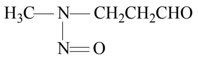
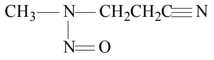
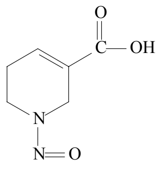
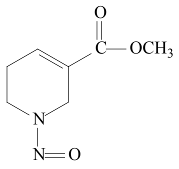
SOME ARECA-NUT-DERIVED *N*-NITROSAMINES

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms and structural and molecular formulae*

Chemical name [Chem. Abstr. Services Reg. No.]	Chem. Abstr. Name [Synonym] IUPAC Systematic Name	Structural and molecular formulae and molecular weight		
3-Methylnitrosamino-propionaldehyde [85502-23-4]	Propanal, 3-(methyl-nitrosoamino) [MNPA] 3-(Methylnitrosamino)-propionaldehyde	$C_4H_8N_2O_2$	 $H_3C-\underset{\overset{\vert}{N=O}}{N}-CH_2CH_2CHO$	Mol. wt: 116.1
3-Methylnitrosamino-propionitrile [60153-49-3]	Propanenitrile, 3-(methyl-nitroso-amino) [MNPN] 3-(Methylnitrosamino)-propionitrile	$C_4H_7N_3O$	 $CH_3-\underset{\overset{\vert}{N=O}}{N}-CH_2CH_2C\equiv N$	Mol. wt: 113.1
N-Nitrosoguvacine [55557-01-2]	3-Pyridinecarboxylic acid, 1,2,5,6-tetrahydro-1-nitroso- [NGC; nitrosoguvacine] 1,2,5,6-Tetrahydro-1-nitrosonicotinic acid	$C_6H_8N_2O_3$		Mol. wt: 156.1
N-Nitrosoguvacoline [55557-02-3]	3-Pyridinecarboxylic acid, 1,2,5,6-tetra-hydro-1-nitroso-, methyl ester [NG; NGL; nitrosoguvacoline] Methyl 1,2,5,6-tetra-hydro-1-nitrosonicotinate	$C_7H_{10}N_2O_3$		Mol. wt: 170.2

1.1.2 *Chemical and physical properties*

Chemical/ Physical property	MNPA	MNPN	NGC	NGL
Description	No data	Light-yellow liquid (Chang *et al.* 1976)	Colourless, crystalline solid (Lijinsky & Taylor, 1976)	Yellow oil (Lijinsky & Taylor, 1976)
Melting-point	No data	No data	175.5–177 °C (Lijinsky & Taylor, 1976)	No data
Boiling-point	No data	102–103 °C (0.04 mm Hg) (Chang *et al.*, 1976); 97 °C (0.075 mm Hg) (Wenke & Hoffmann, 1983)	No data	137–178 °C (4 mm Hg) (Lijinsky & Taylor, 1976)
Spectroscopy data	NMR, UV and MS data have been reported (Wenke & Hoffmann, 1983; Nishikawa *et al.*, 1992)	IR, NMR and MS data have been reported (Chang *et al.*, 1976; Wenke & Hoffmann, 1983). MS data reported for MNPN isolated from saliva of betel-quid chewers (Prokopczyk *et al.*, 1987)	MS data have been reported (Rainey *et al.*, 1978)	MS data have been reported (Rainey *et al.*, 1978)
Synthetic compound	Synthetic MNPA is a mixture of E- and Z-isomers in a ratio of 1.4 (Wenke & Hoffmann, 1983)	Synthetic MNPN is a mixture of E- and Z-isomers in a ratio of 1.7 (Wenke & Hoffmann, 1983)		Synthetic NGL is a mixture of E- and Z-isomers in a ratio of 2.5 (Wenke & Hoffmann, 1983)

MNPA, 3-methylnitrosaminopropionaldehyde; MNPN, 3-methylnitrosaminopropionitrile; NGC, *N*-nitrosoguvacine; NGL, *N*-nitrosoguvacoline; NMR, ^{1}H-nuclear magnetic resonance; UV, ultraviolet; MS, mass spectrometry; IR, infrared

1.2 Production

3-Methylnitrosaminopropionaldehyde (MNPA) was prepared by Wenke and Hoffmann (1983) by the reaction of MNPA diethyl acetal with nitrite, followed by hydrolysis. 3-Methylnitrosaminopropionitrile (MNPN) was prepared by Chang *et al.* (1976) by the reaction of sodium nitrite with a solution of MNPN hydrochloride. *N*-Nitrosoguvacine (NGC) was prepared by Lijinsky and Taylor (1976) by nitrosation of guvacine that was synthesized from 3-carbethoxy-4-piperidone by hydrogenation to the piperidonol, followed by dehydration and de-esterification with hydrogen chloride gas at 200 °C, followed by esterification with diazomethane. *N*-Nitrosoguvacoline (NGL) was also prepared by Lijinsky and Taylor (1976) using the same process as that for NGC.

In in-vitro experiments, *N*-nitrosation of arecoline, the major alkaloid of the areca nut, resulted in the formation of NGL, MNPN and MNPA (Wenke & Hoffmann, 1983).

No evidence was found that any of these compounds has ever been produced in commercial quantities or has any use other than as a laboratory chemical.

1.3 Occurrence

NGL, MNPN and MNPA were not detected in three samples of betel quid without tobacco or in three samples of betel quid with tobacco. NGC was detected in one of each of the three samples with and without tobacco (Nair *et al.*, 1985).

NGL, NGC and MNPN were found in the saliva of chewers of betel quid with tobacco at nanogram per millilitre levels (Table 1). NGL was also reported in the saliva of three of eight smokers (up to 7.6 ng/mL; Wenke *et al.*, 1984a). [The Working Group noted the possibility of analytical problems or the additional use of areca nut by the smokers.] MNPN in saliva was confirmed by mass spectroscopic analysis (Prokopczyk *et al.*, 1987); MNPA was not detected in saliva or any other human biological fluid.

Table 1. Levels (range in ng/mL) of areca-nut-derived nitrosamines detected in the saliva[a] of chewers of betel quid with tobacco (BQ + T) and without tobacco (BQ)

Nitrosamine	BQ + T (no.)[b]	BQ (no.)[b]	Reference
NGL	4.3–45 (5)[c]	2.2–9.5 (5)[c]	Wenke *et al.* (1984a)
	0–7.1 (12)	0–5.9 (12)	Nair *et al.* (1985)
	NR	0–142 (9)	Stich *et al.* (1986)
	3.1–23.5 (10)	0.6–8.8 (10)	Nair *et al.* (1987)
NGC	0–30.4 (6)	0–26.6 (6)	Nair *et al.* (1985)
MNPN	NR	0.5–11.4 (10)	Prokopczyk *et al.* (1987)

NGL, *N*-nitrosoguvacoline; NGC, *N*-nitrosoguvacine; MNPN, 3-methylnitrosaminopropionitrile; NR, not reported

[a] Number in parentheses refers to number of samples

[b] The whole saliva or the supernatant was analysed.

[c] In ppb

In-vitro experiments support the hypothesis that, during the chewing of betel quid, nitrosation of arecoline, the major alkaloid of areca nut, produces NGL and MNPN. It was concluded that the conditions prevailing in the oral cavity of betel-quid chewers are likely to favour the formation of these compounds (see Monograph on Betel-quid and Areca-nut Chewing, Section 4.1.1). In-vitro nitrosation of betel quid with and without tobacco under neutral and acidic pH with nitrite in the presence of thiocyanate yielded both NGL and NGC; the formation of NGC was greater than that of NGL when betel quid without tobacco was nitrosated (Nair *et al.*, 1985). Small amounts of crude phenolic extracts from fresh green areca fruit (< 60 mg/300 mL) significantly inhibited the formation of NGL from arecoline upon the addition of nitrite, whereas larger amounts (> 250 mg/300 mL) enhanced its formation (Wang & Peng, 1996).

1.4 Analysis

Wenke and Hoffmann (1983) reported a method for analysis of MNPN, MNPA and NGC by gas chromatography with a nitrosamine-selective thermal-energy analyser. Analysis of NGC and NGL has also been reported using similar techniques (Nair *et al.*, 1985).