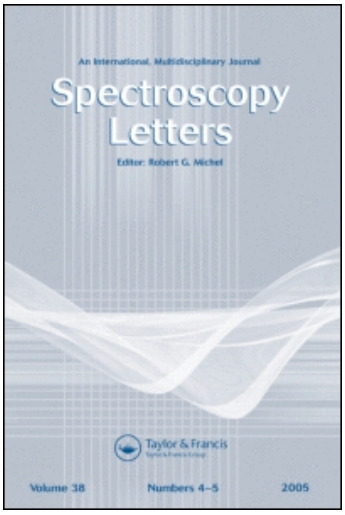

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PMR Assay of Natural Products in Pharmaceuticals I: Assay of Noscapine in Tablets

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PMR ASSAY OF NATURAL PRODUCTS IN PHARMACEUTICALS I: ASSAY OF NOSCAPINE IN TABLETS

Key Words: NMR analysis, Noscapine; NMR analysis, Narcotine, 1-∝-Narcotine; NMR analysis,Tusscapine, Tuscapin.

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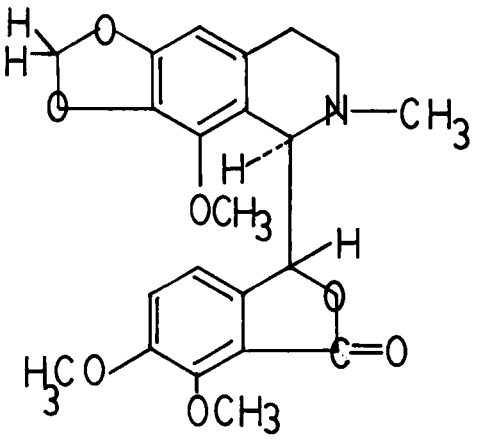
Abstract

A rapid and accurate PMR procedure is reported for the analysis of noscapine as a drug entity and in tablet dosage form. The method is precise with a standard deviation of ± 1.44% and 1.12% in the alkaloid and tablets respectively. The results of synthetic mixtures and tablets are comparable to those obtained by B.P. 1973 and NF. XIII procedures. In addition, the PMR spectrum furnishes a specific means of identification of noscapine.

Introduction

Noscapine I [1-∝-2-methyl-8-methoxy-6-7-methylenedioxy-1-(6,7-dimethoxy-3-pythalidyl)-1,2,3,4-tetratydroisoquinoline] is one of

the opium alkaloids and being nonaddictive, it is widely used as an antitussive in the treatment of unproductive cough. Due to its bronchodilating properties it is used to suppress the cough of bronchitis and for the relief of whooping cough in children (1).



Several approaches have been undertaken for the determination of I. A gravimetric method of determination based on precipitation with tetraphenyl boron has been described (2). Amperometric titration (3) and polarographic (4,5) methods were also reported. In plasma and urine, I has been determined by spectrofluorometry (6). A spectrophotometric method has been described (7) for the estimation of I based on measuring the absorbance of 0.1N HCl solution of the extracted base at 312 nm. This method is adopted by the B.P.C. 1973. A combination of this method with TLC has been described for the determination of I in opium (8). A method using the first derivative curve has also been reported (9) A quantitative

TLC technique was applied for the assay of I in drug mixtures (10). Non-aqueous titration is the method officially adopted by the B.P. 1973 (11) and NF. XIII (12).

By virtue of the relatively high dosage of noscapine (30 mg), the non-specificity of the methods previously described for its analysis and the characteristic resonance pattern of its PMR spectrum, it was deemed of interest to investigate a PMR assay of this alkaloid as a pure drug and in its tablet dosage form.

Experimental

Apparatus and chemicals - NMR spectrometer[1] was used. Standard Noscapine[2], commercial tablets[3] of I, internal standard tert-butanol II[2], deutrated chloroform[4] and ethanol-free chloroform were used.

All chemical shifts reported are in reference to tetramethylsilane at 0 ppm.

Preparation of ethanol-free chloroform (13) - The chloroform is shaken three times with small volume of concentrated sulphuric acid, thoroughly washed with water, dried over anhydrous calcium chloride and distilled.

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1. Varian T-60A, 60MHz.
2. B.D.H. Chemicals, Poole, England.
3. Arab Pharmaceutical Manufacturers Co. Ltd., Sult., Jordan.
4. Koch-Light Laboratories Ltd., Colnbrook Bucks, England.

Preparation of I tablet sample solutions - Weigh and finely powder not less than 20 tablets. Weigh accurately a portion of the powder equivalent to about 100 mg of I, into a glass stoppered centrifuge tube. Add 4 ml. of ethanol-free chloroform containing the specified accurately weighed amount of II. Stopper and shake for 3 min. and then centrifuge. Transfer about 0.5 ml of the clear supernatant solution into a percision NMR spectrometer and obtain the spectrum, adjusting the spin rate to eliminate the spinning side-bands as much as possible. Integrate the peaks of interest (the nine protons of the three - OCH_3 groups of I appearing at 3.83, 4.00 and 4.05 ppm and the nine protons of the three $-CH_3$ groups of II appearing at 1.3 ppm as a singlet) at least three times and determine the average integrals.

The amount of I may then be calculated as follows:

$$\text{mg of I} = \frac{A_x}{A_a} \times \frac{413.43}{74.13} \times \text{mg II}$$

where:

A_x = Integral value of the signal representing I.

A_a = Integral value of the signal representing II.

413.43 = Molecular weight of I.

74.13 = Molecular weight of II.

Results and Discussion

The PMR spectrum of I shown in Fig. 1 displays characteristic signals, the chemical shifts of which are listed in Table I. The signals at 3.83, 4.00 and 4.05 ppm are ascribable to the nine pro-

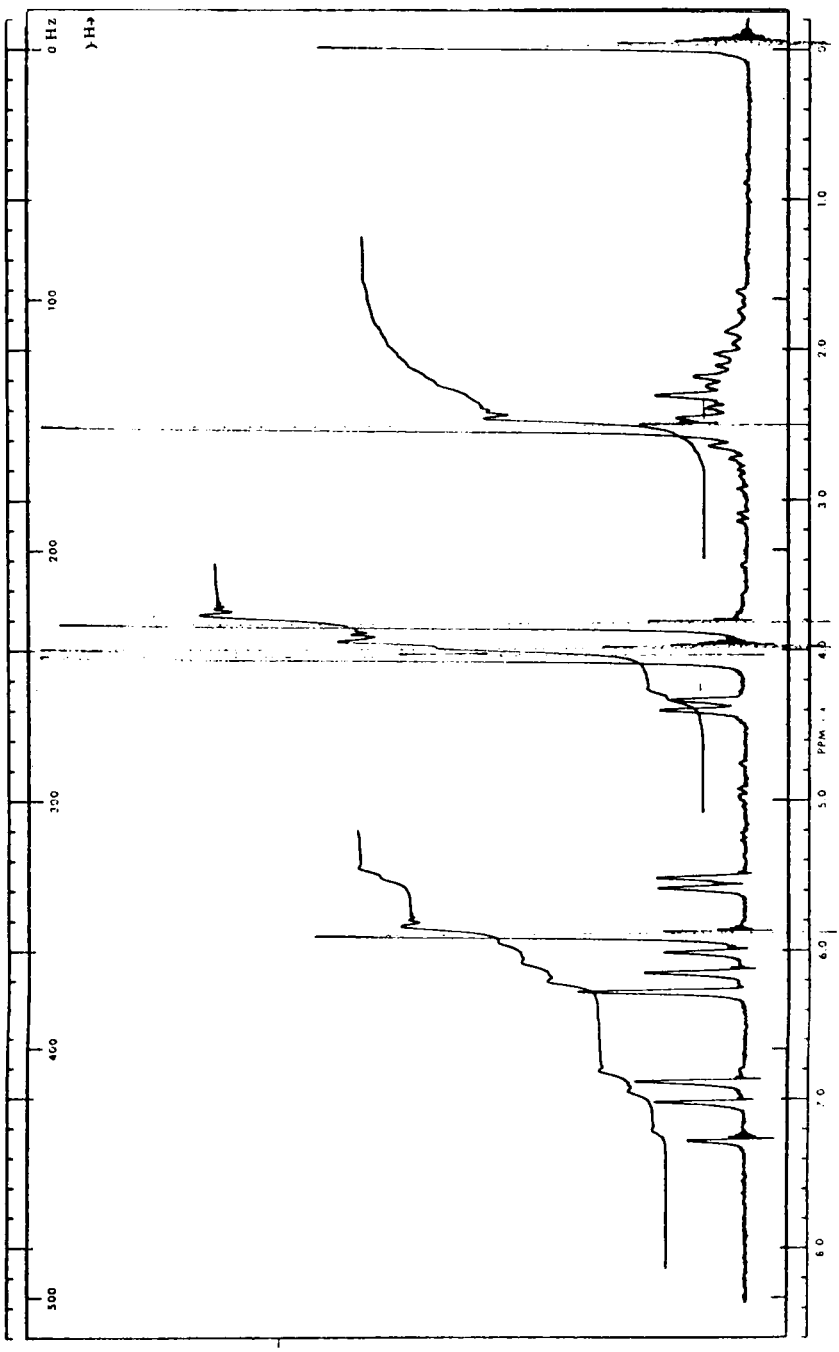

Figure 1 - PMR spectrum of noscapine I and TMS, tetramethylsilane in deteurated chloroform.

Table I - Chemical Shifts of Noscapine in $CDCl_3$

Group	Position	Chemical Shift
$-CH_2-CH_2$	3,4	2.37 (m)
$N-CH_3$	2	2.50 (s)
$O-CH_3$	8	3.83 (s)
$O-CH_3$	6 of phthalidyl	4.00 (s)
$O-CH_3$	7 of phthalidyl	4.05 (s)
-CH-	1	4.37 (d)
$-CH_2-$	methylene dioxy	5.73 (s)
-CH-	3 of phthalidyl	6.10 (d)
-CH-	5	6.27 (s)
-CH-	4,5 of phthalidyl	6.93 (d)

(s) = singlet, (d) = doublet, (m) = multiplet.

tons of the three $-OCH_3$ groups of I. These nine protons were chosen for quantitative analysis, since integration of them gives the largest region for measurement.

tert-Butanol II is employed as an internal standard, since it exhibits (Fig. 2) a nine protons singlet at 1.3 ppm assigned to its

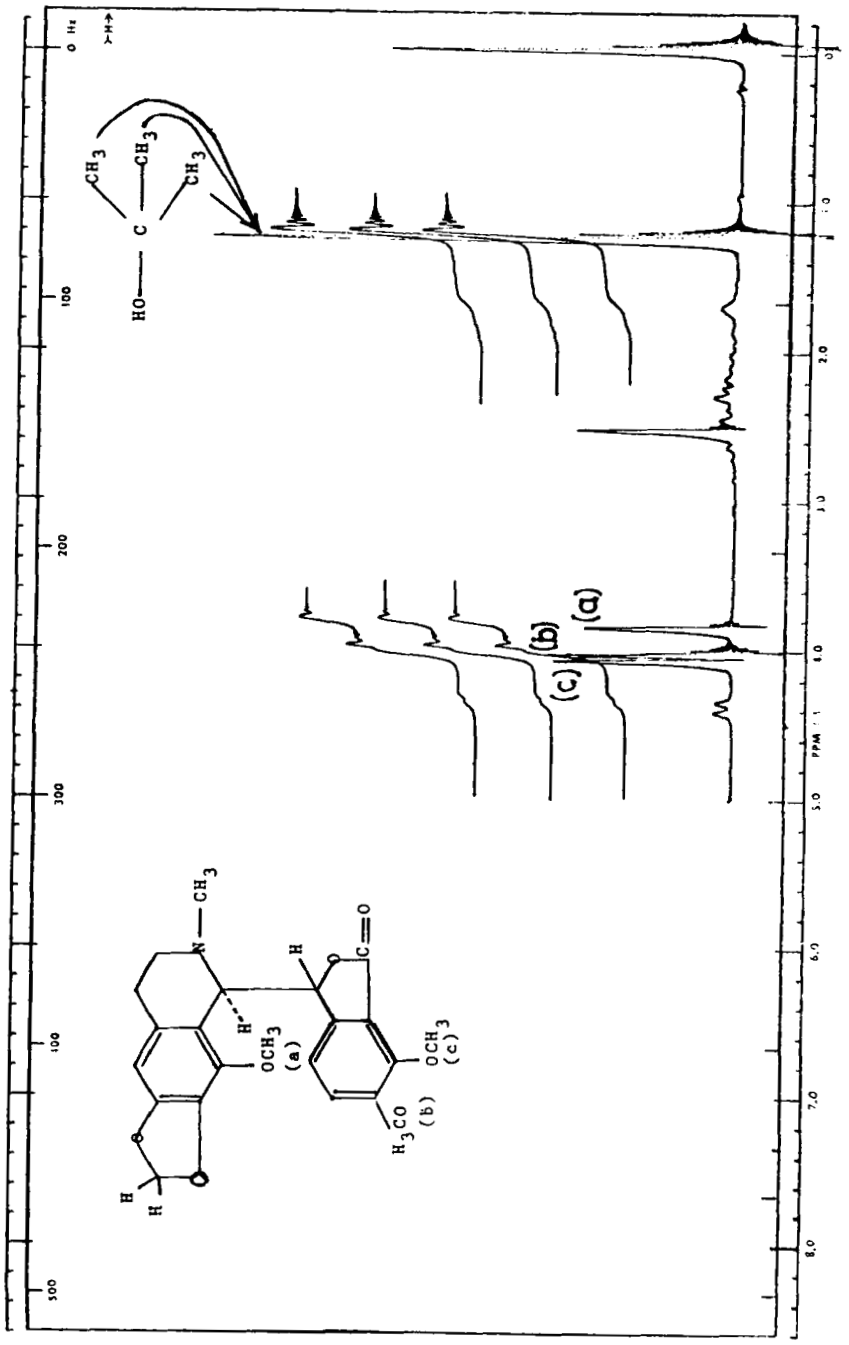

Figure 2 - PMR spectrum of noscapine I, tert-butanol II and TMS, tetramethylsilane in ethanol-free chloroform.

three methyl groups which is widely separated from those chosen for I thus allowing facile and accurate determination. The use of tert-butanol as an internal standard has been previously established (14).

Chloroform was chosen as a solvent, since compound I and II are freely soluble in it. Moreover, its proton signlet at 7.25 ppm does not interfere with the upfield protons of both compounds. Accordingly, the use of deutrated solvent is unnecessary. However, ethanol-free chloroform was used to avoid signal interference due to ethanol usually added as a stabilizer in the commercial product. A series of known standard I mixtures were prepared and assayed by this PMR technique and the results are summarized in Table II. The method is both accurate and precise, with a standard deviation of $\pm$ 1.44%. The accuracy of the determination is not significantly affected by the relative proportions of I to II. Applying this procedure to commercial tablets of I, the results are in good agreement with the declared dosage (Table III). The results are also comparable with those obtained using the official B.P. 1973 and NF. XIII procedure. There is no evidence of interference from excipients present.

The method has distinct advantages over other methods previously described, being rapid, accurate and specific. Moreover, the simultaneous detection of impurities in the sample can be achieved.

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Table II - Determination of Noscapine in Standard Mixtures by PMR.

Standard Mixture	tert-Butanol Internal Standard Added, mg	Noscapine		
		Added, mg	Found, mg	Recovery %
1	56.2	60	59.70	99,50
2	112.4	61	60.98	99.97
3	28.1	82	84.83	103.20
4	28.1	70	69.14	98.77
5	28.1	128	127.34	99.48
6	28.1	95	94.67	99.65
7	28.1	154	151.82	98.58
8	28.1	146	146	100.41
9	28.1	184	184.02	100.01
			Average	99.95
			SD	± 1.44

Table III - Determination of Noscapine Tablets by PMR

Sample	tert-Butanol Internal Standard Added, mg	Noscapine		
		Declared, mg per 4 tablets	Found, mg per 4 tablets	Recovery % w/w
1	22.48	100	97.16	97.16
2	22.48	100	97.85	97.85
3	33.72	100	96.32	96.32
4	33.72	100	97.86	97.86
5	22.48	100	96.32	96.32
6	22.48	100	94.80	94.80
7	22.48	100	94.80	94.80
8	22.48	100	97.06	97.06
9	22.48	100	96.00	96.00
10	22.48	100	95.52	95.52
			Average	96.37
			SD	± 1.12

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