylic, acetic and barbituric acid) where the pK_a difference between codeine (pK_a = 8.2) and the respective acid is higher than 3.5. Another five entries in the Yellow List concern combinations of codeine with 5,5-disubstituted derivatives of barbituric acid, all associated with a small pK_a difference (between 0.2 and 1.1). This suggests that the corresponding two-component systems of codeine and the respective barbiturate exist as cocrystals [7]. Cocrystals are 'solids that are crystalline materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts' [8,9].

One of the barbiturates concerned is cyclopentobarbital (II), 5-allyl-5-(cyclopent-2-en-1-yl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (Scheme 2; alternative names: cyclopal, dormisan). Cyclopentobarbital was invented in the 1940s [10,11] and possesses sedative and anticonvulsant properties with a slow onset of action. Its primary application was as an anaesthetic in veterinary medicine.

The two-component system codeine/cyclopentobarbital is associated with a pK_a difference of just 0.7. It is therefore expected to exist as a cocrystal form, which will be denoted henceforth as (I)·(II). The current study was carried out to unequivocally establish the chemical nature of this phase by means of single-crystal X-ray structure determination, which was accompanied by a characterization with differential scanning calorimetry, hot-stage microscopy and FT-IR spectroscopy.

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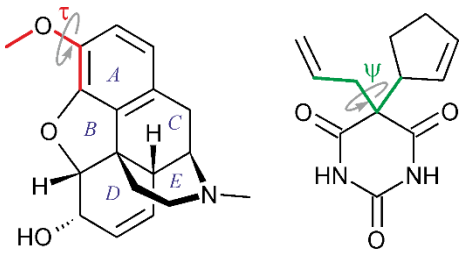

(I) (II)

Scheme 1. Structural formulas of codeine (I) and cyclopentobarbital (II); definition of the torsion angle τ and rings *A*–*E* for (I) and the torsion angle ψ for (II).

2. Results

2.1. Crystal structure

Crystal data and refinement details are collected in Table 1. The asymmetric unit of the orthorhombic crystal structure contains one formula unit (Figure 1), *i.e.* one codeine and one cyclopentobarbital molecule. The hydrogen positions of both NH groups in the molecule of (II), and thus the cocrystal nature of (I)·(II), were confirmed unequivocally.

Table 1. Crystal data and structure refinement.

Compound	(I)·(II)
Moiety formula	$C_{18}H_{21}NO_3 \cdot C_{12}H_{14}N_2O_3$
Empirical formula	$C_{30}H_{35}N_3O_6$
Formula weight	533.61
Temperature (K)	173(2)
Wavelength (Å)	1.5418
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a (Å)	6.9914(3)
b (Å)	14.1455(7)
c (Å)	27.1767(11)
Unit cell volume (Å^3)	2687.7(2)
Z / Z′	4 / 1
Reflections collected / R_{int}	9191 / 0.0447
Data / restraints /parameters	4466 / 133 / 404
Goodness-of-fit on F^2	1.027
$R1$ [$I > 2\,\sigma(I)$]	0.0500
$wR2$ (all data)	0.1289
Largest diff. peak and hole (e · Å^{-3})	0.197 and -0.189
CCDC no.	2278182

The molecular structure of (I) is largely inflexible. The two mean planes defined by the rings *A*/*B*/*C* and *D*/*E* (Scheme 1) are nearly orthogonal, forming an angle of 88.20(6)°, which illustrates the presence of the characteristic T conformation of the opiate family [12]. The Cambridge Structural Database (CSD; version 5.44, June 2023) [13] contains nine unique examples of crystal structures containing the neutral codeine molecule or its cation form, *i.e.*, CSD codes CDNECR [14], CODHBH [15], EZEWAK [16], OPOQAN], ZZZRFQ01, ZZZTZQ02 [17], QITZOK [18], QUBSEM [12], ZZZTSE03 [19]. In this group, the angle characterizing the T geometry of the codeine skeleton varies in a narrow range between 86.0° to 90.0° (Table S1 of the Supporting Information). The orientation of the methoxy group can be described in terms of the torsion angle C4A–C3A–O1A–C18A, denoted as τ in Scheme 1. Its value of 25.2(6)° indicates that the methoxy group is twisted out of the plane of the phenyl ring (*A*) and oriented towards ring *B* (see Scheme 1). Similar conformations (τ = 25.4° and τ = 36.2°) has also been reported for both independent codeine molecules in the monophosphate

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hemihydrate [12]. By contrast, all other codeine structures from the CSD listed above exhibit an orientation of the methoxy group towards the phenyl ring, indicated by absolute τ values between 128.3° and 178.8° (Table S1 of the Supporting Information). This fundamental difference to (I)·(II) may be interpreted as a trade-off effect between an optimal molecular geometry on the one hand and an optimal intermolecular H-bond geometry on the other hand.

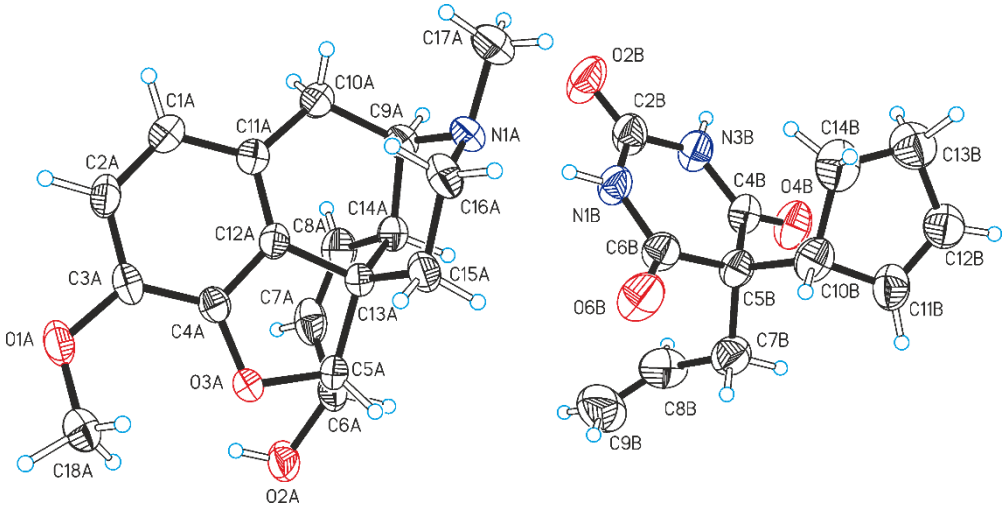

Figure 1. Asymmetric unit of (I)·(II) with non-H atoms depicted as ellipsoids at the 50% probability level and H atoms drawn as spheres of random size (minor disorder omitted for clarity).

In the molecule of (II), the central six-membered ring is nearly planar (rmsd 0.013 Å). The value of the torsion angle C8B–C7B–C5B–C10B (defined as ψ in Scheme 1) is 179.9(4)°, indicating that the allyl and cyclopentenyl substituents bonded to C5B adopt a *trans* conformation along the C7B–C5B bond. The cyclopentenyl was found to be disordered over two orientations with the two disorder components (occupancy ratio 0.65:0.35) being related by a rotation of approximately 180° about the C5B–C10B bond to the pyrimidine ring (Figure 2). Although the existence of four polymorphic forms of cyclopentobarbital (II) has been reported [20], the crystal structure of only one of these has been determined so far [21]. Its two independent molecules differ fundamentally in terms of the torsion angle ψ (Scheme 1). One molecule displays the same *trans* geometry of the ring substituents (ψ = 169.1°) as the cocrystal (I)·(II), whilst the corresponding arrangement in the second molecule is *gauche* (ψ = -44.0°). In addition, the cyclopentenyl group of the first molecule shows a disorder similar to that found in (I)·(II).

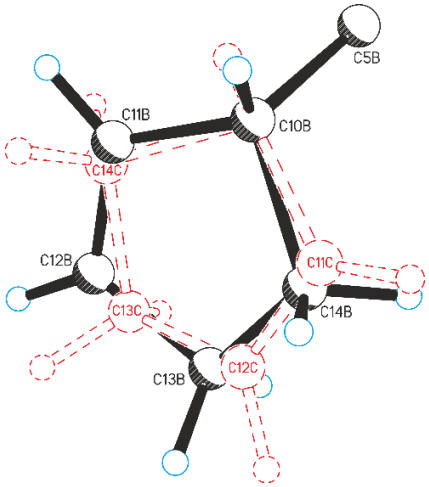

Figure 2. Disorder of the cyclopentenyl ring involving two components, (C10B > C14B; solid lines) and (C10B, C11C > C14C; dashed lines) related by a rotation about the bond C5B–C10B to the pyrimidine ring.

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The central six-membered ring of (II) bears two NH groups which form N1B—H1B···N1A and N3B—H3B···O2A($-x$, y – 1/2, $-z$ + 1/2) bonds to the piperidine and hydroxyl groups belonging to two different codeine molecules (Table 2). These two interactions result in a H-bonded chain of alternating cyclopentobarbital and codeine molecules along the crystallographic b axis (Figure 3, left). Additionally, the OH group of each codeine molecule forms an O2A—H2A···O1A(x – 1/2, $-y$ + 1/2, $-z$) interaction with the methoxy-O atom of a second codeine molecule related to the former by a two-fold screw operation along the a axis (Figure 3, right). Altogether, a H-bonded framework structure is formed (Figure 4). This framework can also be considered as a topological net with H-bonds as the vertices and the molecules of (I) and (II) serving as four- and two-connected nodes, respectively. In this context, single-point connections link each node of (I) to two neighboring nodes of (I) as well as two neighboring nodes of (II), whereas no connections exist between any two nodes of (II).

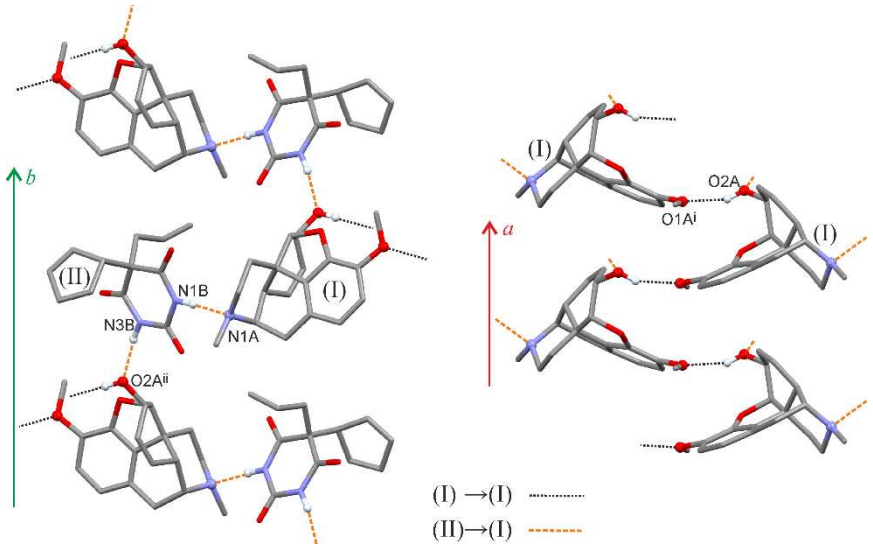

Figure 3. Two fragments of the H-bonded framework of (I)·(II). Left: N1B—H1B···N1A and N3B—H3B···O2A^{ii} bonds resulting in a chain of alternating cyclopentobarbital and codeine molecules which propagates parallel to the b axis. Right: O2A—H2A···O1A^{i} bonded chain formed exclusively by codeine molecules and extending along the a axis (H atoms not engaged H-bond interactions omitted for clarity). Symmetry codes: (i) x–1/2, $-y$+1/2, $-z$; (ii) $-x$, y–1/2, $-z$+1/2.

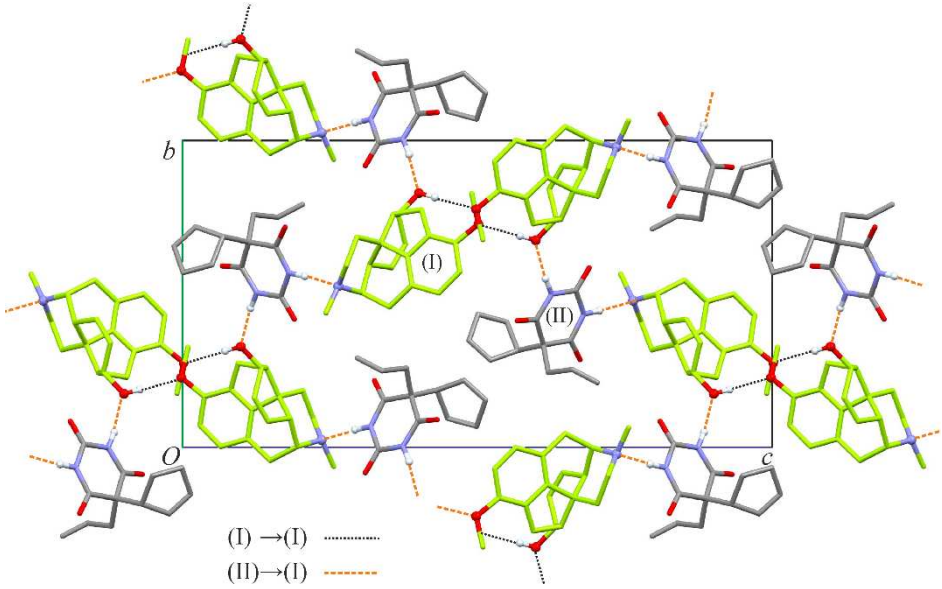

Figure 3. Framework of H-bonded codeine (I) and cyclopentobarbital (II) molecules, viewed along the crystallographic a axis [molecules of (I) highlighted green; H atoms not engaged H-bond interactions omitted for clarity].

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Table 2. Hydrogen bonds (Å and °).

D—H···*A*	d_{D-H}	$d_{H\cdots A}$	$d_{D\cdots A}$	<(*DHA*)
O2A—H2A···O1A^{i}	0.838(14)	1.99(3)	2.784(4)	157(6)
N1B—H1B···N1A	0.886(13)	1.974(15)	2.859(5)	176(4)
N3B—H3B···O2A^{ii}	0.881(13)	1.945(18)	2.811(5)	167(5)

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

2.2. Hot-stage microscopy

On heating of prismatic single crystals of (I)·(II), sublimation occurs at approximately 120 °C. Condensation droplets form at 128 °C, and melting of the cocrystal ensues at 139 °C (Figure S3 of the Supporting Information). The melting equilibrium can be adjusted at 140.1 °C. Seeds of the cocrystal in the melt occurred between 100 and 110 °C, with a maximum growth rate of roughly 140 μm min^{-1} (Figure S4 of the Supporting Information).

The investigation of contact preparations (see section 3.3) of the two components (I) and (II) confirmed the formation of the cocrystal from the melt. The eutectic temperatures of the cocrystal (I)·(II) with its two mother compounds were also determined. On heating, the eutectic E2 between II (polymorph I [20]) and the cocrystal occured, as a black strip under polarized light, at 115 °C. The eutectic E1 between (I) and the cocrystal occured at 128 °C. Polymorph I of (II) crystallizes as from the cyclopentobarbital melt. This phase melts completely at 133 °C. The cocrystal (I)·(II), appearing as a birefringent ribbon between the two (eutectic) liquids (Figure 4), melts between 135 and 137 °C, leaving codeine as the only crystalline phase (Figure S5 of the Supporting Information).

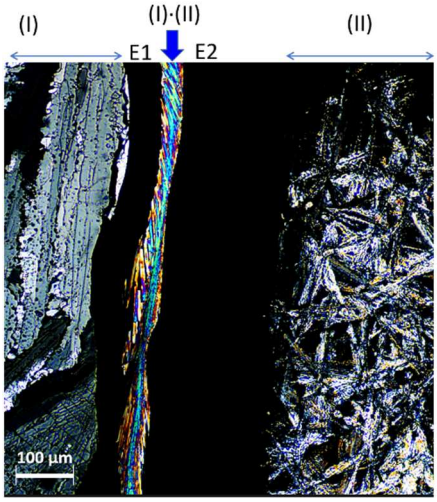

Figure 4. Polarized-light photomicrograph of a contact preparation of codeine (I) with cyclopentobarbital (II; polymorph I). At the center, the contact zone consist of the central cocrystal phase (I)·(II) (arrow) and two surrounding eutectica (E1, E2).

3. Materials and Methods

3.1. Preparation of the cocrystal (I)·(II)

Codeine (I). 20 g of codeine phosphate hemihydrate (Siegfried, Zofingen, Switzerland) were dissolved in 21.5 g of water and 100 ml of NaOH were added to the resulting solution. Drying of the precipitation product for 30 min at 130 °C yielded codeine free base (I) (yield 92.3%).

Cyclopentobarbital (II) was obtained from Alltech, State College, PA, USA.

Cocrystal (I)·(II). The two components were mixed in a 1:1 stoichiometric ratio and dissolved in either EtOH or 2-PrOH. A beige powder or a yellow sticky mass was obtained after evaporation of the solvent at ambient conditions. Treatment of the sticky mass, with a few added drops of an antisolvent (*n*-heptane or *n*-hexane), in a mortar with a pestle yielded the cocrystal (I)·(II). Colourless

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prismatic crystals of (I)·(II) suitable for a single crystal structure determination were obtained by slow evaporation from a 2-PrOH solution containing equimolar amounts of (I) and (II). The cocrystal product was characterized by powder X-ray diffraction, differential scanning calorimetry and FTIR spectroscopy. The corresponding results are shown in Figures S1, S2 and S6, respectively, of the Supporting Information along with reference data for the neat compounds (I) and (II). Thermoanalytical data of the cocrystal are collected in Table S2 of the Supporting Information.

3.2. Single-crystal structure determination

Intensity data were collected at 193 K, using Cu radiation (λ = 1.54184 Å), on an Oxford Diffraction Gemini-R Ultra diffractometer. The data were corrected for absorption effects by means of comparison of equivalent reflections. The crystal structure was solved by Direct Methods with SHELXT [21] and refined with least-squares techniques using SHELXL [22]. H atoms were identified in difference-Fourier maps and those bonded to carbon atoms were refined using a riding model with U_{iso} parameters set to 1.2U_{eq} of the parent C atom (1.5U_{eq} for the methyl groups C17 and C18). The H positions in NH and OH groups were refined with distance restraints, N–H = 0.88(1) Å and N–O = 0.84(1) Å, and their U_{iso}(H) parameters were refined freely. The two disorder components of the cyclopentenyl ring (*i.e.*, C11B > C14B / C11C > C14C) were refined using restraints on chemically equivalent 1,2- and 1,3-distances. The bond distances of the pair C14B–C15B and C14C–C15C were restrained to 1.55(1) Å whilst those of the pair C11B–C12B and C11B–C12B were restrained to 1.32(1) Å. Soft restraints (SIMU) were applied on the anisotropic displacement parameters of the atoms in the two disorder components. The absolute structure was assigned with reference to the known absolute structure of the codeine molecule [absolute structure (Flack) parameter -0.3(3)]. CCDC 2278182 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

3.3. Hot stage microscopy and contact preparation method

Hot stage microscopy investigations were performed with a Reichert Thermovar® polarization microscope equipped with a Kofler hot stage (both Reichert, Vienna, Austria). The temperature was measured with a digital thermometer (Fluke 51 II) and the temperature calibration was performed with WHO melting point standards.

The contact preparation allows to quickly identify whether two meltable compounds form either a eutectic, a cocrystal (molecular compound) or a solid solution. The preparation was performed according to A. Kofler and L. Kofler [23,24], starting with melting a small amount of the higher melting component between a glass slide and a cover slip using a Kofler hot-bench (Reichert, Vienna, Austria). The sample is allowed to crystallize on cooling down and should fill the gap between slide and cover slip only partially. The lower-melting component is then placed on the opposite side of the preparation (empty space between glass slides) and is also melted on a hot bench until its melt is in contact with the higher melting component, resulting in a mixture of the two components within the contact zone. The second component should crystallize on cooling as well as the contact zone. To induce crystallization of the cocrystal (I)·(II), the contact zone was seeded seeds of (I)·(II) harvested from the edges of the cover slip.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Figure S1: Powder X-ray diffractograms; Figure S2: DSC traces; Figure S3: Photomicrographs of the cocrystal (I)·(II); Figure S4: Microscopic film preparation showing the growth of the cocrystal (I)·(II) in the melt; Figure S5: Polarized-light photomicrographs of a contact preparation; Figure S6: FTIR spectra; Table S1: Torsion angle τ (°) and the angle formed by the mean planes defined by the rings A/B/C and D/E (°) in solid forms of codeine; Table S1: Thermoanalytical data of the cocrystal (I)·(II); crystallographic information file (CIF); checkcif report.

Author Contributions: Conceptualization, U.J.G.; formal analysis, J.S., T.G. and U.J.G; investigation, J.S. and T.G.; writing—original draft preparation, T.G.; writing—review and editing, T.G., J.S and U.J.G. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: CCDC 2278182 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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Conflicts of Interest: The authors declare no conflict of interest.

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