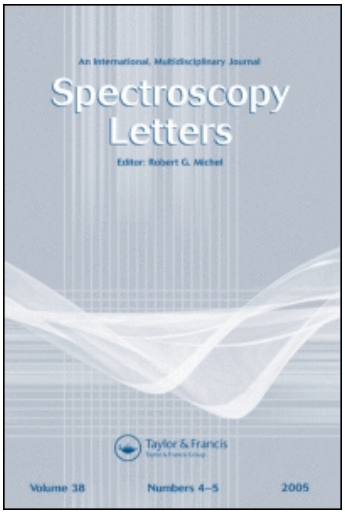


Spectroscopy Letters

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

PMR Spectrometric Analysis of Nikethamide

M. M. A. Hassan[a]; A. I. Jado[a]; M. A. Loutfy[a]
[a] Department of Pharmaceutical Chemistry, Faculty of Pharmacy Riyad University, Riyad, Saudi Arabia.

To cite this Article Hassan, M. M. A. , Jado, A. I. and Loutfy, M. A.(1980) 'PMR Spectrometric Analysis of Nikethamide', Spectroscopy Letters, 13: 9, 595 — 602
To link to this Article: DOI: 10.1080/00387018008076905
URL: http://dx.doi.org/10.1080/00387018008076905

SPECTROSCOPY LETTERS, 13(9), 595-602 (1980)

PMR SPECTROMETRIC ANALYSIS OF NIKETHAMIDE

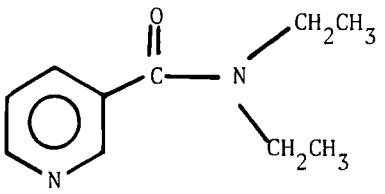
M.M.A. Hassan, A.I. Jado and M.A. Loutfy,
Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
Riyad University, Riyad, Saudi Arabia.

SUMMARY

An NMR procedure is described for the quantitation of nikethamide in bulk drug and injectable dosage formulation. The determination is based on the integration of the 4- and 5- Pyridine protons of the nikethamide relative to that of the methylene protons of succinimide (internal standard). The method is simple, rapid and accurate with a standard deviation of ± 0.48% and ± 1.39 % in the pure drug and injections, respectively.

INTRODUCTION

The chemotherapeutic activity of nikethamide (N, N-diethyl-3-pyridine-carboxamide), as central and respiratory stimulant of low toxicity, is very well known[1].



Several methods[2] have been reported for the quantitative determination of the drug. These comprise acidimetric[3], colorimetric[4], refractometric[5], spectrophotometric[6,7], non-aqueous[8,9], and GLC[10-12] procedures. The method officially adopted by B.P. (1973) involves hydrolysis of the drug and the liberated diethylamine is distilled and determined acidimetrically[13]. All these assay procedures are lengthy, tedious and/or non-specific.

The objective of the present work, is to establish the feasibility of utilising PMR spectroscopy for the assay of nikethamide in bulk drug and in its injectable dosage form.

EXPERIMENTAL

All spectra were recorded on a Varian T-60A, 60 MHz Spectrometer and all chemical shifts reported are in reference to 3-(trimethylsilyl) propionic acid sodium salt (TPS) at 0.00 ppm.

Materials - Standard nikethamide (I), commercial injections

of the drug, succinimide (II) as an internal standard, deutrated water, and distilled water.

Assay of I injection sample solution

Mix the contents of not less than 20 injections. Measure accurately a portion of the solution, equivalent to a specific amount of I, into a glass stoppered centrifuge tube. Add the specified amount of II, accurately weighed, to the sample solution. Transfer about 0.5 ml of the supernatant solution into an analytical NMR tube and obtain the spectrum, adjusting the spin rate to eliminate the spinning side-bands as much as possible. Integrate the peaks of interest [the two protons of 4- and 5-positions of the pyridine ring of the drug (I) appearing at 7.73 ppm and the four protons singlet of the methylene groups of the internal standard (II) appearing at 2.77 ppm]. Record the mean of at least three integrations.

The amount of I may then be calculated as follows:

$$\text{mg of I} = \frac{A_n}{A_s} \times \frac{EW_n}{EW_s} \times W_s$$

where :

A_n = integral value of the signal representing I.

A_s = integral value of the signal representing II.

EW_n = molecular weight of I/2 = 89.12

EW_S = molecular weihgt of II/4 = 24.77

W_S = weight (mg) of II.

Samples of standard I, in the range of 50-200 mg were also analysed using II as an internal standard.

RESULTS AND DISCUSSIONS

The PMR spectrum of nikethamide (I) in D_2O is shown in Fig. 1. It exhibits, among other peaks, a multiplet centered at 7.8 ppm assigned to the 4- and 5-pyridine protons. Since

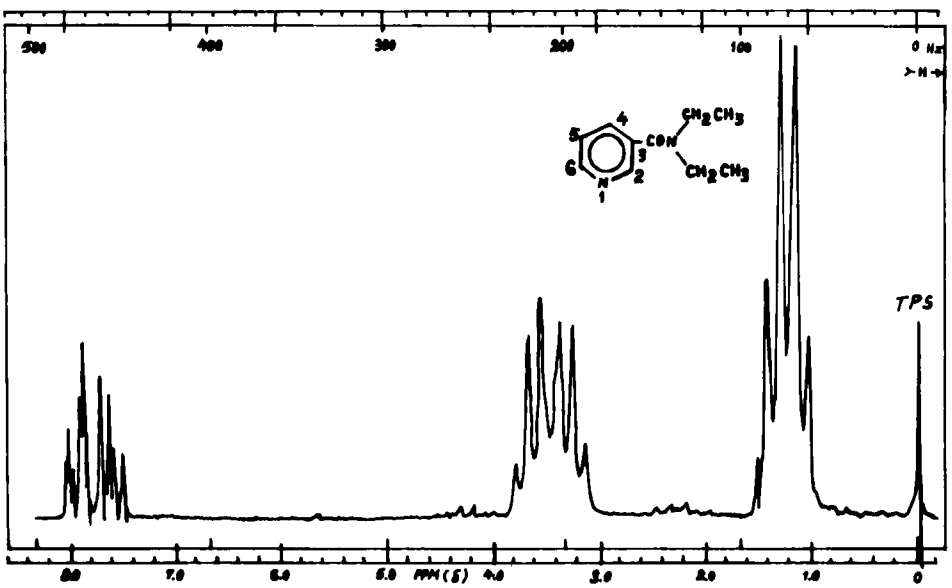


Fig.1 : Nikethamide (I) and 3-(trimethylsilyl) propionic acid, sodium salt in D_2O.

these two protons signals are ideal for precise integration, they are chosen for establishing the method.

Succinimide (II) is employed as an internal standard, since it exhibits a four proton singlet in water, assigned to its methylene protons (Fig. 2). Its signals are widely separated from that of I and that of the solvent signal occurring at 4.73 ppm. Thus allowing facile and accurate determination. The use of succinimide as an internal standard has been previously established[14]. Since compounds I and II are freely soluble in water, it becomes the solvent of choice. Moreover,

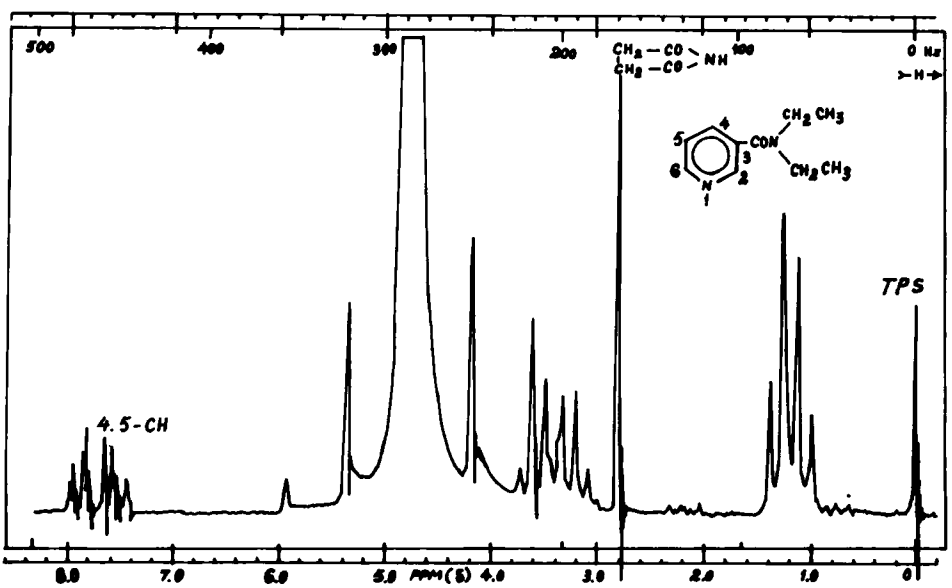


Fig. 2 : Nikethamide (I), succinimide (II) and 3-(trimethyl silyl) propionic acid, sodium salt in H_2O.

Table I - Determination of Nikethamide in Standard Mixture by PMR

Standard Mixture	Internal Standard Added, mg	Kikethamide		
		Added, mg	Found, mg	Recovery,% w/w
1	50	66	66.88	101.33
2	70	80	78.52	98.15
3	82	95	96.29	101.36
4	110	130	130.95	100.73
5	129	150	146.93	97.95
6	145	160	156.87	98.04
7	164	170	167.09	98.29
8	186	186	182.43	98.08
9	194	202	198.07	98.06
10	200	200	197.74	98.87
			Average =	99.07
			S.D. =	0.48

its two protons singlet appearing at 4.73 ppm does not interfere with the upfield protons of II and the downfield protons of I. Accordingly, the use of the expensive deuterium oxide is unnecessary.

A series of known standard I mixtures were prepared and determined by this PMR technique and the results are summarised

Table II - Determination of Nikethamide Infections by PMR.

Sample	Internal Standard, mg.	Nikethamide		
		Declared per injection,mg	Found, per injection,mg	Recovery,% w/w
1	69	375	365.09	97.36
2	73	375	365.77	97.54
3	77	375	365.13	97.11
4	278	375	377.38	100.64
5	280	375	382.55	102.01
6	286	375	355.42	94.78
7	300	375	372.82	99.42
8	305	375	380.57	101.49
9	317	375	393.22	104.86
10	340	375	387.95	103.45
			Average =	99.87
			S.D. =	1.39

in Table 1. The method is both accurate and precise, with a mean of 99.07 ± 0.48. The accuracy of the method is not significantly affected by the relative proportions of I and II. By applying this procedure to commercial injections of I, the results are in good agreement with the declared dosages (Table II).

The PMR method has distinct advantages over the other methods previously reported for the assay of I, being simple,

rapid and accurate. Moreover, the method provides an identification of the drug, thereby contributing to the specificity of the assay.

REFERENCES

1. Martindale, The Extra Pharmacopoeia, 27th Ed., p. 316, Pharmaceutical Press, London, 1977.

2. D.C. Garratt, "The Quantitative Analysis of Drugs", 3rd Ed., p. 444, Chapman and Hall Ltd., London, 1964.

3. J. Subert, M. Bachrata, L. Knazko, and A. Stemberova, Anal. Abstr., 1976, 30, 1E1.

4. Y.A. Beltagy, A. Issa, and S.M. Rida, Pharmazie, 1976, 31, 484.

5. S.P. Miskidzh'yan, Anal. Abstr., 1958, 5, 1350.

6. O. Pelletier and J.A. Campbell, J. Pharm. Sci., 1962, 51, 594.

7. W.M. Carmichael, Analyst, 1971, 96, 716.

8. M. Rink, R. Lux, and E. Franken, Anal. Abstr., 1959, 6, 1885.

9. H.Y. Yu and D. Tao, Anal. Abstr., 1959, 6, 4952.

10. G. Cavazzutti, V. Quercia, and A. Calo, Anal. Abstr., 1970, 18, 2740.

11. J.M. Newton, Anal. Abstr., 1971, 21, 537.

12. Ibid., 1976, 31, 3E29.

13. British Pharmacopoeia, p. 320, Her Majesty's Stationery Office, London, 1973.

14. M.A. Loutfy and M.M.A. Hassan, Spec. Lett., 1979, 12 (7 and 8), 591.

Received: June 10, 1980
Accepted: June 24, 1980