The structure of a confiscated street drug: 6-Monoacetyl morphine hydrochloride trihydrate - C₁₉H₂₂NO₄Cl·3H₂O

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ABSTRACT

Since street drugs are frequently and rapidly modified, in order to circumvent the current laws that make them illicit, it is necessary to fully identify them by single crystal X-ray diffraction; subsequently, ideal powder patterns are computed for rapid identification of additional confiscations, which are mostly available in powder form. Monoacetyl morphine is found in samples of heroin as a by-product of incomplete synthesis, or from degradation of diacetyl morphine caused by heat, humidity, or pH changes. It is formed by the hydrolysis of the acetyl function on the benzene moiety of the morphine ring, thereby inserting an OH moiety at that site. This compound, 6-monoacetyl morphine, is the primary and active metabolite of heroin, rapidly hydrolyzed in the user’s blood. Herein, we describe the structure of 6-monoacetyl morphine, IUPAC name: [(4R,4aR,7S,7aR,12bS) -9-hydroxy-3,6α,4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl] acetate (A), as the trihydrated hydrochloride, whose structure has not been described previously. Our crystals belong in space group P2₁2₁2₁ with cell parameters of a = 6.9367(2) Å, b = 13.0374(3) Å, c = 21.9856(6) Å; its composition is C₁₉H₂₂NO₄Cl·3H₂O, and Z = 4. A full sphere of data was collected at 100 K using CuKα radiation (λ = 1.54178 Å), yielding 3594 unique reflections measured and a final R-factor = 4.1%, with a Flack parameter = 0.05(1).

1. Introduction

In the past, we have determined [1-3] the structure of confiscated street drugs in order to add them to the list of illicit substances examined by law-enforcing agencies. The current species is a tri-hydrated, 6-mono-acetylated derivative of morphine that has not previously been characterized. This compound is important in forensic toxicology casework as 6-monoacetyl morphine is the primary and active metabolite of heroin, which is rapidly hydrolyzed in the user’s blood [4,5]. It constitutes an interesting crystalline example of hydrogen bonding by water since, in this lattice, water acts as both an acid and as a base, confirming its amphoteric nature and its ability to form highly crystalline, useful crystallographic specimens by its ambidextrous ability to link suitable substrates through strong hydrogen bonds. Finally, in the published record, there is only one example [6,7] of a hydrated acetylated form of morphine, which is a di-acetyl mono-hydrated species appearing in CSD [7] as FAZDAM, determined at 296 K, crystallizing in the trigtoral space group P4₁2₁2₁; Z = 8.0. There also is the structure of a closely-related derivative of morphine, 6-azoxy-4,5-epoxy-3-methoxy-17-methylmorphin-7-ene, that has been determined at two different temperatures [8,9]. They are listed in the CSD as DATCEH (90 K) [7,8] and DATCEHO1 (RT) [7,9].

2. Experimental

2.1. Preparation of the crystalline sample

A specimen of 6-monoacetyl morphine was obtained from a law enforcement seizure of suspected heroin (diacetyl morphine). A few milligrams of a specimen assumed to be heroin were dissolved on a glass slide in H₂O and diluted (~1 M) HCl was added. Upon evaporation, crystals of 6-acetyl morphine hydrochloride trihydrate (A) formed, as documented below.

2.2. Single crystal X-ray diffraction collection

A suitable crystal of compound A was mounted on a Bruker-AXS SMART APEX II CCD diffractometer at 100(1) K in a Cryoloop using Paratone-N oil. The cell dimensions and intensities were measured with CuKα radiation (λ = 1.54178 Å). Data processing, Lorentz-polarization, and face-indexed numerical absorption corrections were performed using SAINT, APEX, and more.

https://dx.doi.org/10.5155/eurjchem.12.1.52-55
Table 1. Crystal data and structure refinement for compound A.

| Empirical formula | C_{19}H_{22}NO_4Cl, 3H_2O |
|-------------------|-----------------------------|
| Formula weight    | 417.87                      |
| Temperature (K)   | 100(2)                      |
| Crystal system    | Orthorhombic                |
| Space group       | P2_12_12                   |
| a (Å)             | 6.9367(2)                   |
| b (Å)             | 13.0374(3)                  |
| c (Å)             | 21.9856(6)                  |
| α (°)             | 90                          |
| β (°)             | 90                          |
| γ (°)             | 90                          |
| Volume (Å^3)      | 1988.30(9)                  |
| Z                 | 4                           |
| \(\rho_{calc}\) (g/cm^3) | 1.396                  |
| \(\mu\) (mm^{-1}) | 2.066                      |
| F(000)            | 888.0                       |
| Crystal size/mm^3 | 0.209 × 0.121 × 0.101       |
| Radiation         | CuKα (\(\lambda = 1.54178\))|
| 2θ range for data collection (°) | 8.042 to 138.232          |
| Index ranges      | -8 ≤ h ≤ 8, -15 ≤ k ≤ 15, -26 ≤ l ≤ 26 |
| Reflections collected | 18382                  |
| Independent reflections | 3594 [R(int) = 0.0517, R(sigma) = 0.0456] |
| Data/restraints/parameters | 3594/7/271               |
| No. of observed \((I>2\sigma(I))\) reflections | 3181                     |
| Tmin, Tmax        | 0.710, 0.849               |
| Absorption correction | Numerical                  |
| (\(\sin \theta/\lambda\))_{max} (Å^{-1}) | 0.606                   |
| Goodness-of-fit on \(F^2\) | 1.037                     |
| Final R indexes \([l>2\sigma(l)]\) | R_1 = 0.0414, wR_2 = 0.0984 |
| Final R indexes \(all data\) | R_1 = 0.0489, wR_2 = 0.1026 |
| Largest diff. peak/hole / (e Å^{-3}) | 0.50/0.44                |
| Flack parameter   | 0.05(1)                     |
| CCDC number       | 2054880                     |
| Computer programs | Bruker (2008) SAINT, APEX, SADABS, Sheldrick (2015) SHELXL [11,12], Putz & Brandenburg (2019) DIAMOND [13]. |

Table 2. Bond Lengths for compound A.

| Atom   | Atom | Length (Å) | Atom   | Atom | Length (Å) |
|--------|------|------------|--------|------|------------|
| C1     | C13  | 1.375(4)   | C6     | C5   | 1.546(5)   |
| C1     | C13  | 1.467(4)   | C5     | C10  | 1.528(5)   |
| C10    | C18  | 1.345(5)   | C11    | C12  | 1.384(5)   |
| C10    | C11  | 1.491(5)   | C16    | C12  | 1.397(5)   |
| C9     | C14  | 1.450(4)   | C11    | C10  | 1.500(5)   |
| C9     | C14  | 1.366(4)   | C12    | C10  | 1.780(5)   |
| C9     | C14  | 1.500(5)   | C2     | C3   | 1.532(5)   |
| N1     | C1    | 1.523(5)   | C2     | C1   | 1.543(5)   |
| N2     | C18  | 1.211(5)   | C15    | C16  | 1.508(5)   |
| N3     | C12  | 1.376(5)   | C3     | C4   | 1.520(5)   |
| N4     | C14  | 1.392(5)   | C7     | C8   | 1.324(5)   |
| N5     | C15  | 1.396(5)   | C1     | C9   | 1.542(5)   |
| C6     | C7   | 1.503(5)   | C18    | C19  | 1.486(6)   |
| C6     | C2   | 1.544(5)   | C8     | C8   | 1.508(5)   |

Figure 1. N1 is the protonated site, whose proton links the individual 6-monoacetyl-morphine cations via chlorides and waters. O1 and O4 are hydrogen-bonded in a bidentate form to water O5, which is acting as both an acid and a base; also, O6 and O7 act as both hydrogen donors and acceptors.

SADABS computer programs [10-12] and those data are given in Table 1. The structure was solved by direct methods and refined by full-matrix least-squares methods on \(F^2\), using the SHELXTL V6.14 program package, Table 1 [13,14]. All non-hydrogen atoms were refined anisotropically. All H atoms were found in electron-density difference maps and allowed to ride on their respective C, N, or O atoms with thermal displacement parameters fixed at 1.2Ueq(C), 1.5Ueq(N), and 1.5Ueq(O). The numbers in parentheses are the errors in the least significant digit.
adds to the coherence of the lattice. Also note that the phenyl rings of the drug are oriented in a way to form \( \pi \)-\( \pi \) bonds, separated by an \( \pi \)-translation (ca. 6.94 Å), which is substantial and adds to the coherence of the lattice.

Figures were drawn using the graphics program DIAMOND [15]. The crystallographic data have been deposited in the Cambridge Crystallographic Data Center; the deposition number is 2054880 and is given in Table 1.

### 3. Results and discussion

In the crystalline state, the mono-acetylated morphinium cations are hydrogen-bonded to one another through three water molecules and the chloride counter-anion in an infinite fashion as shown in **Figure 1**. Bond lengths and angles are given in Tables 2 and 3. In Table 4, we list some of the strongest hydrogen bonds present in the lattice to quantify the above assertions.

#### 3.1. Packing of the acetyl morphine cations and water-chloride-cluster anions

An interesting observation, suggested by a referee, upon observation of **Figure 1**, is that the entire lattice may be a massively hydrogen-bonded ensemble. Indeed, such is the case and the result is displayed in **Figure 2**.

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**Table 3. Bond Angles for compound A.**

| Atom | Atom | Atom | Angle (°) | Atom | Atom | Atom | Angle (°) |
|------|------|------|----------|------|------|------|----------|
| C10  | O1   | C1   | 107.3(3) | C12  | C2   | C3   | 112.0(3) |
| C17  | O3   | C9   | 116.3(3) | C12  | C2   | C1   | 108.8(3) |
| C12  | N1   | C4   | 110.9(3) | C3   | C2   | C1   | 118.6(3) |
| C12  | C11  | O5   | 113.8(3) | C12  | C2   | C6   | 106.6(3) |
| C12  | O7   | C5   | 113.0(3) | C3   | C2   | C6   | 109.1(3) |
| O1   | N1   | C12  | 111.9(3) | C3   | C2   | C6   | 117.4(3) |
| O1   | C13  | C14  | 127.2(3) | C12  | C1   | C6   | 112.9(3) |
| O1   | C13  | C14  | 120.8(3) | C4   | C3   | C2   | 112.3(3) |
| O4   | C14  | C13  | 125.4(3) | C8   | C7   | C6   | 120.1(3) |
| O4   | C14  | C15  | 118.0(3) | O1   | C1   | C9   | 111.3(3) |
| C7   | C6   | C2   | 110.3(3) | C9   | C1   | C2   | 112.7(3) |
| C7   | C6   | C5   | 113.9(3) | C11  | C10  | C5   | 114.2(3) |
| C2   | C6   | C5   | 110.7(3) | C15  | C16  | C11  | 120.8(3) |
| C1   | C5   | C10  | 112.2(3) | N1   | C4   | C3   | 111.1(3) |
| N1   | C5   | C6   | 106.6(3) | O2   | C18  | O3   | 122.6(4) |
| C10  | C5   | C6   | 115.1(3) | O2   | C18  | C19  | 125.6(4) |
| C12  | C11  | C16  | 115.8(3) | O3   | C18  | C19  | 111.7(4) |
| C12  | C11  | C10  | 118.9(3) | C3   | C18  | O3   | 106.0(3) |
| C16  | C11  | C10  | 124.9(3) | O3   | C9   | C1   | 111.7(3) |
| C13  | C12  | C11  | 123.4(3) | C8   | C9   | C1   | 115.1(3) |
| C13  | C12  | C2   | 109.6(3) | C7   | C8   | C9   | 121.7(3) |
| C11  | C12  | C2   | 126.7(3) | C1   | C1   | C3   | 118.4(3) |

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**Table 4. Hydrogen bonding in structure A.**

| D-H···A | d(D-H) (Å) | d(H···A) (Å) | z | D-H···A (°) | d(D-A) (Å) |
|---------|------------|-------------|---|-------------|------------|
| 04-H4Å--O5 | 0.840 | 1.774 | 168.54 | 2.603(4) |
| 06-H22Å--C11 | 0.837 | 2.355 | 163.89 | 3.167(2) |
| 06-H23Å--C11 | 0.849 | 2.254 | 163.44 | 3.073(17) |
| 06-H23Å--O15 | 0.880 | 2.217 | 168(3) | 3.081(3) |
| 05-H20Å--O7 | 0.840 | 1.927(15) | 165(6) | 2.747(4) |
| 05-H21Å--O1 | 0.840 | 2.504 | 110(4) | 2.920(4) |
| 05-H21Å--O2 | 0.840 | 2.201(3) | 145(4) | 2.925(5) |
| 07-H24Å--C11 | 0.840 | 2.31(2) | 160(5) | 3.115(3) |
| 07-H25Å--O6 | 0.840 | 1.931 | 162(5) | 2.743(4) |

$\alpha = x+1/2$, $y = y+1/2$, $z = z+1$; $\beta = x, y+1, z$; $\gamma = x+1/2$, $y = y+1/2$, $z = z+1$; $\delta = x-1, y, z$. 

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**Figure 2.** Fused pentagonal clusters in the form of pleated sheets extend in the \( a \)-direction while acting as linkages to hydrogen-bonded acetyl morphinium cations. Also note that the phenyl rings of the drug are oriented in a way to form \( \pi \)-\( \pi \) bonds, separated by an \( \alpha \)-translation (ca. 6.94 Å), which is substantial and adds to the coherence of the lattice. 

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4. Conclusions

Above, we describe a new form of monoacetylated morphine in order to totally document its composition and structure in crystalline form, as obtained in a drug seizure and prepared for X-ray diffraction as described above. Its powder diffraction can readily be computed by the coordinates available in the CIF document previously deposited, Figure 3 (CCDC 2054880 [7]). Morphine has been modified by a variety of substitution methods, some of which are very useful acetylated forms [6,16,17], these are available in the CSD database [7].

Acknowledgements

We acknowledge interesting conversations on this topic with colleagues at our respective institutions and to the National Science Foundation for NSF-CRIF Grant No. 0443538 for part of the purchase of the X-ray diffractometer. We are pleased to acknowledge the contribution of a referee who pointed out to us the attractive feature of the water-chloride clusters in these crystals. It is refreshing to have such positive and useful observations.

Supporting information

CCDC-2054880 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

Funding

We acknowledge the National Science Foundation for NSF-CRIF Grant No. 0443538 for part of the purchase of the X-ray diffractometer.

Disclosure statement

Conflict of interest: The authors have declared that no competing interests exist.

Author contributions: Matthew R. Wood, Ivan Bernal and Roger Lalancette wrote the manuscript. Competing interests: The authors have declared that no competing interests exist. Ethical approval: All ethical guidelines have been adhered.

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Figure 3. Powder pattern of compound A generated from single crystal data.