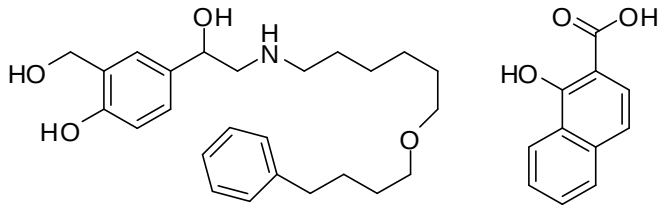
REFERENCE MATERIAL PRODUCT INFORMATION SHEET

Report ID: M904.2018.01

Compound Name: **Salmeterol hydroxynaphthoate**
Collection Number: M904
Chemical Formula: $C_{36}H_{45}NO_7$
CAS Number: 94749-08-3

Description: White solid
Batch Number: 07-D-03
Molecular Weight: 603.75
Release date: 27th November 2008

Structure:



Synonyms: Salmeterol xinafoate

Purity (mass fraction): 97.6 ± 1.1% (95 % coverage interval)

The purity value was obtained from quantitative nuclear magnetic resonance (qNMR). The purity estimate by qNMR was obtained using one proton doublet at 8.4 ppm against a certified internal standard of potassium hydrogen maleate. Supporting evidence is provided by Karl Fischer analysis, thermogravimetric analysis and elemental microanalysis.

qNMR:	Instrument:	Bruker DMX-400	
	Field strength:	400 MHz	Solvent: d_6-DMSO/D_2O
	Internal standard:	Potassium hydrogen maleate	
	Initial analysis:	Mean (8.2 ppm) = 98.6%, s = 0.5% (5 sub samples, November 2008)	
	Re-analysis:	Mean (8.2 ppm) = 97.6%, s = 0.5% (3 sub samples, December 2013)	
qNMR:	Instrument:	Bruker Avance-500	
	Field strength:	500 MHz	Solvent: d4-Acetic acid (2.05 ppm)
	Internal standard:	Potassium hydrogen maleate	
	Re-analysis:	Mean (8.4 ppm) = 97.4%, s = 0.2% (3 sub samples, November 2018)	
Thermogravimetric analysis:		Volatile content < 0.1% and non volatile residue < 0.2% mass fraction (June 2007)	
Karl Fischer analysis:		Moisture content < 0.7% mass fraction (June 2007) Moisture content < 0.2% mass fraction (December 2013)	

Spectroscopic and other characterisation data

GC-MS: *Tris*-TMS derivative

Instrument:	Agilent 5973MSD	
Column:	HP-1MS, 30 m × 0.2 mm I.D. × 0.2 μm	
Program:	150 °C (1 min), 20 °C/min to 300 °C, (10 min)	
Injector:	250°C	Transfer line temp: 320 °C
Carrier:	Helium, 1.5 mL/min	Split ratio: 20/1

The retention time of the *bis*-TMS derivative of hydroxynaphthoate (6.2 mins) and the *tris* TMS derivative of salmeterol (15.8 mins) are reported along with the major peaks in the mass spectrum. The latter are reported as mass to charge ratios and (in brackets) as a percentage relative to the base peak.

6.2 min:	332 (M^+, 1), 319 (11), 318 (28) 317 (100), 243 (5), 185 (8) 147 (7), 141 (4), 73 (16) *m/z*
15.8 min:	616 (1), 526 (2), 371 (8), 370 (18), 369 (53), 263 (19), 262 (100), 207 (3), 147 (4), 112 (6), 91 (12), 73 (19) 44 (4) *m/z*

ESI-MS:

Instrument:	Micromass Quatro Micro
Operation:	Positive ion mode, direct infusion at 5 μL/min
Ionisation:	ESI spray voltage at 3.0 kV positive ion
EM voltage:	500 V
Cone voltage:	20 V
Peak:	416.1 ($M+H^+$) *m/z*

IR:

Instrument:	Biorad FTS300MX FT-IR
Range:	4000-400cm^{-1}, KBr powder
Peaks:	3309, 2940, 2859, 2361, 1579, 1557, 1466, 1409, 1302, 1275, 1096, 998, 884, 799, 775, 698 cm^{-1}

^{1}H NMR:

Instrument:	Bruker DMX600	
Field strength:	600 MHz	Solvent: CD_3OD (3.31 ppm)
Spectral data:	δ 1.32-1.40 (4H, m), 1.48-1.57 (4H, m), 1.60-1.65 (2H, m), 1.65-1.74 (2H, m), 2.59 (2H, t, *J* = 7.6 Hz), 2.99 (2H, m), 3.06-3.12 (2H, m), 3.35 (2H, t, *J* = 6.4 Hz), 3.37 (2H, t, *J* = 6.5 Hz), 4.66 (2H, s), 4.89 (1H, m), 6.78 (1H, d, *J* = 8.2 Hz), 7.11-7.25 (7H, m), 7.35 (1H, d, *J* = 2.2 Hz), 7.41 (1H, ddd, *J* =1.2, 6.8, 9.5 Hz), 7.48 (1H, ddd, *J* = 1.3, 6.9, 9.5 Hz), 7.72 (1H, bd, *J* = 8.2 Hz), 7.88 (1H, d, *J* = 8.6 Hz), 8.29 (1H, dt, *J* = 0.6, 8.3 Hz) ppm	

^{13}C NMR:

Instrument:	Gyro 300	
Field strength:	150 MHz	Solvent: CD_3OD (49.0 ppm)
Spectral data:	δ 26.8, 27.0, 27.4, 29.2, 30.3, 30.4, 36.6, 55.2, 60.8, 70.1, 71.6, 71.7, 112.9, 116.0, 117.7, 124.4, 125.6, 126.6, 126.7, 126.9, 127.0, 127.8, 128.3, 128.6, 128.9, 129.3, 129.4, 132.9, 137.9, 143.7, 156.3, 161.0, 176.9 ppm	

Melting point: 138-140°C

Microanalysis: Found: C = 72.1 %; H = 7.4 %; N = 2.3% (June 2007)
Calc: C = 71.6 %; H = 7.5 %; N = 2.3% (Calculated for $C_{36}H_{45}NO_7$)

Expiration of certification
The property values are valid till 22nd November 2023, 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.

The long-term stability of the compound in solution has not been examined.

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.

Homogeneity assessment
The homogeneity of the material was assessed using purity assay by qNMR on five randomly selected 20-30 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.

Recommended storage
When not in use this material should be stored at or below 4 ºC in a closed container in a dry, dark area.

Intended use
This reference material should be used for qualitative analysis only.

Caution
Treat as hazardous substance. Use appropriate work practices when handling to avoid skin or eye contact, ingestion or inhalation of dust.

Legal notice
Neither NMI nor any person acting on NMI'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 certificate.

Authorised by:

S. R. Davies

Dr Stephen R. Davies,
Team Leader,
Chemical Reference Materials, NMI.
Dated: 29 November, 2018.

Characterisation data and property values specified in this report supersede those in all reports issued prior to 29th November 2018.