Australian Government
Department of Industry, Science and Resources

National Measurement Institute

NATA
WORLD RECOGNISED ACCREDITATION

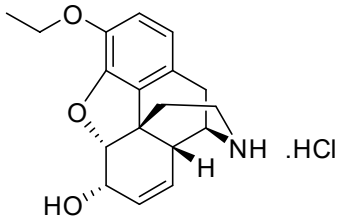
CERTIFIED REFERENCE MATERIAL CERTIFICATE OF ANALYSIS

NMIA D1085: Norethylmorphine hydrochloride

Report ID: D1085.2024.01

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

Molecular Weight: 335.8 g/mol (HCl), 299.4 (base)



Certified value

Batch No.	CAS No.	Purity (mass fraction)
21-D-08	72165-34-5 (base)	96.5 ± 2.8%

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

IUPAC name: (5α,6α)-3-Ethoxy-7,8-didehydro-4,5-epoxymorphinan-6-ol.

Expiration of certification: The property values are valid till 18 July 2027, three 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 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 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 all impurities are quantified as a mass fraction and subtracted from 100%.

Stability: In the absence of long term stability data the measurement uncertainty at the 95% coverage interval has been expanded to accommodate any potential change in the property value. The measurement uncertainty at the 95% confidence interval includes a stability component which has been estimated from annual and accelerated stability trials, the latter conducted at 40 ºC and 75% humidity for a 14 day period. 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 August 2024
This report supersedes any issued prior to 5 August 2024.

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 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 elemental microanalysis.

Warning: **This material is sensitive to the quality of the silanised glass liner when injected at elevated temperature (~ 250 ºC) into a GC instrument.**

GC-FID:	Instrument:	Agilent 8890
	Column:	HP-1MS, 30 m × 0.32 mm I.D. × 0.25 μm
	Program:	230 °C (1 min), 10 °C/min to 300 °C (5 min)
	Injector:	200 °C
	Detector Temp:	320 °C
	Carrier:	Helium
	Split ratio:	20/1
	Relative mass fraction of the main component as the free base:	
	Initial analysis:	Mean = 98.4%, s = 0.1% (6 sub samples in duplicate, February 2022)
	Re-analysis:	Mean = 98.3%, s = 0.06% (5 sub samples in duplicate, November 2022)
	Re-analysis:	Mean = 98.9%, s = 0.1% (5 sub samples in duplicate, August 2023)
	Re-analysis:	Mean = 98.5%, s = 0.1% (5 sub samples in duplicate, July 2024)
Karl Fischer analysis:		Moisture content 1.5% mass fraction (December 2021) Moisture content 1.7% mass fraction (October 2022) Moisture content 1.5% mass fraction (August 2023) Moisture content 1.8% mass fraction (July 2024)
Thermogravimetric analysis:		Non-volatile residue 0.2% mass fraction (December 2021)

Spectroscopic and other characterisation data

GC-MS:	Instrument:	Agilent 6890/5973
	Column:	DB-5MS, 30 m x 0.25 mm I.D. x 0.25 μm
	Program:	230 °C (10 min), 10 °C/min to 300 °C (5 min)
	Injector:	250 °C
	Split ratio:	20/1
	Transfer line temp:	280 °C
	Carrier:	Helium
	Scan range:	50-550 *m/z*
	The retention time of the free base is reported with the major peaks in the mass spectra. The latter are reported as mass/charge ratios and (in brackets) as a percentage relative to the base peak.	
	Free base (10.9 min):	299 (M^+, 100), 229 (29), 178 (11), 148 (33), 132 (13), 115 (21), 81 (43) *m/z*
TLC:	Conditions:	Kieselgel 60F_{254}. Dichloromethane/methanol (1:1) Single spot observed, R_f = 0.2. Visualisation with UV at 254 nm.
IR:	Instrument:	Bruker Alpha Platinum ATR
	Range:	4000-400 cm^{-1}, neat
	Peaks:	3406, 2935, 2910, 2849, 2743, 2685, 2666, 2578, 2487, 2470, 1597, 1285, 1054, 836, 792 cm^{-1}
^{1}H NMR:	Instrument:	Bruker Avance III-500
	Field strength:	500 MHz
	Solvent:	D_2O (4.79 ppm)
	Spectral data:	δ 1.35 (3H, d, *J* = 7.0 Hz), 2.19 (1H, dd, *J* = 3.5, 14.0 Hz), 2.30 (1H, td, *J* = 5.0, 9.0 Hz), 2.94 (1H, quintet, *J* = 3.0 Hz), 3.05-3.11 (2H, m), 3.17 (1H, dd, *J* = 4.0, 13.5 Hz), 3.39 (1H, dd, *J* = 4.5, 8.5 Hz), 4.12-4.23 (2H, m), 4.35-4.41 (2H, m), 5.09 (1H, dd, *J* =1.0, 6.5 Hz), 5.41 (1H, dt, *J* = 2.5, 10.0 Hz), 5.78 (1H, m), 6.78 (1H, d, *J* = 8.5 Hz), 6.94 (1H, d, *J* = 8.5 Hz) ppm
^{1}H NMR:	Instrument:	Bruker Avance III-500
	Field strength:	500 MHz
	Solvent:	MeOH-d_4 (3.31 ppm)
	Spectral data:	δ 1.35 (3H, d, *J* = 6.7 Hz), 2.09 (1H, dd, *J* = 3.5, 14.0 Hz), 2.26 (1H, td, *J* = 13.5, 5.0 Hz), 2.85 (1H, quintet, *J* = 2.4 Hz), 2.99-3.15 (3H, m), 3.33 (1H, d, *J* = 5.0 Hz), 4.06-4.18 (2H, m), 4.25-4.27 (2H, m), 4.92 (1H, dd, *J* =1.5, 6.0 Hz), 5.35 (1H, dd, *J* = 2.5, 9.9 Hz), 5.78 (1H, d, *J* = 9.9 Hz), 6.63 (1H, d, *J* = 8.3 Hz), 6.77 (1H, d, *J* = 8.3 Hz) ppm
		Ethanol estimated at 0.2% mass fraction was observed in the ^{1}H NMR
^{13}C NMR:	Instrument:	Bruker Avance III-500
	Field strength:	126 MHz
	Solvent:	MeOH-d_4 (49.0 ppm)
	Spectral data:	δ 15.3, 27.4, 33.7, 38.5, 38.6, 43.8, 53.3, 66.5, 67.7, 92.5, 117.7, 120.9, 125.3, 126.4, 130.5, 135.8, 143.2, 149.2 ppm
Melting point:		> 300 °C
Microanalysis:	Found:	C = 64.4%; H = 6.9%; N = 4.1% (January 2022)
	Calculated:	C = 64.4%; H = 6.6%; N = 4.2% (Calculated for $C_{18}H_{21}NO_3$.HCl)