NMIA D766c: 3-Monoacetylmorphine sulfamate

Report ID: D766c.2022.01 (Bottled 150520)

Chemical Formula: C19H21NO4.H3NSO3

Molecular Weight: 424.5 g/mol (sulfamate), 327.4 g/mol (base)

# Property value

|  |  |  |
| --- | --- | --- |
| **Batch No.** | **CAS No.** | **Purity estimate** |
| **15-D-08** | **62319-25-9 (sulfamate)**  **5140-28-3 (base)** | **97.1 ± 1.4%** |

IUPAC name: (5α,6α)-6-Hydroxy-17-methyl-7,8-didehydro-4,5-epoxymorphinan-3-yl acetate, sulfamate.

Expiration of certification: The property values are valid till 23 September 2027, i.e. five years from the date of re-certification provided the **unopened** material is handled and stored in accordance with the recommendations below. The material as issued in the unopened container and stored as recommended below should be suitable for use beyond this date, subject to confirmation of batch stability from the issuing body. The expiry date/shelf life does not apply to sample bottles that have been opened. In such cases it is recommended that the end-user conduct their own in-house stability trials.

**Description:** White solid prepared by synthesis, and certified for identity and purity by NMIA. Packaged in amber glass bottles with a septum and crimped aluminium cap or screw top cap.

Intended use: This reference material is recommended for qualitative analysis only.

**Instructions for use:** Equilibrate the bottled material to room temperature before opening.

Recommended storage: When not in use this material should be stored at or below 25 ºC in a closed container in a dry, dark area.

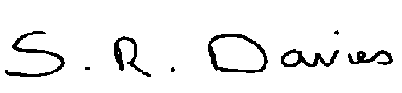
Metrological traceability: The certified purity value is traceable to the SI unit for mass (kg) through Australian national standards via balance calibration. In the mass balance approach all impurities are quantified as a mass fraction and subtracted from 100%. Quantitative NMR provides an independent direct measure of the mass fraction of the analyte of interest, calibrated with an internal standard certified for purity (mass fraction).

**Stability:** At the recommended storage conditions this material has demonstrated stability for a period of five years. The measurement uncertainty includes components for long term stability at the recommended storage conditions.

The long-term stability of the compound in solution has not been examined.

Homogeneity assessment: The homogeneity of the material was assessed using purity assay by HPLC with UV detection on ten randomly selected 1-2 mg sub samples of the material. The material was judged to be sufficiently homogeneous at this level of sampling as the variation in analysis results between samples was not significantly different at a 95% confidence level from that observed on repeat analysis of the same sample.

Safety: Treat as a hazardous substance. Use appropriate work practices when handling to avoid skin or eye contact, ingestion or inhalation of dust. Refer to the provided safety data sheet.



Dr Stephen R. Davies,

Team Leader,

Chemical Reference Materials, NMI.

5 January 2023

This report supersedes any issued prior to 05 January 2023.

NATA Accreditation No. 198 / Corporate Site No. 14214.

**Legal notice:** Terms and Conditions associated with the provision of this reference material can be found on the NMIA website.

Characterisation Report:

The identity was confirmed by a range of spectroscopic techniques, NMR, IR and MS. The certified purity value was obtained by mass balance from a combination of traditional analytical techniques, including HPLC with UV detection, thermogravimetric analysis, Karl Fischer analysis, and 1H NMR spectroscopy. The purity value is calculated as per Equation 1.

Purity = (100 % - IORG) x (100 % - IVOL – INVR) Equation 1

IORG = Organic impurities of related structure, IVOL = volatile impurities, INVR = non-volatile residue.

Supporting evidence is provided by quantitative nuclear magnetic resonance (qNMR), using the aromatic proton at 6.9 ppm, measured against a certified internal standard of potassium hydrogen maleate.

**Note: 3-Monoacetylmorphine sulfamate is susceptible to hydrolysis to morphine when dissolved in aqueous solution.**

HPLC: Instrument: Shimadzu Binary pump LC-20AB, SIL-20 A HT auto sampler

Column: X-BridgeC-18, 5 m (4.6 mm x 150 mm)

Column oven: 40 °C

Mobile Phase: A = MilliQ water buffered at pH 10 using 10 mM NH4OAc; B = Acetonitrile

Isocratic 30% B

Flow rate: 1 mL/min

Detector: Shimadzu SPD-M20A PDA operating at 280 nm

Relative mass fraction of the main component:

Initial analysis: Mean = 98.0%, s = 0.05% (5 sub samples in duplicate, September 2022)

HPLC: Instrument: Shimadzu Binary pump LC-20AB, SIL-20 A HT auto sampler

Column: Pursuit XRs C-18, 5 m (4.6 mm x 250 mm)

Column oven: 40 °C

Mobile Phase: A = MilliQ water buffered at pH 4.6 using 20 mM NaH2PO4 and H3PO4; B = Acetonitrile

0-24 min 8-30% B; 24-25 min 30-70% B; 25-29 min 70% B; 29-30 min 70-8% B;

30-35 min 8% B [2015]/0-12 min 15-45% B; 12-13 min 45-80% B; 13-19 min 80% B; 19-20 min 80-15% B; 20-26 min 15% B

Flow rate: 1 mL/min

Detector: Shimadzu SPD-M20A PDA operating at 210 nm [2015]/280 nm [2016]

Relative mass fraction of the main component:

Initial analysis: Mean = 99.7%, s = 0.24% (10 sub samples in duplicate, April 2015)

Re-analysis: Mean = 98.3%, s = 0.04% (5 sub samples in duplicate, July 2016)

Karl Fischer analysis: Moisture content 0.5% mass fraction (April 2015)

Moisture content 0.7% mass fraction (April 2016)

Moisture content 0.5% mass fraction (October 2022)

Thermogravimetric analysis: Volatile content > 0.1% and non-volatile residue < 0.2% mass fraction (April 2015)

QNMR: Instrument: Bruker Avance-III-500

Field strength: 500 MHz

Solvent: D2O (4.79 ppm)

Internal standard: Potassium hydrogen maleate (99.6% mass fraction)

Initial analysis: Mean (5.40 ppm) = 98.3%, s = 0.5% (8 sub samples, April 2015)

Initial analysis: Mean (5.73 ppm) = 98.3%, s = 0.4% (5 sub samples, April 2015)

Initial analysis: Mean (6.8-6.9 ppm) = 98.6%, s = 0.4% (5 sub samples, April 2015)

Re-analysis: Mean (6.9 ppm) = 97.7%, s = 0.6% (5 sub samples, June 2016)

Re-analysis: Mean (6.9 ppm) = 96.6%, s = 0.3% (5 sub samples, June 2017)

**Spectroscopic and other characterisation data**

GC-MS: Instrument: Agilent 6890/5973

Column: TG-1MS, 30 m × 0.25 mm I.D. × 0.25 m

Program: 200 °C (1 min), 7 °C/min to 260 °C, 25 °C/min to 300 °C (3 min)

Injector: 180 °C

Split ratio: 20/1

Transfer line temp: 280 °C

Carrier: Helium, 1.0 mL/min

Scan range: 50-550 *m/z*

The retention time of the free base is reported along with the major peaks in the mass spectrum. The latter are reported as mass/charge ratios and (in brackets) as a percentage relative to the base peak.

Free base (9.6 min): 327 (M+, 94), 310 (7), 285 (100), 215 (35), 162 (51), 124 (19), 115 (19), 81 (17) *m/z*

HS-GC-MS: Instrument: Agilent 6890/5973/G1888

Column: DB-624, 30 m x 0.25 mm I.D. x 1.4 m

Program: 50 °C (5 min), 7 °C/min to 120 °C, 15 °C/min to 220 °C (8.3 min)

Injector: 150 °C

Split ratio: 50/1

Transfer line temp: 280 °C

Carrier: Helium, 1.2 mL/min

Solvents detected: Ethanol, isopropanol

TLC: Conditions: Kieselgel 60F254. MeOH/NH3 (100:1.5)

Single spot observed, Rf = 0.5. Visualisation with UV at 254 nm

IR: Instrument: Bruker Alpha FT-IR

Range: 4000-400 cm-1, neat

Peaks: 3561, 3310, 2975, 2673, 1748, 1620, 1454, 1231, 1211, 1044, 790, 562 cm-1 (This data was first reported in the C of A of D766A)

1H NMR: Instrument: Bruker Avance III 500

Field strength: 500 MHz

Solvent: MeOH-*d*4 (3.31 ppm)

Spectral data:  2.12 (1H, m), 2.27 (3H, s) 2.43 (1H, m), 2.89-3.16 (3H, m), 3.05 (3H, s), 3.28-3.42 (2H, m), 4.21 (1H, dd, *J* = 2.9, *J* = 6.6 Hz), 4.29 (1H, m), 5.00 (1H, dd, *J* = 1.0, *J* = 6.4 Hz), 5.36 (1H, ddd, *J* = 2.5, 2.5, 10.0 Hz), 5.77 (1H, m), 6.74 (1H, d, *J* = 8.2 Hz), 6.87 (1H, d, *J* = 8.2 Hz) ppm

Ethanol and ethyl sulfamate estimated at 0.03% and 0.4% mass fraction respectively were quantified by 1H NMR.

13C NMR: Instrument: Bruker Avance III 500

Field strength: 126 MHz

Solvent: MeOH-*d*4 (49.0 ppm)

Spectral data:  20.5, 41.6, 43.2, 62.1, 67.3, 92.9, 121.0, 123.9, 126.0, 130.5, 131.4, 133.7, 136.1, 151.3, 170.3 ppm (This data was first reported in the C of A of D766a)

Melting point: Sample decomposed > 230 °C

Microanalysis: Found: C = 53.8%; H = 5.6%; N = 6.6%; S = 7.6% (May 2015)

Calculated: C = 53.8%; H = 5.7%; N = 6.6%; S = 7.6% (Calculated for C19H21NO4.H3NSO3)

**Amendment record**

Original report ID: D766c.2015.01 (GT/SRD)

Date of issue: 19 May, 2015

Date of revision: 1 July 2015 (TD/MM)

Revised report ID: D766c.2015.01 (Bottled 150520)

Revisions:

* Report ID updated to show the sampling date of the crimped bottles

Date of revision: 11 July 2016 (SB/MM)

Revised report ID: D766c.2016.01 (Bottled 150520)

Revisions:

* Updated purity value and purity statement
* Added HPLC, QNMR and KF data
* Added HPLC conditions
* Updated expiry date

Date of revision: 9 June, 2017 (SM/GT/MM)

Revised report ID: D766c.2017.01 (Bottled 150520)

Revisions:

* Updated purity value and purity statement
* Added QNMR and KF data

Date of revision: 28 April 2020 (SY/BC)

Revised report ID: D766c.2017.02

Revisions:

* Update report into new template
* Remove uncertainty

Revised report ID: D766c.2017.02 (TD)

Revisions:

* Update bottling date in the footer
* Add-in sulfamate in the IUPAC name

Date of revision: 3 August 2021 (TD)

Revised report ID: D766c.2017.03 (Bottled 150520)

Revisions:

* Update the correct corporate site number

Date of revision: 15 September 2022 (TD)

Revised report ID: D766c.2017.04

Revisions:

* Update to the new template (change departmental name, NATA logo…)

Date of revision: 5 January 2023 (BF/SRD)

Revised report ID: D766c.2022.01

Revisions:

* Routine stability trial. Drop in organic purity and slight drop in water content.
* Relative UV response factor of morphine was reassessed.
* New HPLC method was developed

Date of revision: 30 May 2023 (Staff member/Approver)

Revised report ID: D1083.2023.01

Revisions:

* Routine stability trial. No change in purity.
* Other important information (not detailed in the comments section of the excel workbook)