European Journal of Chemistry 12 (1) (2021) 52-55

European Journal of Chemistry

ATLANTA PUBLISHING HOUSE

View Journal Online
View Article Online

The structure of a confiscated street drug: 6-Monoacetyl morphine hydrochloride trihydrate - $C_{19}H_{22}NO_4Cl\cdot3H_2O$

Matthew R. Wood [1], Ivan Bernal [1,2] and Roger A. Lalancette [1,*]

[1] *Carl A. Olson Memorial Laboratories, Department of Chemistry, Rutgers University, 73 Warren St., Newark, NJ, 07102 USA*
matthewr.wood@gmail.com (M.R.W.), bernalibg@gmail.com (I.B.), roger.lalancette@gmail.com (R.A.L.)
[2] *Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, Private Bag 3, 2050 Johannesburg ZA South Africa*

* *Corresponding author at: Carl A. Olson Memorial Laboratories, Department of Chemistry, Rutgers University, 73 Warren St., Newark, NJ, 07102 USA.*
e-mail: roger.lalancette@gmail.com (R.A. Lalancette).

RESEARCH ARTICLE

10.5155/eurjchem.12.1.52-55.2077

Received: 22 January 2021
Received in revised form: 10 February 2021
Accepted: 18 February 2021
Published online: 31 March 2021
Printed: 31 March 2021

KEYWORDS

Heroin
Morphine
Pi-pi bonds
Water clusters
Hydrogen bonds
Water amphoterism

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-methyl-2,4,4a,7,7a,13-hexahydro-1*H*-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 $P2_12_12_1$ with cell parameters of a = 6.9367(2), b = 13.0374(3), c = 21.9856(6) Å, V = 1988.30 (9) Å^3; its composition is $C_{19}H_{22}NO_4Cl\cdot3H_2O$, and Z = 4.0. 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).

Cite this: *Eur. J. Chem.* **2021**, *12(1)*, 52-55 **Journal website**: www.eurjchem.com

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 tetragonal space group $P4_12_12_1$, Z = 8.0. There also is the structure of a closely-related derivative of morphine, 6α-acetoxy-4, 5α-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 DATCEH01 (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 H_2O and diluted (~1 M) HCl was added. Upon evaporation, crystals of 6-acetylmorphine 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

https://dx.doi.org/10.5155/eurjchem.12.1.52-55.2077

Table 1. Crystal data and structure refinement for compound **A**.

Empirical formula	$C_{19}H_{22}NO_4$, Cl, $3H_2O$
Formula weight	417.87
Temperature (K)	100(2)
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
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
ρ_{calc} (g/cm^3)	1.396
μ (mm^{-1})	2.066
F(000)	888.0
Crystal size/mm^3)	0.209 × 0.121 × 0.101
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection (°)	8.042 to 138.232
Index ranges	$-8 \le h \le 8$, $-15 \le k \le 15$, $-26 \le l \le 26$
Reflections collected	18382
Independent reflections	3594 [R_{int} = 0.0517, R_{sigma} = 0.0456]
Data/restraints/parameters	3594/7/271
No. of observed [I>2σ(I)] reflections	3181
T_{min}, T_{max}	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 [I≥2σ (I)]	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)
O1	C13	1.375(4)	C6	C5	1.546(5)
O1	C1	1.467(4)	C5	C10	1.528(5)
O3	C18	1.345(5)	C11	C12	1.384(5)
O3	C9	1.450(4)	C11	C16	1.397(5)
O4	C14	1.366(4)	C11	C10	1.500(5)
N1	C17	1.491(5)	C12	C2	1.498(5)
N1	C4	1.500(5)	C2	C3	1.532(5)
N1	C5	1.523(5)	C2	C1	1.543(5)
O2	C18	1.211(5)	C15	C16	1.380(5)
C13	C12	1.376(5)	C3	C4	1.520(5)
C13	C14	1.392(5)	C7	C8	1.324(5)
C14	C15	1.396(5)	C1	C9	1.542(5)
C6	C7	1.503(5)	C18	C19	1.486(6)
C6	C2	1.544(5)	C9	C8	1.508(5)

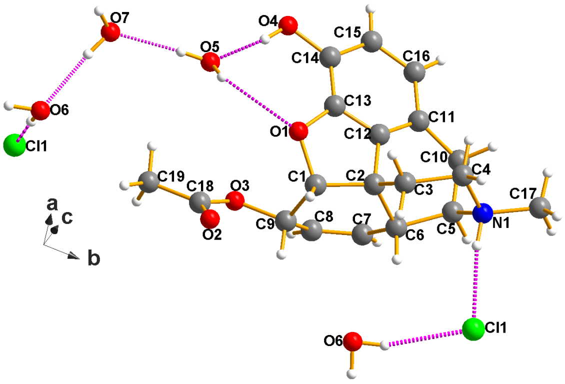

Figure 1. N1 is the protonated site, whose proton links the individual 6-monoacetyl-morphine cations via chlorides and waters. O1 and O4 are hydrogen-bonded in a bidentate form to water O5, which is acting as both an acid and a base; also, O6 and O7 act as both hydrogen donors and acceptors.

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), 1.2Ueq(N), and 1.5Ueq(O). The numbers in parentheses are the errors in the least significant digit.

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

Atom	Atom	Atom	Angle (°)	Atom	Atom	Atom	Angle (°)
C13	O1	C1	107.3(3)	C12	C2	C3	112.0(3)
C18	O3	C9	116.3(3)	C12	C2	C1	100.8(3)
C17	N1	C4	110.9(3)	C3	C2	C1	110.6(3)
C17	N1	C5	113.8(3)	C12	C2	C6	106.6(3)
C4	N1	C5	113.0(3)	C3	C2	C6	109.1(3)
O1	C13	C12	111.9(3)	C1	C2	C6	117.4(3)
O1	C13	C14	127.2(3)	C16	C15	C14	122.9(3)
C12	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	118.8(3)	O1	C1	C9	111.3(3)
C13	C14	C15	115.8(3)	O1	C1	C2	105.5(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	107.0(3)	C15	C16	C11	120.8(3)
N1	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)	O3	C9	C8	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)				

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

D–H···A	d(D–H) (Å)	d(H···A) (Å)	∠D–H···A (°)	d(D···A) (Å)
O4-H4···O5	0.840	1.774	168.54	2.603(4)
O6-H22···Cl1 i	0.837	2.355	163.89	3.1672(16)
O6-H23···Cl1	0.849	2.254	163.44	3.0773(17)
N1-H3···Cl1	0.880	2.217	168(3)	3.083(3)
O5-H20···O7 ii	0.840	1.927(15)	165(6)	2.747(4)
O5-H21···O1	0.840	2.504	110(4)	2.902(4)
O5-H21···O2 iii	0.840	2.20(3)	145(4)	2.925(5)
O7-H24···Cl1 iv	0.840	2.31(2)	160(5)	3.115(3)
O7-H25···O6	0.840	1.931	162(5)	2.743(4)

i = *x*-1/2, -*y*+1/2, -*z*+1; ii = *x*, *y*+1, *z*; iii = *x*+1/2, -*y*+1/2, -*z*+1; iv = *x*-1, *y*, *z*.

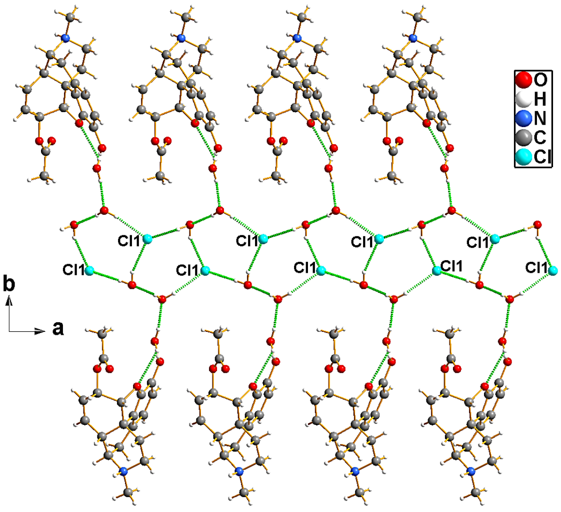

Figure 2. Fused pentagonal clusters in the form of pleated sheets extend in the *a*-direction while acting as linkages to hydrogen-bonded acetyl morphinium cations. Also note that the phenyl rings of the drug are oriented in a way to form pi-pi bonds, separated by an *a*-translation (ca. 6.94 Å), which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

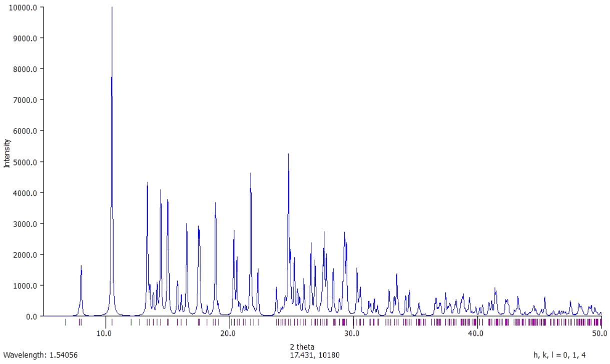

Figure 3. Powder pattern of compound **A** generated from single crystal data.

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 S

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 DS

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.

ORCID iD

Matthew R. Wood
iD https://orcid.org/0000-0001-9579-5317
Ivan Bernal
iD https://orcid.org/0000-0002-8168-5907
Roger Lalancette
iD https://orcid.org/0000-0002-3470-532X

References

[1]. Wood, M. R.; Lalancette, R. A.; Bernal, I. *Acta Crystallogr. C* **2015**, *71 (1)*, 32–38.
[2]. Wood, M. R.; Bernal, I.; Lalancette, R. A. *Acta Crystallogr. C* **2016**, *72 (1)*, 48–51.
[3]. Wood, M. R.; Bernal, I.; Lalancette, R. A. *Struct. Chem.* **2017**, *28 (5)*, 1369–1376.
[4]. Andersen, J. M.; Ripel, A.; Boix, F.; Normann, P. T.; Morland, J. *J. Pharmacol. Exp. Ther.* **2009**, *331 (1)*, 153–161.
[5]. Boix, F.; Andersen, J. M.; Morland, J. *Addiction Biology* **2011**, *18 (1)*, 1–7.
[6]. Balchin, E.; Malcolme-Lawes, D. J.; Rowe, M. D.; S. Smith, J. A.; Bearpark, M. J.; Steed, J. W.; Wu, W.; Horsewill, A. J.; Stephenson, D. *New J. Chem.* **2004**, *28 (11)*, 1309-1314.
[7]. Cambridge Structural Database CCSD (2019), http://www.ccdc.cam.ac.uk, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
[8]. Sonar, V. N.; Parkin, S.; Crooks, P. A. *Acta Crystallogr. E* **2005**, *61 (8)*, o2579–o2581.
[9]. Kolev, T.; Bakalska, R.; Shivachev, B.; Petrova, R. *Acta Crystallogr. E* **2005**, *61 (8)*, o2582–o2584.
[10]. Bruker (2008). SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.
[11]. Bruker (2009). APEX2. Bruker AXS Inc., Madison, Wisconsin, USA.
[12]. Sheldrick, G. M. SADABS. University of Gottingen, Germany, 1996.
[13]. Sheldrick, G. M. *Acta Crystallogr. A* **2015**, *71 (1)*, 3–8.
[14]. Sheldrick, G. M. *Acta Crystallogr. C* **2015**, *71 (1)*, 3–8.
[15]. Diamond - Crystal and Molecular Structure Visualization, Crystal Impact - H. Putz and K. Brandenburg GbR, Kreuzherrenstr. 102, 53227 Bonn, Germany
[16]. Canfield, D.; Barrick, J.; Giessen, B. C. *Acta Crystallogr. B* **1979**, *35 (11)*, 2806–2809.
[17]. Deschamps, J. R.; George, C.; Flippen-Anderson, J. L. *Acta Crystallogr. C* **1996**, *52 (3)*, 698–700.