Australian Government
Department of Industry, Science and Resources

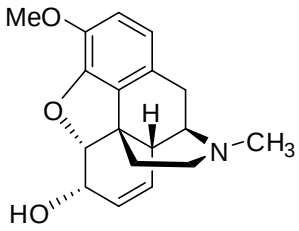
National Measurement Institute

CIPM MRA

NATA
WORLD RECOGNISED ACCREDITATION

CERTIFIED REFERENCE MATERIAL CERTIFICATE OF ANALYSIS

NMIA D671b: Codeine base



Report ID: D671b.2024.01 (Bottled 221214)

Chemical Formula: $C_{18}H_{21}NO_3$

Molecular Weight: 299.4 g/mol

Certified value

Batch No.	CAS No.	Purity (mass fraction)
09-D-13	**76-57-3**	**99.6 ± 0.3%**

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

IUPAC: (5α,6α)-3-Methoxy-17-methyl-7,8-didehydro-4,5-epoxymorphinan-6-ol

Expiration of certification: The property values are valid till 26 September 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: White crystalline powder sourced from an external supplier, 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%.

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 thirteen randomly selected 1-2 mg sub samples of the material. The material was judged to be 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.
1 October 2024.

This report supersedes any issued prior to 01 October 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 CIPM MRA drawn up by the CIPM. Under the CIPM MRA, all participating institutes recognize the validity of each other's calibration and measurement certificates for the quantities, ranges and measurement uncertainties specified in Appendix C. The "CIPM MRA Logo" and this statement attest only to the measurement(s) applied for determining the certified values on the certificate (for details see http://www.bipm.org).

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 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 qualitative headspace GC-MS analysis of occluded solvents and elemental microanalysis.

GC-FID:	Instrument:	Agilent 6890 or 7890
	Column:	HP-1, 30 m x 0.32 mm I.D. x 0.25 µm
	Program:	190 °C (1 min), 2 °C/min to 220 °C (6 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:	
	Initial analysis:	Mean = 99.8%, s = 0.01% (13 sub samples in duplicate, May 2009)
	Re-analysis:	Mean = 99.8%, s = 0.03% (5 sub samples in duplicate, May 2011)
	Re-analysis:	Mean = 99.8%, s = 0.01% (5 sub samples in duplicate, March 2012)
	Re-analysis:	Mean = 99.5%, s = 0.03% (5 sub samples in duplicate, March 2015)
	Re-analysis:	Mean = 99.9%, s = 0.02% (5 sub samples in duplicate, February 2020)
	Re-analysis:	Mean = 99.8%, s = 0.01% (5 sub samples in duplicate, September 2024)
GC-FID:	Instrument:	Varian CP-3800
	Column:	HP-5, 30 m x 0.32 mm I.D. x 0.25 µm
	Program:	190 °C, 2 °C/min to 220 °C (6 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:	
	Initial analysis:	Mean = 99.8%, s = 0.03% (5 sub samples in duplicate, May 2010)
Thermogravimetric analysis:		Volatiles content not determined due to the nature of the material Non-volatile residue < 0.2% mass fraction (May 2009)
Karl Fischer analysis:		Moisture content 0.4% mass fraction (May 2009) Moisture content < 0.2% mass fraction (May 2010) Moisture content 0.2% mass fraction (May 2011) Moisture content 0.1% mass fraction (April 2012) Moisture content 0.1% mass fraction (February 2015) Moisture content < 0.1% mass fraction (November 2019) Moisture content 0.2% mass fraction (September 2024)

Spectroscopic and other characterisation data

GC-MS:	Instrument:	Agilent 6890/5973
	Column:	VF-1ms, 15 m x 0.25 mm I.D. x 0.3 µm
	Program:	200 °C (1 min), 4 °C/min to 260 °C, 20 °C/min to 300 °C (3 min)
	Injector Temp:	250 °C
	Transfer line temp:	300 °C
	Carrier:	Helium, 1.0 mL/min
	Split ratio:	40/1
	The retention time of the parent compound is reported along with the major peaks observed in the mass spectrum. The latter are reported as mass to charge ratios and (in brackets) as a percentage relative to the base peak.	
	6.0 min:	299 (M^+, 100), 282 (11), 229 (23), 214 (16), 188 (12), 162 (30), 124 (14) *m/z*
TLC:	Conditions:	Kieselgel 60F_{254}. *Tert*-butylmethylether/diethylether/diethylamine (45/45/10). Single spot observed, R_f = 0.3 (3 sub samples). Visualised under $UV_{254\ nm}$ lamp.
IR:	Instrument:	Biorad FTS300MX FT-IR
	Range:	4000-400 cm^{-1}, KBr powder
	Peaks:	3533, 3021, 2963, 2929, 2834, 2789, 2762, 1636 1604, 1502, 1276, 1055, 937 cm^{-1}
^{1}H NMR:	Instrument:	Bruker DMX-500
	Field strength:	500 MHz
	Solvent:	$CDCl_3$ (7.26 ppm)
	Key spectral data:	δ 1.87 (1H, m), 2.06 (1H, ddd, *J* = 5.1, 12.5, 12.5 Hz), 2.29 (1H, dd, *J* = 6.2, 18.6 Hz), 2.39 (1H, ddd, *J* = 3.7, 12.3, 12.3 Hz), 2.43 (3H, s), 2.58 (1H, dd, *J* = 4.1, 12.3 Hz), 2.66 (1H, m), 2.97 (1H, s), 3.04 (1H, d, *J* = 18.6 Hz), 3.34 (1H, dd, *J* = 3.2, 6.1 Hz), 3.83 (3H, s), 4.17 (1H, m), 4.88 (1H, dd, *J* = 1.0, 6.5 Hz), 5.29 (1H, ddd, *J* = 2.6, 2.6, 7.2 Hz), 5.70 (1H, m), 6.56 (1H, d, *J* = 8.2 Hz), 6.65 (1H, d, *J* = 8.3 Hz) ppm
^{13}C NMR:	Instrument:	Bruker gyro 300
	Field strength:	75 MHz
	Solvent:	$CDCl_3$ (77.0 ppm)
	Spectral data:	δ 20.3, 35.8, 40.8, 42.9, 43.1, 46.4, 56.3, 58.8, 66.4, 91.3, 112.8, 119.5, 127.2, 128.3, 131.0, 133.4, 142.1, 146.2 ppm
Melting point:		154 - 156 °C
Microanalysis:	Found:	C = 72.2%; H = 6.8%; N = 4.7% (April, 2009)
	Calculated:	C = 72.2%; H = 7.1%; N = 4.7% (Calculated for $C_{18}H_{21}NO_3$)