Australian Government
Department of Industry, Science and Resources

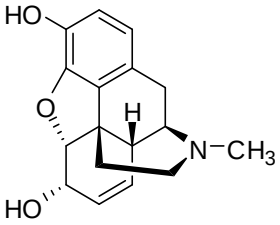
National Measurement Institute

CIPM MRA

NATA
WORLD RECOGNISED ACCREDITATION

CERTIFIED REFERENCE MATERIAL CERTIFICATE OF ANALYSIS

NMIA D408e: Morphine free base



Report ID: D408e.2024.01 (Bottled 180627)

Chemical Formula: $C_{17}H_{19}NO_3$

Molecular Weight: 285.3 g/mol (free base)

Certified value

Batch No.	CAS No.	Purity (mass fraction)
09-D-26	**6009-81-0 (monohydrate)** **57-27-2 (free base)**	**93.5 ± 0.7%**

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

IUPAC name: (5α,6α)-17-Methyl-7,8-didehydro-4,5-epoxymorphinan-3,6-diol

Expiration of certification: The property values are valid till 23 January 2029, 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: Off-white powder sourced from an external supplier 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 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: This material has demonstrated stability over a minimum period of five years. The measurement uncertainty at the 95% coverage 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 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.
25 January 2024

This report supersedes any issued prior to 25 January 2024.

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: Neither NMIA as a representative of the Commonwealth of Australia, nor any person acting on NMIA's behalf, assumes any liability with respect to the use of, or for damages resulting from the use of, this reference material or the information contained in this document.

Characterisation Report:

The identity was confirmed by a range of spectroscopic techniques, NMR, infrared and MS. The certified purity value was obtained by mass balance from a combination of traditional analytical techniques, including GC-FID, thermogravimetric analysis, Karl Fischer analysis and ^{1}H NMR spectroscopy. The purity value is calculated as per Equation 1.

Purity = (100 % - I_{ORG}) x (100 % - I_{VOL} – I_{NVR}) Equation 1

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

Supporting evidence is provided by quantitative NMR and elemental microanalysis.

GC-FID:	Instrument:	Varian CP3800
	Column:	VF-1MS, 30 m × 0.32 mm I.D. × 0.25 μm
	Program:	200 °C (1 min), 4 °C/min to 260 °C (3 mins), 20 °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:	
	Initial analysis:	Mean = 99.8%, s = 0.07% (10 sub samples in duplicate, September 2009)
	Re-analysis:	Mean = 99.7%, s = 0.05% (5 sub samples in duplicate, June 2011)
GC-FID:	Instrument:	Agilent 6890 or 7890
	Column:	HP-1, 30 m × 0.32 mm I.D. × 0.25 μm
	Program:	200 °C (1 min), 4 °C/min to 260 °C (3 min), 20 °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:	
	Re-analysis:	Mean = 99.5%, s = 0.04% (5 sub samples in duplicate, April 2014)
	Re-analysis:	Mean = 99.7%, s = 0.01% (5 sub samples in duplicate, March 2017)
GC-FID:	Instrument:	Varian CP3800
	Column:	HP-1 or HP-5, 30 m × 0.32 mm I.D. × 0.25 μm
	Program:	200 °C (1 min), 5 °C/min to 280 °C (5 min)
	Injector:	200 °C
	Detector Temp:	320 °C
	Carrier:	Helium
	Split ratio:	20/1
	Relative mass fraction of the main component as *bis*-TMS derivative:	
	Initial analysis:	Mean = 99.6%, s = 0.01% (5 sub samples in duplicate, February 2020)
	Re-analysis:	Mean = 99.6%, s = 0.01% (5 sub samples in duplicate, January 2024)
QNMR:	Instrument:	Bruker Avance III 400
	Field strength:	400 MHz
	Solvent:	DMSO-d_6 (2.50 ppm)
	Internal standard:	Dimethyl terephthalate
	Initial analysis:	Mean = 93.5%, s = 0.4% (5 sub samples, September 2011)
Thermogravimetric analysis:		Initial volatile content 6.1 % and non volatile residue < 0.2% mass fraction (September 2009)
Karl Fischer analysis:		Moisture content 6.4% mass fraction (September 2009) Moisture content 6.1% mass fraction (June 2011) Moisture content 5.9% mass fraction (April 2014) Moisture content 6.5% mass fraction (March 2017) Moisture content 6.1% mass fraction (February 2020 and January 2024)

Spectroscopic and other characterisation data

GC-MS:	Instrument:	Agilent 6890/5973
	Column:	DB-1MS 25.0 m × 0.20 mm I.D. × 0.33 μm
	Program:	200 °C (1 min), 4 °C/min to 260 °C, 20 °C/min to 300 °C (3 min)
	Injector:	250°C
	Transfer line temp:	280 °C
	Carrier:	Helium, 1.0 mL/min
	Split ratio:	Split less
	The retention time of the parent compound 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.	
	12.5 min:	285 (M^+, 100), 268 (14), 215 (23), 174 (12), 162 (28), 124 (10), 115 (12) *m/z*
TLC:	Conditions:	Kieselgel 60F_{254}. Methanol/Ammonium solution (28%) (100/1.5) Single spot observed, R_f = 0.6. Visualisation with UV at 254 nm
IR:	Instrument:	Biorad FTS300MX FT-IR
	Range:	4000-400cm^{-1}, KBr powder
	Peaks:	3198, 2940, 1472, 1446, 1247, 1120, 978, 802, 523 cm^{-1}
^{1}H NMR:	Instrument:	Bruker Avance 600
	Field strength:	600 MHz
	Solvent:	MeOH-d_4 (3.31 ppm)
	Spectral data:	δ 1.81 (1H, m), 2.08 (1H, ddd, *J* = 5.1, 12.8, 12.8 Hz), 2.34 (1H, dd, *J* = 6.4, 18.7 Hz), 2.43 (3H, s), 2.45 (1H, ddd, *J* = 3.6, 12.4, 12.4 Hz), 2.60 (1H, dd, *J* = 4.2, 12.3 Hz), 2.65 (1H, m, *J* = 2.8 Hz), 3.03 (1H, d, *J* = 18.8 Hz), 3.38 (1H, dd, *J* = 3.2, 6.3 Hz), 4.18 (1H, m), 4.80 (1H, dd, *J* = 1.2, 6.3 Hz), 5.31 (1H, ddd, *J* = 2.8, 2.8, 9.8 Hz), 5.62 (1H, m), 6.44 (1H, d, *J* = 8.2 Hz), 6.53 (1H, d, *J* = 8.1 Hz) ppm
^{13}C NMR:	Instrument:	Bruker Avance III 400
	Field strength:	400 MHz
	Solvent:	MeOH-d_4 (49.0 ppm)
	Spectral data:	δ 21.6, 36.3, 41.5, 43.1, 44.4, 47.5, 48.4, 48.6, 60.2, 67.9, 92.9, 117.9, 120.5, 127.1, 129.5, 132.0, 133.9, 139.8, 147.4 ppm
Melting point:		257-258 °C
Microanalysis:	Found:	C = 67.3%; H = 7.1%; N = 4.6% (September 2009)
	Calculated:	C = 67.3%; H = 7.0%; N = 4.6% (Calculated for $C_{17}H_{19}NO_3.H_2O$)