Journal of Pharmaceutical & Biomedical Analysis
Vol. 10, No. 4, pp. 303–307, 1992
Printed in Great Britain

0731–7085/92 $5.00 + 0.00

Short Communication

Synthesis and spectroscopic studies of norethylmorphine

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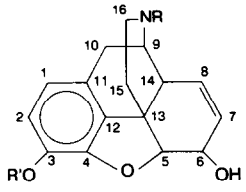
Keywords: *Ethylmorphine (EM); norethylmorphine (NEM); synthesis; NMR; MS; IR; UV.*

Introduction

Ethylmorphine (EM, Fig. 1, Ia) is a 3-ethoxy derivative of morphine (M, Fig. 1, Ib), which is widely used as an antitussive and a mild analgesic. Since norethylmorphine (NEM, Fig. 1, Ic) is one of the major metabolites of EM [1, 2], it is required as a reference substance for identification and quantification in metabolic studies of EM. Although NEM has previously been synthesized [2], the product has not been characterized by melting point and spectroscopic data. The aim of the present work was to synthesize and characterize NEM by means of mass spectroscopy (MS), infrared spectroscopy (IR), ultraviolet spectroscopy (UV) and nuclear magnetic resonance spectroscopy (NMR).



Ia R = CH_3, R' = CH_2CH_3
Ib R = CH_3, R' = H
Ic R = H, R' = CH_2CH_3

Figure 1
Structure of ethylmorphine (Ia), morphine (Ib) and norethylmorphine (Ic).

Experimental

Apparatus

Melting point: (uncorrected) Kofler hot stage microscope. NMR: Varian Gemini-200 (200 MHz for ^1H; 50 MHz for ^{13}C) with software furnished by the supplier (Palo Alto, CA, USA). IR: Beckman Acculab 2 (Beckman Instruments, Fullerton, CA, USA). UV spectra: Perkin–Elmer Lambda 15 UV–vis Spectrophotometer (Beaconsfield, Bucks, UK). MS: VG 12-250 quadrupole Mass Spectrometer (Manchester, UK) combined to 11/24 PDP Data System. Gas chromatography–mass spectroscopy (GC–MS): Hewlett–Packard (HP) model 5890/5971 (Avondale, PA, USA) combined to HP G1034B DOS series ChemStation (HP Vectra Q5/165). Capillary column: HP fused-silica column (12.5 m × 0.2 mm i.d. 0.33 μm cross-linked methylsilicone).

Chemicals and reagents

Ethylmorphine hydrochloride was obtained from Weiders Farmasøytiske (Oslo, Norway). Bis(trimethylsilyl)trifluoroacetamide (BSTFA) and pentafluoropropionic anhydride (PFPA) were purchased from Supelco (Bellefonte, PA, USA). All other reagents were of analytical grade and used as received.

Synthetic preparation of NEM (Ic)

An aqueous solution of EM hydrochloride

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was made basic with ammonia and the precipitated EM base filtered, dried and used as such. EM base (4.7 g, 15 mmol) was dissolved in 200 ml of chloroform. Potassium bicarbonate (18 g) and phenyl chloroformate (15 g) were added to the solution. The reaction mixture was refluxed with stirring for 18 h, cooled, filtered and the filtrate was evaporated to dryness to give a syrupy carbamate intermediate, which was used without purification. Hydrazine hydrate (98%, 40 ml) was added slowly and the solution was refluxed under N_2 for 8 h, cooled and evaporated to dryness in vacuo. The residue was dissolved in chloroform (100 ml) and extracted with 10% potassium hydroxide (3 × 20 ml). The chloroform layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated to dryness in vacuo to give 3.4 g of NEM. Recrystallization from ethanol gave 3.1 g (70%) of crystalline NEM (m.p. 154–156°C).

IR (KBr disk). The five strongest peaks at wavenumbers 1500, 1450, 1120, 1250 and 780 cm^{-1} (Fig. 2).

UV. 10 μg ml^{-1} in methanol, aqueous acid and alkali, λ_{max}^{MeOH} nm (log ε): 218(4.36), 243_{sh}, 288(3.20); $\lambda_{max}^{0.1N\ NaOH}$ nm (log ε): 226(4.03), 240_{sh}, 284(3.21); $\lambda_{max}^{0.1N\ HCl}$ nm (log ε): 212(4.38), 238_{sh}, 287(3.12).

Results

High-performance liquid chromatography (HPLC) [3]

Only one peak with retention time different from EM was detected.

MS (direct inlet) EI-mode

Principal fragments at *m/z* (relative abundance): 299(M^+, 100%), 270(11%), 229(31%), 200(22%), 178(23%), 148(43%), 115(25%), and 81(61%). The molecular ion peak was

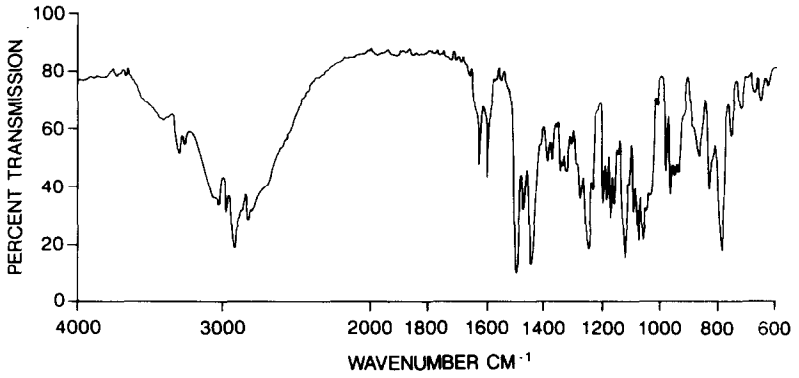

Figure 2
Infrared spectrum of NEM (2 mg per 200 mg KBr).

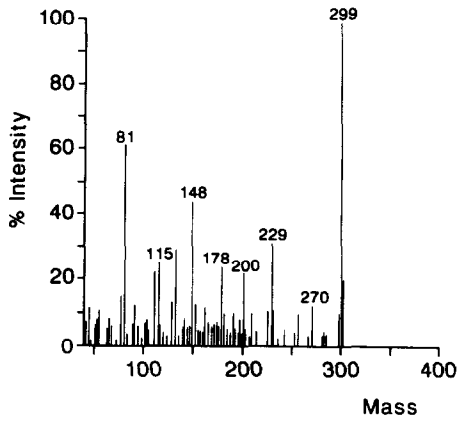

Figure 3
EI-mode mass spectrum of norethylmorphine (direct inlet). The electron energy was 70 eV and ion source temperature was 200°C.

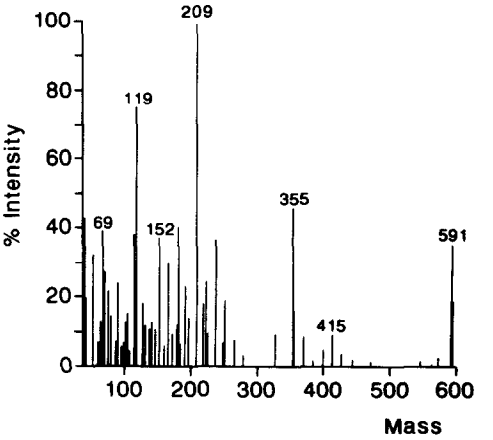

Figure 4
EI-mode mass spectrum of norethylmorphine-PFPA derivative.

consistent with the known molecular weight for NEM (299.15) (Fig. 3).

GC–MS analysis of NEM derivatives

BSTFA and PFPA derivatives of NEM were prepared according to a method previously described [4]. Only one PFPA derivative was detected (Fig. 4). BSTFA derivatization gave three different products.

NMR spectroscopy

The ^{1}H NMR spectrum of NEM is similar to that of EM, but the three-proton singlet at δ 2.39, which arises from the *N*-methyl substituent, is missing. Using two-dimensional proton–proton correlation spectroscopy (COSY), all the signals in the spectrum can be assigned. The COSY spectrum (with correlations between signals shown) is depicted in Fig. 5. Some long-range couplings are seen which do not give rise to visible multiplets in the 1D spectrum, although line broadening (lower peak heights) is observed. Spectral positions, multiplicities, coupling constants and assignments of signals are given in Table 1. The ^{13}C NMR spectrum of NEM shows some similarities to the spectrum of EM, as well, but missing the signal from the *N*-methyl group which in the latter compound is found at δ 43.3. Demethylation of EM results in a decrease in shift of *ca* 8 ppm for C-9 and C-16, and an increase of *ca* 10 ppm for C-10. This phenomenon, which has been noted previously [5–7], is due to the steric effect of the *N*-methyl group.

Multiplicities in the ^{13}C NMR spectrum have been determined from APT (attached proton test) and DEPT (distortionless enhancement by polarization transfer) experiments. Based on signal positions, multiplicities, and correlations with the ^{13}C NMR spectra of related alkaloids [5–7], signals have been assigned as shown in Table 2, in which the spectrum of EM is given for comparison.

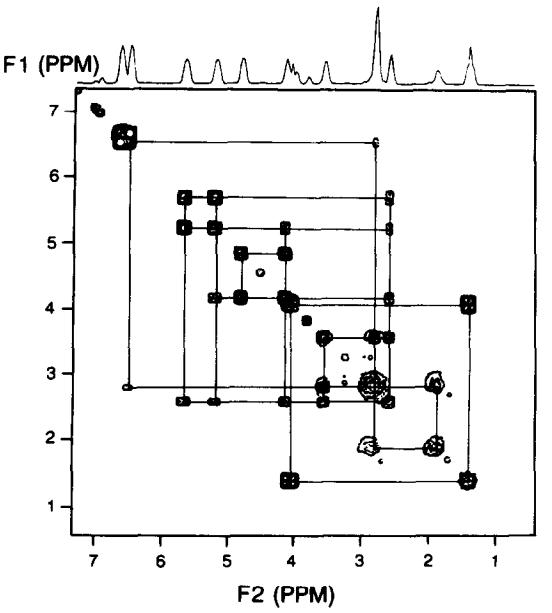

Figure 5
Two-dimensional proton correlation (COSY) spectrum of NEM ($CDCl_3$ as solvent, shift positions relative to tetramethylsilane).

Discussion

NEM has earlier been synthesized by Jarvi *et al.* [2] employing a method similar to that described for norcodeine [8]. This method is however, complicated and tedious and the products are obtained in low yields.

In the present study, NEM has been synthesized by a modification of Rice's method

Table 1
^{1}H NMR spectrum of norethylmorphine ($CDCl_3$ as solvent, shift positions relative to tetramethylsilane)

Shift value (ppm)	Number of protons	Multiplicity	Coupling constants (Hz)	Position in molecule
1.33	3	t	7.0	Ethyl-CH_3
1.78–1.88	2	m		15
2.53	1	dd	2.5, 2.5	14
2.75–2.87	4	m		10, 16
3.2–3.3	2	broad s		OH and NH
3.53	1	m		9
4.02	2	q	7.0	Ethyl-CH_2
4.09–4.14	1	m		6
4.78	1	d	6.4	5
5.17	1	ddd	2.5, 2.5, 9.9	8
5.64	1	d	9.9	7
6.47	1	d	8.2	1
6.61	1	d	8.2	2

Table 2
^{13}C NMR spectrum of norethylmorphine (NEM) and ethylmorphine (EM) ($CDCl_3$ as solvent, shift positions relative to tetramethylsilane)

Shift values for NEM (ppm)	Shift values for EM (ppm)	Multiplicity	Position in molecules
15.6	15.6	q	Ethyl-CH_3
31.5	21.0	t	10
36.8	36.1	t	15
38.5	46.6	t	16
41.3	41.0	d	14
—	43.3	q	*N*-CH_3
44.1	43.2	s	13
51.8	59.0	d	9
65.1	65.0	t	Ethyl-CH_2
66.5	66.5	d	6
92.0	91.1	d	5
114.3	114.1	d	2
118.7	118.9	d	1
127.0	126.6	s	11
127.4	127.4	d	8
130.6	130.4	s	12
133.1	132.5	d	7
140.2	140.4	s	3
146.2	145.9	s	4

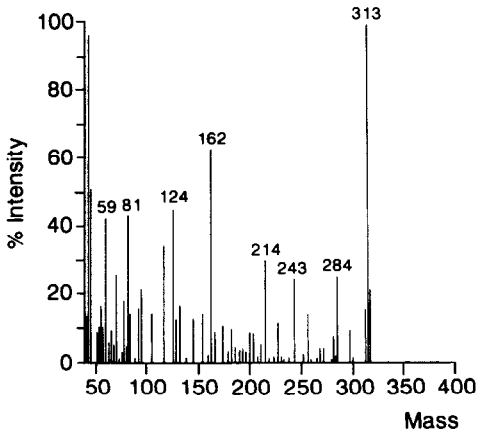

Figure 6
EI-mode mass spectrum of ethylmorphine (direct inlet). The electron energy was 70 eV and ion source temperature was 200°C.

[9–10] for the synthesis of norcodeine from codeine. First an intermediate carbamate, *N*-carbophenoxynorethylmorphine, was prepared by reacting EM base with phenyl chloroformate. The carbamate was then subjected to hydrazinolytic cleavage with hydrazine hydrate to give NEM. Our procedure differs from the norcodeine method [9–10] in that: (1) only hydrazine hydrate was used and not the more explosive 95% hydrazine; (2) a shorter reaction time (8 h) was used for cleavage of the intermediate carbamate. After recrystallization from ethanol, the colourless crystalline NEM was obtained in 70% yield with a sharp melting point. In comparison with the full scan mass spectrum of EM (Fig. 6), the molecular ion (M^+) and main fragments of NEM in high mass region (above 148 mass units), are 14 mass units lower than the EM mass fragments, respectively. This is consistent with the demethylation of tertiary methylamine in the parent compound.

GC–MS combined with derivatization, is often used for the identification of products in metabolic studies. This study showed the *N*,*O*-diacylated product formed by PFPA derivatization, is convenient for the identification of NEM (Fig. 4). The derivative is stable at room temperature for more than 8 h. GC–MS analysis of the three different products formed by BSTFA derivatization, showed compounds consistent with *N*-silylation, *O*-silylation and *N*, *O*-disilylation.

Conclusion

The present report describes a procedure for the preparation of pure NEM in good yield. The product has been characterized by MS, GC–MS, HPLC, IR, UV and ^1H and ^{13}C-NMR. All the signals in the NMR spectra have been assigned from COSY, APT and DEPT experiments and compared with those reported for related compounds.

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[Received for review 13 September 1991; revised manuscript received 31 October 1991]