



CERTIFIED REFERENCE MATERIAL CERTIFICATE OF ANALYSIS

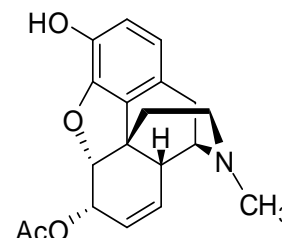
NMIA D777c: 6-Monoacetylmorphine

Report ID: D777c.2020.03 (Bottled 221110)

Chemical Formula: C₁₉H₂₁NO₄

Molecular Weight: 327.4 g/mol

Certified value



Batch No.

CAS No.

Purity (mass fraction)

13-D-04

2784-73-8

98.7 ± 0.5%

The uncertainty has been calculated according to ISO Guide 35 and is stated at the 95% confidence limit ($k = 2$).

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

Expiration of certification: The property values are valid till 21 January 2025, 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 powder 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 certified reference material is suitable for use as a primary calibrator.

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 °C 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: This material has demonstrated stability over a minimum period of three years. The measurement uncertainty at the 95% confidence interval includes a stability component which has been estimated from annual stability trials. 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 GC-FID 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.

S. R. Davies

Dr Stephen R. Davies,
Team Leader,
Chemical Reference Materials, NMI.
5 January 2023

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

CIPM MRA notice: This certificate is consistent with the capabilities that are included in Appendix C of the MRA drawn up by the CIPM. Under the CIPM MRA, all participating institutes recognise the validity of each other's calibration and measurement certificates for the quantities, ranges and measurement uncertainties specified in the KCDB (for details see <http://www.bipm.org/kcdb/>). The "CIPM MRA Logo" and this statement attest only to the measurement(s) applied for determining the certified values on the certificate.

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

Characterisation Report:

The purity value was obtained from a combination of traditional analytical techniques and quantitative nuclear magnetic resonance (qNMR). The techniques used in the mass balance approach include GC-FID, thermogravimetric analysis, Karl Fischer analysis and ¹H NMR spectroscopy. The purity value is calculated as per Equation 1.

$$\text{Purity} = (100\% - I_{\text{ORG}}) \times (100\% - I_{\text{VOL}} - I_{\text{NVR}}) \quad \text{Equation 1}$$

I_{ORG} = Organic impurities of related structure, I_{VOL} = volatile impurities, I_{NVR} = non-volatile residue.

The purity estimate by QNMR was obtained using the two aromatic proton doublets between 6.3-6.5 ppm against a certified internal standard of dimethyl terephthalate.

Supporting evidence is provided by headspace GC-MS analysis of occluded solvents and elemental microanalysis.

GC-FID: Instrument: Agilent 6890N
 Column: HP-1, 30 m × 0.32 mm I.D. × 0.25 μm
 Program: 200 °C (1 min), 4 °C/min to 240 °C, 30 °C/min to 300 °C (3 min)
 Injector: 250 °C
 Detector Temp: 320 °C
 Carrier: Helium
 Split ratio: 20/1
 Relative mass fraction of the main component as the *mono*-TMS derivative:
 Initial analysis: Mean = 99.8%, s = 0.004% (10 sub samples in duplicate, April 2013)

GC-FID: Instrument: Varian CP3800
 Column: HP-1, 30 m × 0.32 mm I.D. × 0.25 μm
 Program: 200 °C (1 min), 4 °C/min to 250 °C, 30 °C/min to 300 °C (3 min)
 Injector: 200 °C
 Detector Temp: 320 °C
 Carrier: Helium
 Split ratio: 20/1
 Relative mass fraction of the main component as the *mono*-TMS derivative:
 Re- analysis: Mean = 99.8%, s = 0.01% (7 sub samples in duplicate, March 2014)
 Re- analysis: Mean = 99.7%, s = 0.05% (4 sub samples in duplicate, February 2017)
 Re- analysis: Mean = 99.9%, s = 0.02% (5 sub samples in duplicate, January 2020)

Thermogravimetric analysis: The volatile content 0.4% and non-volatile residue < 0.1% mass fraction (April 2013)

Karl Fischer analysis: Moisture content 0.3% mass fraction (April 2013)
 Moisture content 0.4% mass fraction (March 2014, February 2017, November 2019)

QNMR: Instrument: Bruker Avance-500
 Field strength: 500 MHz
 Solvent: DMSO-*d*₆ (2.5 ppm)
 Internal standard: Dimethyl terephthalate (100% mass fraction)
 Initial analysis: Mean (6.3-6.5 ppm) = 99.1%, s = 0.4% (4 sub samples, May 2013)

Spectroscopic and other characterisation data

GC-MS:	Instrument:	Agilent 6890/5973
	Column:	TG-1MS, 30 m x 0.25 mm I.D. x 0.25 μ m
	Program:	60 °C (1 min), 10 °C/min to 300 °C (3 min)
	Injector:	250 °C
	Transfer line temp:	280 °C
	Carrier:	Helium, 1.0 mL/min
	Split ratio:	20/1
	The retention times of the parent compound and <i>mono</i> -TMS derivative are 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.	
	Parent (22.2 min):	327 (M ⁺ , 100), 284 (10), 268 (88), 215 (28), 211 (13), 181 (10), 162 (15), 146 (20), 115 (14), 81 (12), 43 (31) <i>m/z</i>
	<i>Mono</i> -TMS (22.7 min):	399 (M ⁺ , 100), 356 (6), 340 (65), 324 (12), 287 (36), 266 (12), 204 (19), 162 (10), 146 (7), 124 (11), 94 (7), 73 (40), 59 (16), 43(19) <i>m/z</i>
HS-GC-MS:	Instrument:	Agilent 6890/5973/G1888
	Column:	DB-624, 30 m x 0.25 mm I.D. x 1.4 μ m
	Program:	50 °C (5 min), 7 °C/min to 120 °C, 15 °C/min to 220 °C (8.3 min)
	Injector:	150 °C
	Transfer line temp:	280 °C
	Carrier:	Helium, 1.2 mL/min
	Split ratio:	50/1
	Solvents detected:	Diethyl ether, dichloromethane
TLC:	Conditions:	Kieselgel 60F ₂₅₄ . Diisopropylether/diethylether /diethylamine (45/45/10) Single spot observed, R _f = 0.2. Visualisation with UV at 254 nm
IR:	Instrument:	Biorad FTS300MX FT-IR
	Range:	4000-400cm ⁻¹ , KBr powder
	Peaks:	3619, 3436, 2928, 1733, 1603, 1451, 1244, 1055, 984, 842, 662, 520 cm ⁻¹
¹ H NMR:	Instrument:	Bruker Avance-400
	Field strength:	400 MHz
	Solvent:	CDCl ₃ (7.26 ppm)
	Spectral data:	δ 1.83 (1H, dm, <i>J</i> = 12.7 Hz), 2.07 (1H, dt, <i>J</i> = 5.0, 12.6 Hz), 2.14 (3H, s), 2.32 (1H, dd, <i>J</i> = 6.2, 18.7 Hz), 2.40 (1H, dt, <i>J</i> = 3.6, 12.4 Hz), 2.45 (3H, s), 2.63 (1H, dd, <i>J</i> = 3.9, 12.2 Hz), 2.76 (1H, quintet, <i>J</i> = 2.9 Hz), 3.03 (1H, d, <i>J</i> = 18.6 Hz), 3.41 (1H, dd, <i>J</i> = 3.3, 6.0 Hz), 5.05 (1H, dd, <i>J</i> = 1.0, 6.5 Hz), 5.14 (1H, m), 5.42 (1H, dt, <i>J</i> = 9.9, 2.5 Hz), 5.59 (1H, doublet of septet, <i>J</i> = 10.1, 1.0 Hz), 6.50 (1H, d, <i>J</i> = 8.1 Hz), 6.62 (1H, d, <i>J</i> = 8.0 Hz) ppm Diethyl ether (0.39%) and dichloromethane (0.41%) estimated mass fraction was observed in the ¹ H NMR (April and May 2013, January 2020)
¹³ C NMR:	Instrument:	Bruker DMX-500
	Field strength:	125 MHz
	Solvent:	CDCl ₃
	Spectral data:	δ 20.8, 21.3, 35.5, 40.8, 43.1, 43.4, 46.9, 59.2, 68.9, 88.7, 117.4, 119.9, 126.2, 128.5, 130.0, 130.5, 138.6, 145.3, 170.9 ppm
Melting point:		192-193 °C
Microanalysis:	Found:	C = 69.6%; H = 6.6%; N = 4.3% (April 2013)
	Calculated:	C = 69.7 %; H = 6.5%; N = 4.3% (for C ₁₉ H ₂₁ NO ₄)