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PMR DETERMINATION OF PRAZIQUANTEL

Mamdouh F. Metwally, Abdallah A. El-Shanawany
Analytical Chemistry Department, Faculty of Pharmacy, Zagazig University, Egypt.

Abd El-Aziz Bayomi
Analytical Chemistry Department, Faculty of Pharmacy, Cairo University, Egypt.

Mohsin M. El-Zareh
Department of Chemistry, Faculty of Science, Zagazig University, Egypt.

ABSTRACT

Pmr techniques have been used for the determination of praziquantel as sum integeral of the cyclohexane protons as multiplet that appear at 1.1-2 ppm and as compared to the sum integeral of the 1,4-disubstituted aromatic protons system as doublet of doublet that appear at 7.5-8.5 ppm using N,N-dimethylaminobenzaldehyde as internal standard. The obtained results shows % recovery of mean average 100.39. The method is valid for the determination of praziquantel in tablet and in presence of its induced degradation products.

INTRODUCTION

The anthelmintic activity of pyrazinoisoquinoline derivatives was first discovered by Merck in 1972[1-3]. Praziquantel is antibilharzial drug used in treatment of Schistosomiasis having no side effects and free from toxic properties. The synthesis and structure of the drug (shown in figure 1)as 2-(cyclohexylcarbonyl)-1,2,3,6,7-11b hexhydro-4H-pyrazino-(2,1-a.isoquinoline-4-one) has been reported[4].

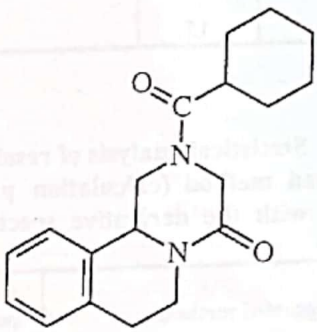

Fig. (1): Structure of praziquantel

Many methods have been described for the quantitative determination of praziquantel including fluorometric methods [5,6], gas chromatography [7], colorimetry [10], and HPLC [11-13].

The present paper describes a quantitative method for the determination of praziquantel using ^{1}HNMR technique and application of this method in pharmaceutical tablets.

EXPERIMENTAL

Materials and Apparatus:

1-Praziquantel was obtained from Merck, Darmstadt, Germany and Biltericide tablets from Bayer Leverkusen, Germany. Each tablet is lablled to contain 600 mg of praziquantel.

2-N,N-dimethylaminobenzaldehyde was obtained from Prolabo Chemical Co.

3-Solvents: Chloroform (spectroscopic grade) and deuterated dimethyl sulfoxide (DMSO-d_6) were obtained from May and Baker Chemical Co.

Apparatus:

^{1}H nmr spectra were carried out using Varian EM 360 a nuclear magnetic resonance spectrometer, measuring frequency 90 MHz and Bruker AM 300 nuclear magnetic resonance spectrometer: measuring frequency 300 MHz Am.

METHODS:

Quantitative Determination of Praziquantel:

Assay of praziquantel authentic sample and in tablet dosage form, was carried out as follows : A specified weight of praziquantel (10-120 mg) was accurately weighed, and transferred into a weighing bettle containing 20 mg of the internal standard N,N-dimethylaminobenzaldehyde as well as one ml of deuterated dimethylsulfoxide (DMSO-d_6). The mixture was shaked up vigrously by the aid of gentle warming and then filtered. The clear filtrate was transferred to a clean NMR tube and the spectrum was run. Integration was observed at the peaks δ 1-2, 6.85-7.25 and 7.5-8.5 for three separate experiments and the avarage of these experiments was calculated. The amount of drug was then calculated in the usual manner[14,15].

The same procedure was applied to the tablets after grinding and extraction with chloroform, evaporated under reduced pressure, and the reuslting dried powder was used for the assay.

All experiments of the Pmr technique were carried out at constant room temperature. (10°C).

RESULTS AND DISCUSSION

^{1}Hnmr of praziquantel has shown the following signals (table 1) using 300 MHz frequency and AM 300 nmr spectrometer apparatus according to the structure in fig.1. The ^{1}Hnmr was given the following assignment.

Table (1): ^{1}Hnmr of praziquantel, (DMSO-d_6) using measuring frequency 300 MHz (TMS as int. stand).

ppm	Multiplicity	Assignment
1.1-2	m.	Cyclogexane protons
2.27	m.	H - 8
2.43	m.	H - 6
2.48	m.	H - 2
2.71	m.	H - 9
3.76	d.	H - 5
4.28	d.	H - 4
4.41	dd.	H - 1
4.84	m.	H - 7
5.16	m.	H - 3
6.59-7.25		aromatic protons

^{1}Hnmr of praziquantel (fig.1)using measuring frequency 90 MHz showed isolated peak of aromatic protons at 7.95 ppm integerating four protons due to the aromatic benzene nucleus. Also the spectra showed complex multiplet pattern at 5.2 ppm, integerating four protons H_1, H_3, H_4 and H_7 and a multiplet of cyclohexane protons integerating eleven protons at 1.1-2 ppm. These integerated signals are quite separated from each other, and can be used for determination of the pure drug accurately.N,N-dimethyl-aminobenzaldehyde which is inert toward the praziquantel shows ^{1}Hnmr absorption signals (fig 2) doublet of doublet at 7.5, 8.5 ppm due to 1,4-disubstituted benzene (AA'X'X' system), this peak itegrating 4 hydrogen is far from the integrated cyclohexane protons (11 H at 1.1-2 ppm) and far from the integrated 4 protons of aromatic nucleus of praziquantel (4H at 7.95 ppm) Therefore, the internal standard N,N-dimethylaminobenzaldehyde can be used as internal standard to be compared with the pure drug praziquantel. Besides this advantage the free solubility of the standard in the solvent used and its high purity as well as the stability and compatibility in contact with the drug offer advantage also for the use of N,N-dimethylaminobenzaldehyde.

Table (2) describes the result obtained from the tablet analysis by Pmr suggested method. The Pmr spectrum (fig 3) shows a representing example of one experiment. The result as shown in table (2) have average % recovery of 100.39 with S.D. = 1.99 and t_{cal} = 0.937.

The suggested method reveals that it can be used for qualitative identification of the purity of drug and also for quantitative determination either in pure form or in presence of acid and alkaline induced degradation products gives absorption signals that either down field o up field to the signals used for determining the drug and therefore they will no interfere in the determination of the intact drug (fig. 4,5) Other Products that may removed by extraction process and filtration also do not interfere in the determination. The method is compared with the derivative spectroscopic method[16] used for determining the drug in tablet, Table (3)

Table (2): Determination of praziquantel by Pmr method using the two calculations.

Drug Added In mg	Drug Found* in mg (I)	% Recovery	Drug Found* in mg (II)	% Recovery
25.0	25.03	100.10	24.29	97.1
51.6	51.33	99.48	51.75	100.29
		96.90		100.39
		95.93		98.91
97.6	67.70	100.30	69.38	102.78
		100.40		102.33
		102.24		103.50
81.3	81.17	100.21	80.42	99.06
		100.58		102.13
		100.8		102.71
101.7	101.93	100.23	98.93	97.37
		102.00		
120.4	120.44	100.03	120.18	99.82
		99.04		99.65
		99.45		99.24
X-(mean)		99.84		100.39
N		15		14

Table (3): Statistical analysis of results obtained by the suggested method (calculation procedures I,II) compared with the derivative spectrophotometric method.

Suggested method		Derivative spectrophotometric method
	Calculations I	Calculations II	
n (Number of set of results)	15 (n_1)	14 (n_2)	6 (n_3)
X (Mean average of results)	99.84	100.39	100.72
(S) (Standard deviation)	1.31	1.99	1.18
W (range = X (highest) - x lowest)	6.31	5.44	2.81
Absolute error	- 0.16	+ 0.39	0.72
(Pooled Standard deviation	0.197	0.955	
Relative range	0.063	0.054	0.028
Fo when	1.53 (2.79)	2.81 (2.85)	
1- $P = n1 + n2 - 2$	P1 = 14	P_2 = 13	
2- $P_1 = n_1 - 1$, $P_2 = n_2 - 1$	P_3 = 5	P_3 = 5	
3- $P_3 = n_3 - 1$			
t_{cal}	1.19 (2.093) at P = 19	0.937 (2.16) at P = 18	
	P = $n_1 + n_2 - 2$	P = $n_2 + n_3 - 2$	

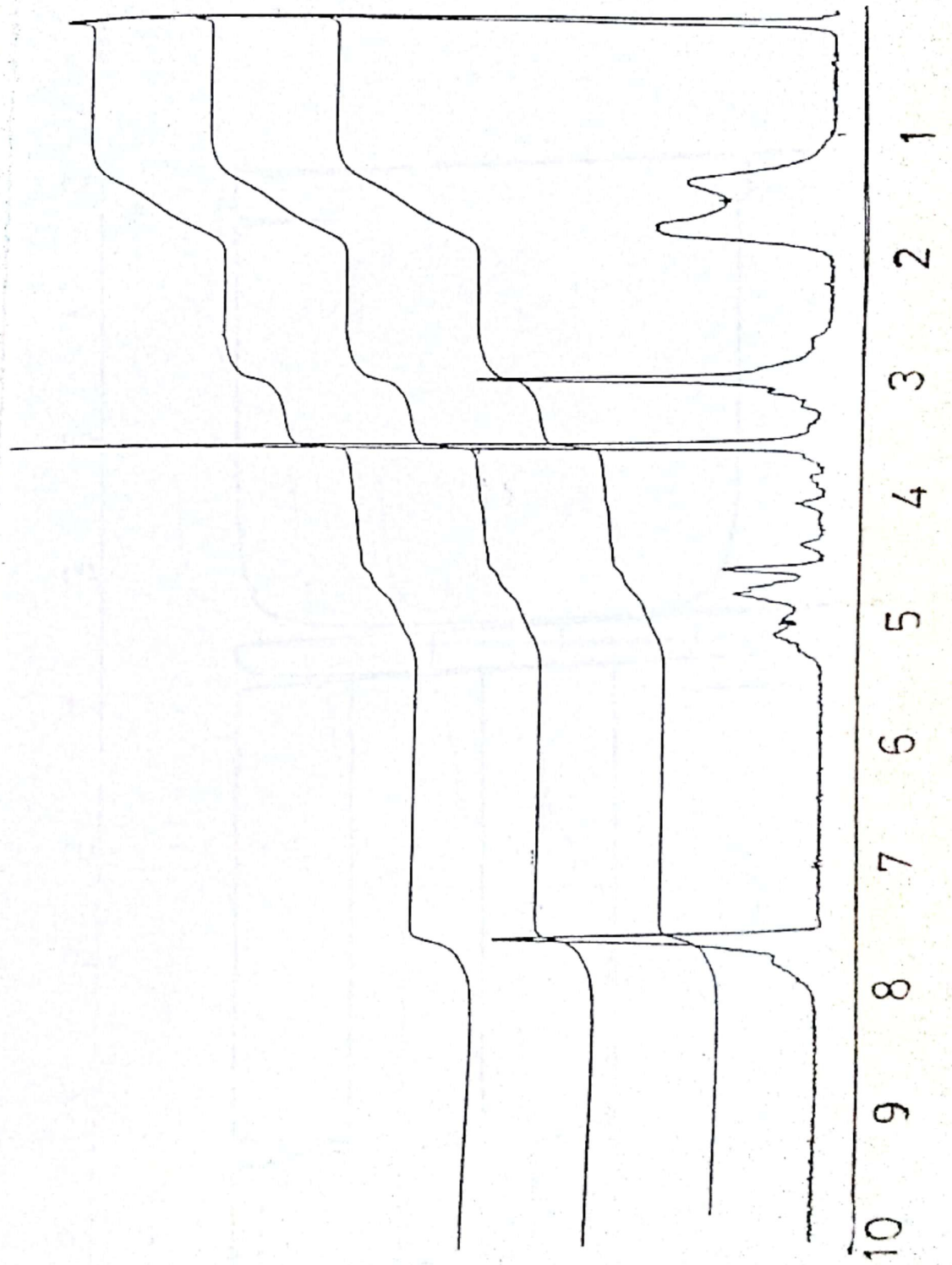

Figure (1) : ^{1}H NMR of praziquantel (60 mg).

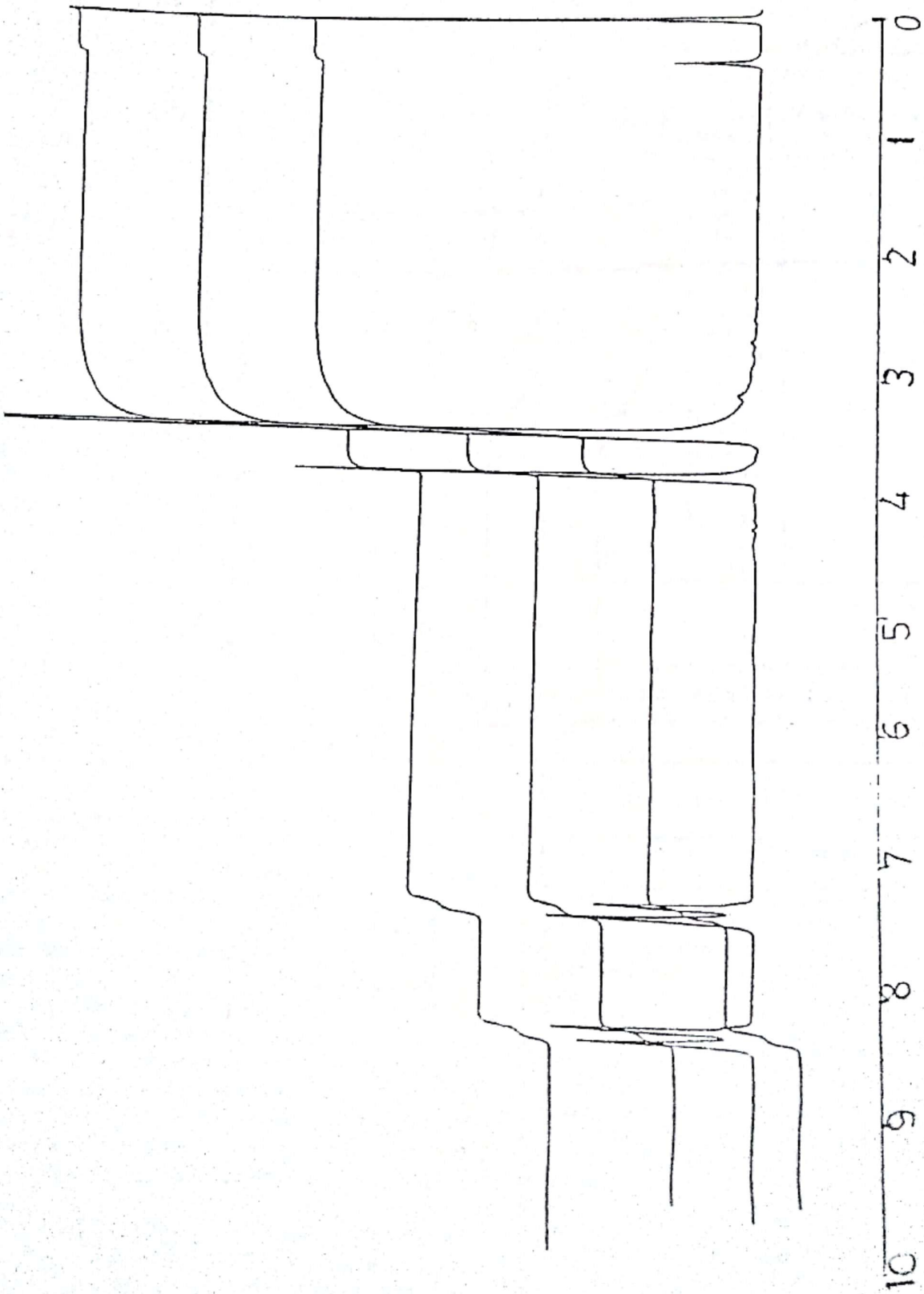

Figure (2) :- H^1 NMR of N,N-dimethylaminbenzaldehyde (20 mg).

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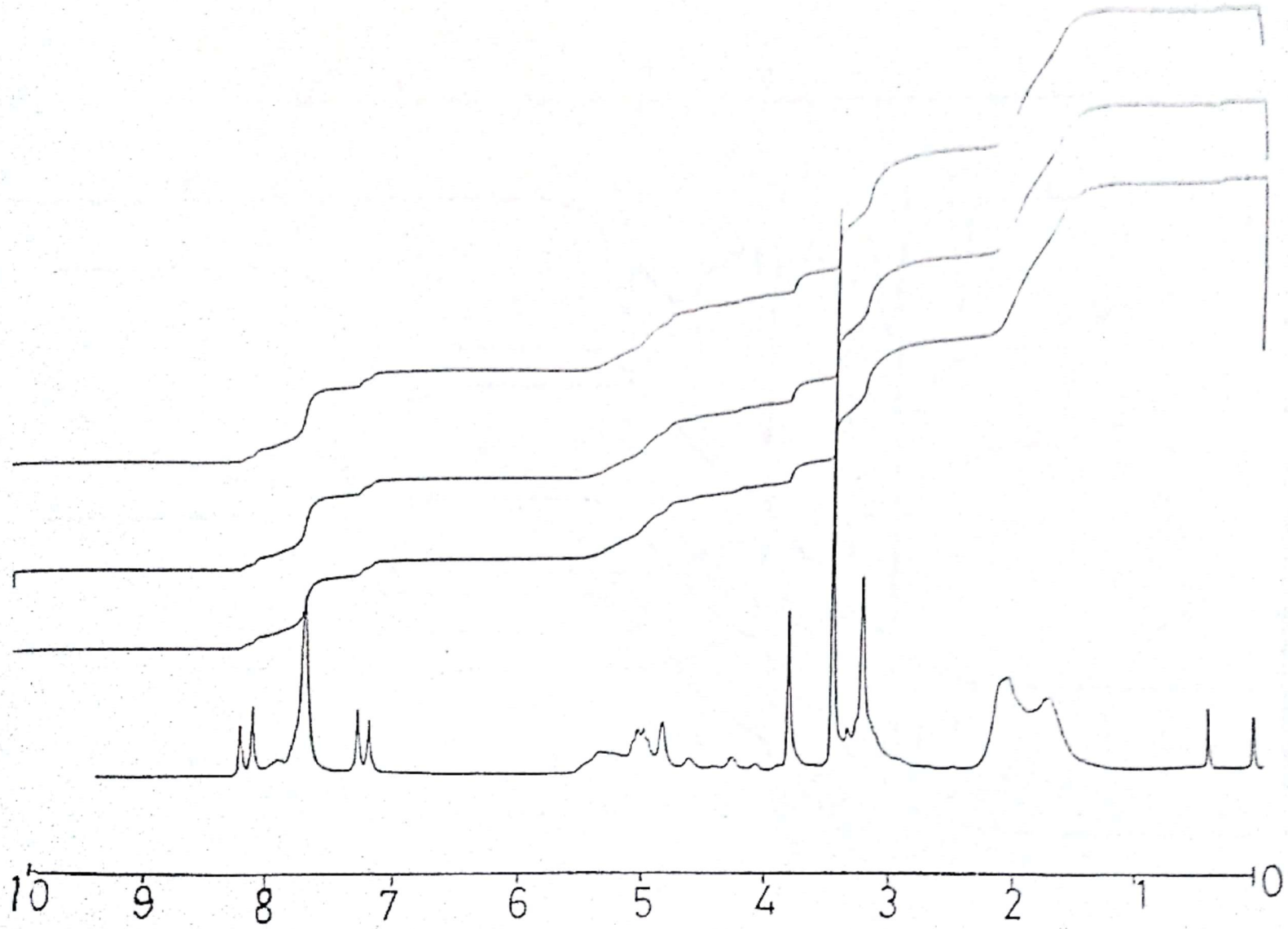

Figure (3) :- H^1 NMR of praziquantel (80 mg) and N,N-dimethylaminobenzaldehyde (20 mg) as internal standard.

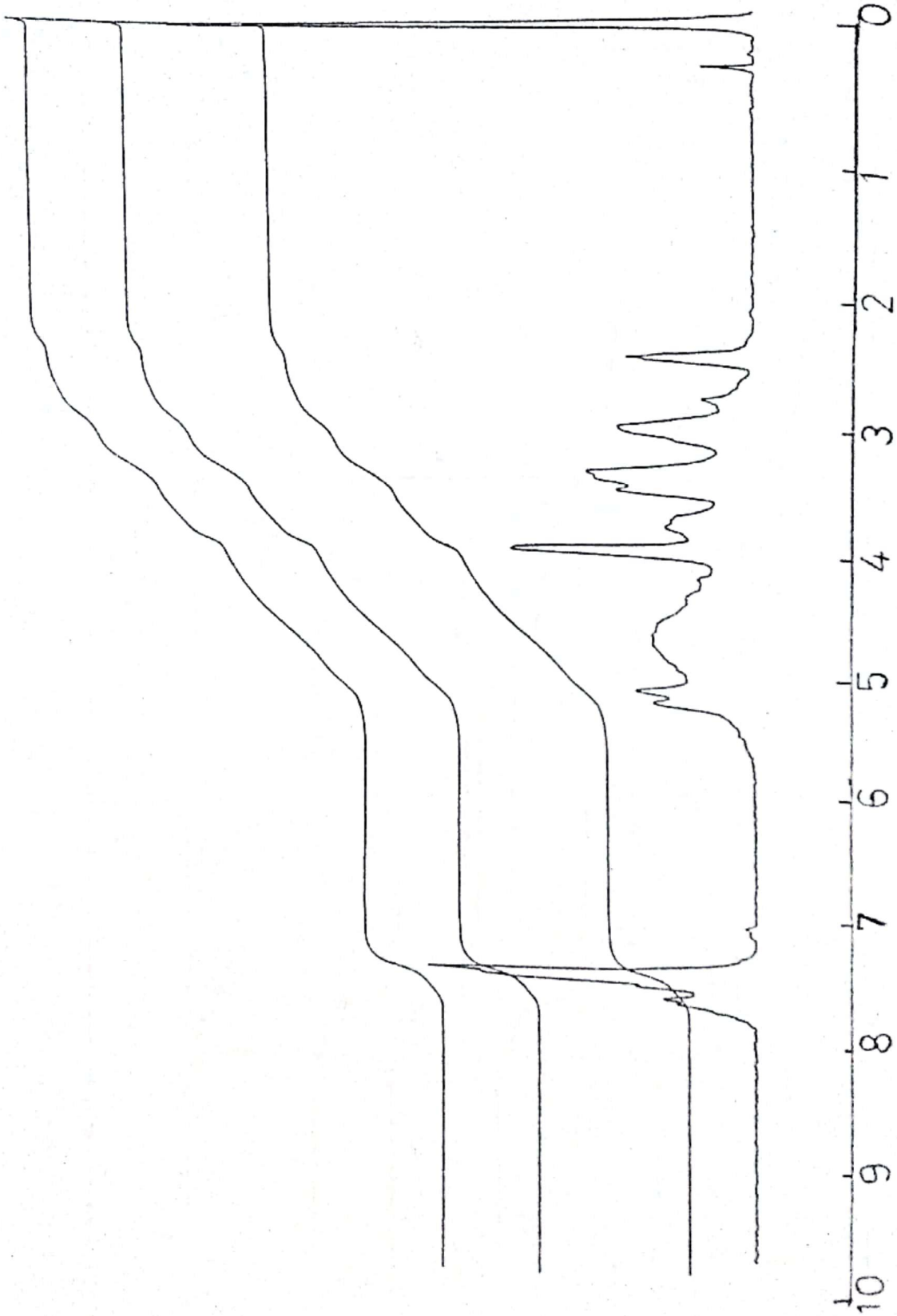

Figure (4) : ^{1}H NMR of acid induced degradation products of *praziquantel (24.7 mg)* without praziquantel.

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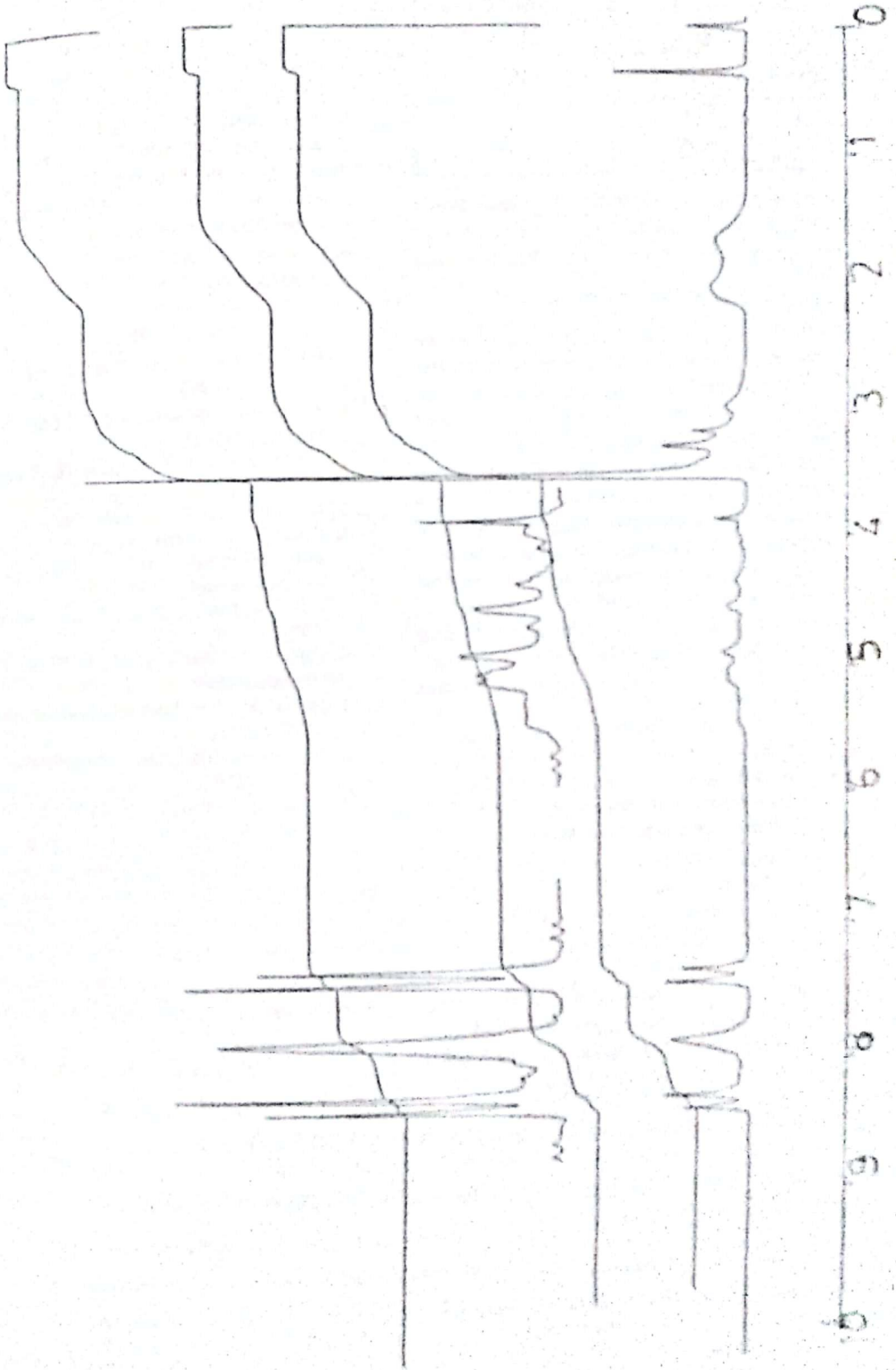

Figure (5): ^{1}H NMR of prazepamol (20.3 mg) and acid reduced degradation products of prazepam (15.1 mg) and N,N- dimethylaminobenzaldehyde (21.1 mg) as internal standard.

Table (4): Results of analysis of biltericide by the proposed pmr method.

Amount added of standard mg	Amount added in mg of drug	% Recovery
21.4	101.7	100.14
20.8	81.3	99.67
25.2	67.0	101.25
20.37	59.22	100.003
21.04	59.43	100.12

The broadening of the peak of cyclohexane is being affected by temperature. Thus, carrying out all the experiments at constant temperature has overcome this problem [15].

Statistical Analysis

Statistical analysis of the results obtained by the suggested method (procedure A) compared with the derivative spectrophotometric method, shown in table (3) revealed that proposed method is more precise and accurate than the spectrophotometric method.

The calculation based on the use of integrated (4H) of the 1,4- disubstituted benzene, AAX'X' system of the internal standard and the integrated (11 H) of cyclohexane protons of the drug. The ratio of the peak length of the drug to the peak length of internal standard ld/ls in mm was calculated and plotted against the concentration Wd/Ws in mg (the ratio of drug weight in mg to the weight of internal standard in mg) gave straight line and the regression equation was calculated and found to be :

$$Y = - 0.047 x + 1.325, \text{ (calculation II)}$$

and $r^2 = 0.999$

where: r^2 = correlation coefficient

x = concentration ratio in mg.

Y = peak length ratio in mm.

The validity of the above regression equation was tested by the assay of tablets and the results showed good accuracy as shown by the % recovery and precision (table 4).

Also the concentration ratio of the drug to internal standard in mg showed linear relationship to the height length ratio of the drug to internal standard in mm using (4H) integeration of AAX'X' system of internal standard and the (4H) integeration of AA'B' system of the benzene ring of praziquantel. The concentration ratio in mg was found to be linear with the peak height ratio in m.m. The equation of the regression analysis $Y = 0.061 + 0.44 x$, where $r^2 = 0.99$ (calculation I).

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تعيين البرازيكوانتيل بإستخدام الرنين النووى المغناطيسى

ممدوح محمد فكرى – عبد الله الشنوانى – عبد العزيز بيومى*– محسن الزارع**

قسم الكيمياء التحليلية – كلية الصيدلة – جامعة الزقازيق– و* جامعة القاهرة.

** قسم الكيمياء – كلية العلوم – جامعة الزقازيق – مصر.

تم تعيين البرازيكوانتيل بإستخدام طريقة الرنين المغناطيسى للنواة بقياس مجموع ما بين الطورين كمجموع البروتينات المتعددة للسيكلوهيكسان التى تظهر عند ١,١ –٢ جزء من المليون والمقارنة لمقياس المجموع ما بين الطورين كمجموع البروتينات الحلقية الثنائى – الثنائى الخير مستبدلة التى تظهر عند ٧,٥ – ٨,٥ جزء من المليون بإستخدام ن – ن داى ميثيل امينوبنزالدهيد كمعيارى داخلى لتعيين البرازيكوانتيل.

النتائج وجدت تعطى نسبة تعيين بمتوسط نسبى قدر ١٠٠،٣٩ والطريقة محققة لتعيين البرازيكوانتيل فى الأقراص وفى وجود المواد التجريبية المقتطة.