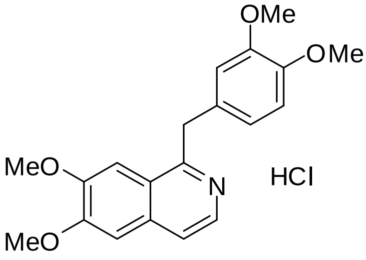
Australian Government
Department of Industry, Science and Resources

National Measurement Institute

NATA
WORLD RECOGNISED ACCREDITATION

CERTIFIED REFERENCE MATERIAL CERTIFICATE OF ANALYSIS

NMIA D750b: Papaverine hydrochloride



Report ID: D750b.2021.02 (Bottled 180629)

Chemical Formula: $C_{20}H_{21}NO_4.HCl$

Molecular Weight: 375.8 g/mol (HCl), 339.4 g/mol (base)

Certified value

Batch No.	CAS No.	Purity (mass fraction)
17-D-07	**61-25-6 (HCl)** **58-74-2 (base)**	**99.8 ± 0.9%**

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

IUPAC name 1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline hydrochloride

Expiration of certification: The property values are valid till 1 June 2026, 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: Off-white 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%. 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% confidence interval includes a stability component which has been estimated from annual and accelerated 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.

15 September 2022

This report supersedes any issued prior to 15 September 2022.

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

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 ^{1}H NMR spectroscopy. The purity value is calculated as per Equation 1.

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

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

The purity value by qNMR was obtained using a combination of the one-proton singlets at 7.3 and 7.4 ppm, the one-proton doublet at 7.9 ppm and the one-proton doublet at 8.1 ppm measured against a certified internal standard of dimethyl sulfone.

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

GC-FID:
Instrument: Agilent 6890
Column: HP-1, 30 m × 0.32 mm I.D. × 0.25 µm
Program: 200 °C (0.5 min), 6 °C/min to 280 °C (1 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 main component:
Initial analysis: Mean = 100%, s = 0.02% (10 sub samples in duplicate, July 2017)
Re-analysis: Mean = 100%, s = 0.01% (5 sub samples in duplicate, July 2018)
Re-analysis: Mean = 100%, s = 0.01% (5 sub samples in duplicate, June 2021)

Thermogravimetric analysis: Volatile content, 0.1% and non volatile residue < 0.2% mass fraction (June 2016)

Karl Fischer analysis: Moisture content ≤ 0.2% mass fraction (July 2017, June 2018 and April 2021)

QNMR:
Instrument: Bruker Avance-III-500
Field strength: 500 MHz
Solvent: D_2O (4.79 ppm)
Internal standard: Dimethyl sulfone (100% mass fraction)
Initial analysis: Mean (7.3 & 7.4 ppm) = 99.6%, s = 0.3% (5 sub samples, November 2017)
Initial analysis: Mean (7.9 ppm) = 99.5%, s = 0.4% (5 sub samples, November 2017)
Initial analysis: Mean (8.1 ppm) = 99.8%, s = 0.2% (5 sub samples, November 2017)

Spectroscopic and other characterisation data

ESI-MS:	Instrument:	Micromass Quatro LC Micro
	Operation:	Positive ion mode, direct infusion at 10 µL/min
	Ionisation:	ESI spray voltage at 3.2 kV positive ion
	EM voltage:	650 V
	Cone voltage:	45 V
	Peak:	340.2 $(M+H^+)$ *m/z*
GC-MS:	Instrument:	Agilent 6890/5973
	Column:	HP-1MS, 30 m x 0.25 mm I.D. x 0.25 µm
	Program:	180 °C (1 min), 15 °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 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 (10.7 min):	339 $(M^+$, 74), 338 (100), 324 (89), 308 (22), 293 (11), 281 (11), 207 (19), 154 (13) *m/z*
HS-GC-MS:	Instrument:	Agilent 6890/5973/G1888
	Column:	DB-624, 30 m x 0.25 mm I.D. x 1.4 µm
	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:	Toluene, acetone
TLC:	Conditions:	Kieselgel 60F254. Methanol / 33% aqueous ammonia (200/3) Single spot observed, $R_f = 0.8$. Visualisation with UV at 254 nm
IR:	Instrument:	Biorad FTS300MX FT-IR
	Range:	4000-400 cm^{-1}, KBr powder
	Peaks:	2500, 1994, 1955, 1635, 1608, 1508, 1436, 1409, 1282, 1146 cm^{-1}
^1H NMR:	Instrument:	Bruker Avance III 500
	Field strength:	500 MHz
	Solvent:	D_2O (4.79 ppm)
	Spectral data:	δ 3.63 (3H, s), 3.70 (3H, s), 3.84 (3H, s) 3.87 (3H, s), 6.72 (1H, dd, $J = 1.8$, 8.3 Hz), 6.79 (1H, d, $J = 8.3$ Hz), 6.91 (1H, d, $J = 1.7$ Hz), 7.21 (1H, s), 7.35 (1H, s), 7.82 (1H, d, $J = 6.5$ Hz), 8.10 (1H, d, $J = 6.5$ Hz) ppm Acetone estimated at 0.03% mass fraction was observed in the 1H NMR.
^{13}C NMR:	Instrument:	Bruker Avance III 500
	Field strength:	126 MHz
	Solvent:	D_2O
	Spectral data:	δ 36.6, 55.6, 55.7, 56.3, 56.6, 104.6, 106.4, 112.1, 112.3, 121.7, 122.1, 122.2, 127.9, 129.5, 137.1, 147.8, 148.7, 151.9, 154.0, 156.4 ppm
Melting point:		221.0-225.2 °C
Microanalysis:	Found:	C = 63.7%; H = 5.9%; N = 3.8%, Cl = 9.4% (August 2017)
	Calculated:	C = 63.9%; H = 5.9%; N = 3.7%, Cl = 9.4% (Calculated for $C_{20}H_{21}NO_4.HCl$)