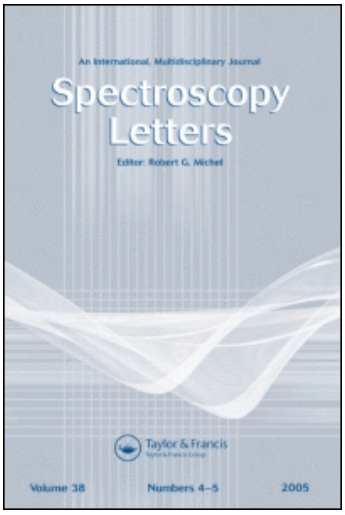

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Development of an Analytical Proton Magnetic Resonance (PMR) Spectroscopic Method for the Determination of Etilefrine in Bulk and Pharmaceutical Forms

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DEVELOPMENT OF AN ANALYTICAL PROTON MAGNETIC RESONANCE (PMR) SPECTROSCOPIC METHOD FOR THE DETERMINATION OF ETILEFRINE IN BULK AND PHARMACEUTICAL FORMS

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ABSTRACT :

An analytical proton magnetic resonance (PMR) spectroscopic method was developed for the determination of etilefrine hydrochloride [943-17-9] in bulk, I, tablets, II, drops, III, and injectables, IV,. The method is advantageous over those in the literature offering a fast, simple, specific, and accurate procedure.

INTRODUCTION :

Etilefrine hydrochloride, I, [943-17-9], is 2 ethylamino-1-(3 hydroxyphenyl)ethanol hydrochloride. I is a sympathomimetic compound[1-4] used in cases of hypotension.

Among the reported works pertaining to the analysis of I and its base, [709-55-7], a titration method involving the formation and subsequent extraction of ion-pairs with bromothymol blue[5], a spectral densitometric determination through thin layer chromatography, TLC, and fluorescence measurement[6], polarographic investigations of the nitroso derivatives[7], and an oxidation procedure followed by the transformation to the acetal forms[8], were previously performed. For the screening in biological fluids, different techniques were assessed,e.g. the capillary gas chromatography-negative chemical ionization mass spectrometry[9], high-pressure liquid chromatography,

HPLC,[10], mass spectrometry[11], TLC-spectrofluorometry [12], TLC [13], and a combination of TLC, gas liquid chromatography, and reversed phase HPLC[14].

The present work aimed at developing an accurate and specific method which is advantageous over those in the literature for the quantitation of etilefrine hydrochloride in bulk, I, tablets, II, drops, III, and injectables, IV, by using the PMR spectroscopy.

EXPERIMENTAL :

A Varian 90 MHz NMR EM 390 spectrometer was used to record all spectra. Authentic samples of etilefrine hydrochloride, I,(Boehringer Ingelheim, Ger.), and Effortil tablets, II, containing 5 mg of I/tablet, Effortil drops, III, containing 7.5 mg of I/g , and Effortil for injection, IV, containing 10 mg of I/ml were obtained from Chemical Industries Development Company "CID" / Boehringer Ingelheim International, Ger. Tetramethylsilane,(i), (BDH Chemicals, Ltd. Poole, England), deuterated dimethylsulfoxide-d6, (ii), (BDH Chemicals) containing 4% of deuterium oxide, 99.8% isotopic purity (Mallinckrodt Chemical Works, St. Louis, Mo.), and maleic acid, (iii), (PROLABO, Rhone-Poulenc) as an internal standard were used.

PROCEDURES :

PMR Determination of Authentic Samples of Etilefrine Hydrochloride, I.

Dissolve and centrifuge accurately weighed amounts of about 80 mg of I in a 1 ml of (ii) in a glass-stoppered centrifuge tube. Transfer 0.5 ml of the solution to an NMR tube containing 1 drop of (i). Add an accurately weighed amount of about 40 mg of (iii), dissolve and mix well. Place in an NMR spectrometer. Adjust the spin rate. Record the spectrum. Obtain an integral spectrum of the peaks of interest at least five times : the multiplet approximately between 6.7 and 7.36 ppm representing I, and the singlet at about 6.36 ppm of the internal standard, (iii).

PMR Determination of Etilefrine Hydrochloride Tablets, II,.

Weigh accurately one by one, 20 tablets and get the average of one tablet. Finely powder 20 tablets and weigh an accurate portion equivalent to 40 mg of I. Mix well with 1 ml of (ii) and centrifuge. Transfer 0.5 ml of the solution to an NMR tube containing 1 drop of (i). Add an accurately weighed amount of about 20 mg of (iii), dissolve and mix well. Proceed as earlier described starting with "... Place in an NMR ...".

PMR Determination of Etilefrine Hydrochloride in Liquid Preparations: Drops, III, and Injectables, IV. Mix the contents of each of 15 bottles or ampoules of III or IV respectively. Take an accurate portion equivalent to 80 mg of I in a 25 ml glass-stoppered conical flask. Evaporate to dryness, cool to room temperature, and dry well. Dissolve in 1 ml of (ii). Proceed as earlier mentioned beginning with "... Transfer 0.5 ml of the solution...".

The amount of etilefrine hydrochloride, I, as $C_{10}H_{15}N\,O_2$,HCl , under study is calculated as follows[15]:

$$\text{mg of sample analysed} = \frac{EWu}{EWs} \times \frac{Au}{As} \times Ws$$

EWu : formula weight of etilefrine hydrochloride, I, = 217.7 / 4 = 54.425

EWs : formula weight of maleic acid, (iii), = 116.07 / 2 116.07 / 2 = 58.04

Au : average value of integration of signals representing I.

As : average value of integration of the signal representing (iii).

Ws : weight in mg of the internal standard, (iii).

RESULTS AND DISCUSSION :

Figure 1 displays the PMR spectrum of etilefrine hydrochloride, I, under the given experimental conditions. The resonance peaks are referenced to tetramethylsilane, (i), of δ = 0.00 ppm. Deuterated dimethylsulfoxide-d6, (ii), proved to be a good solvent

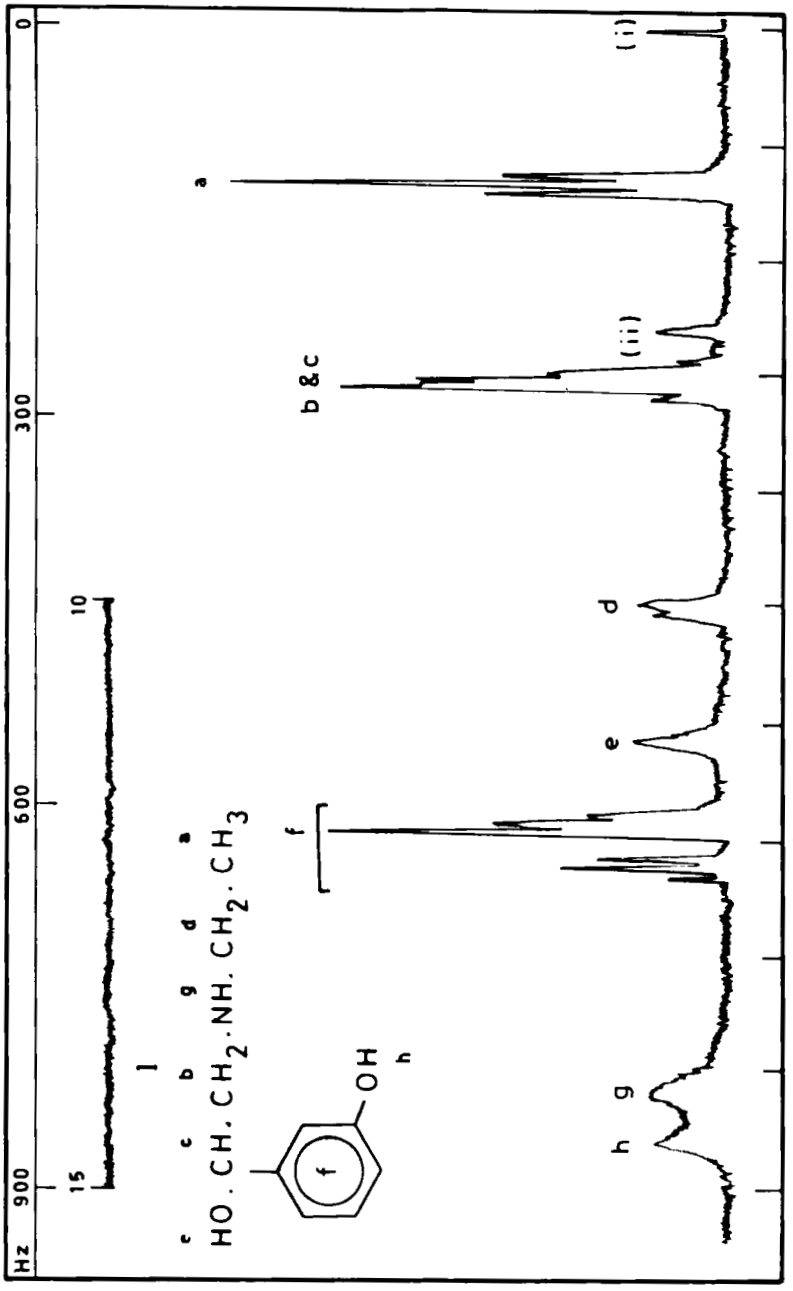

Figure (1) : 90 MHz spectrum of etilefrine hydrochloride, 1, and tetramethyl-silane, (i), in deuterated dimethylsulfoxide, (ii).

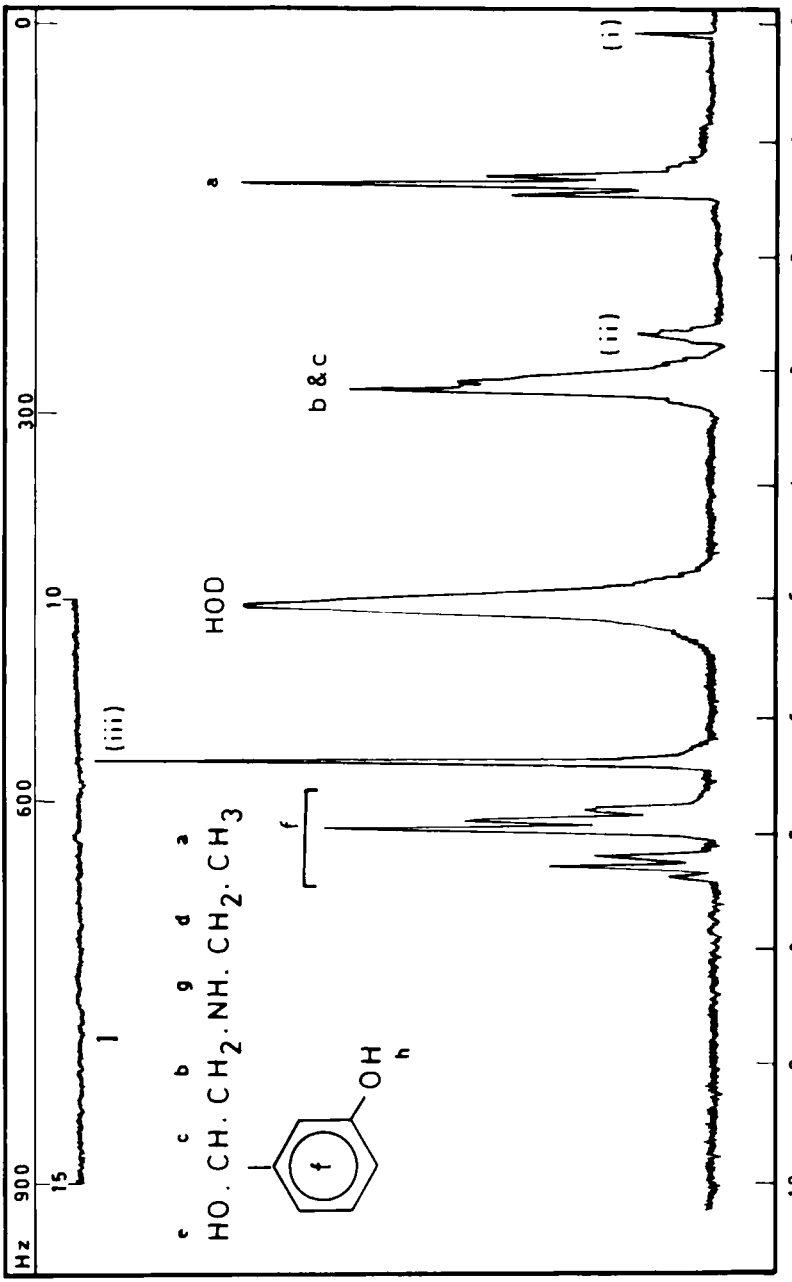

Figure (2) : 90 MHz spectrum of etilefrine hydrochloride, 1, tetramethyl-silane, (i), and maleic acid, (iii), in deuterated dimethyl-sulfoxide, (ii), and deuterium oxide.

Table (1): PMR spectroscopic determination of etilefrine hydrochloride in authentic mixtures: I, tablets: II, drops: III, and injectables: IV.

No.	I			II	III	IV
	Taken mg	Found mg	Recovery %	Recovery %	Recovery %	Recovery %
1	80.25	80.83	100.72	100.42	100.93	99.38
2	81.11	80.94	99.79	99.36	99.49	101.06
3	79.50	78.91	99.26	99.28	99.70	100.65
4	82.36	83.60	101.51	101.35	98.88	99.26
5	81.74	81.11	99.24	98.88	100.72	99.18
6	79.95	78.97	98.77			
7	80.90	80.49	99.50			
8	78.62	78.65	100.05			
Average percentage recovery ($\bar{x}$ %)			99.86 %	99.86 %	99.94 %	99.91 %
Standard deviation (s)			± 0.89	± 1.01	± 0.86	± 0.88
Variance			0.80	1.02	0.74	0.78
Coefficient of variation			0.89	1.01	0.86	0.88

of a chemical shift at about 2.6 ppm and did not interfere with the signals of I. Hence, all signals were evidently recorded.

The three methyl protons positioned (a) appeared as a triplet centered at about 1.35 ppm. The multiplet in the region between 2.84 and 3.25 ppm is due to the protons designated (b= 2H) and (c= 1H). The proton (d) showed a quartet approximately between 4.86 and 5.13 ppm which is overlapped by the peak of HOD in figure 2. The proton (e) of the alcoholic -OH group is manifested as a characteristic broad singlet centered at about 6.15 ppm which disappeared on using deuterium oxide giving obviously room to the peak of the internal standard (Figure 2). The distinguished broad singlets downfield centered at about 9.21 and 9.64 ppm are ascribable to the protons (g= 1H) and (h= 1H) of the -NH and the phenolic -OH groups respectively which disappeared in figure 2 exchanging with deuterium oxide . The m-substituted ring (f) is shown as a multiplet in the region nearly between 6.7 and 7.36 ppm due to the four aromatic protons, the integration of which favored the analytical measurement . Maleic acid, (iii), was chosen as an internal standard since it appears as an isolated strong singlet at approximately 6.36 ppm due to the olefinic protons contributing to the quantitation of I. The relative proportion of (iii) to I seemed to be satisfactory for the given range of concentration.

Table 1 compiles the results of the PMR spectroscopic determination of I and its pharmaceutical forms of tablets, II, drops, III, and injectables, IV. The dosage forms were assayed in a concentration favoring the analytical conditions. The method proved to be of fairly relevant precision, specific, and provides a time saving and simple manipulating technique compared to those in the literature.

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