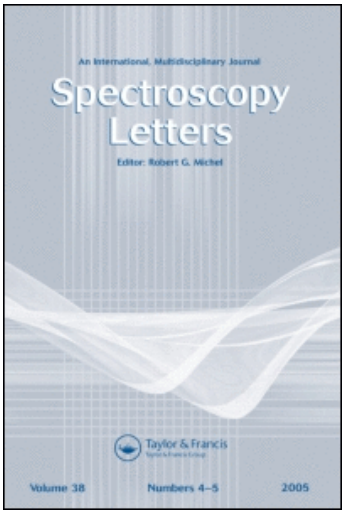

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Application of PMR Spectrometry in Pharmaceutical Analysis

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APPLICATION OF PMR SPECTROMETRY IN PHARMACEUTICAL ANALYSIS

II. ASSAY OF TOLAZOLINE*

Key Words: PMR Spectrometry, Pharmaceutical Analysis, Assay of Tolazoline.

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Abstract:

A new method, involving the application of PMR spectrometry for the assay of tolazoline and its tablets, is proposed. The PMR spectrum of tolazoline has two well-defined singlets. The proposed method involves: 1) The extraction of tolazoline from alkaline medium with carbon tetrachloride containing hexamethylcyclotrisilazane as internal standard. 2) Comparing the integral of one of the singlets of tolazoline to that of the sharp singlet of hexamethylcyclotrisilazane.

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* For previous paper in this series see reference 1.

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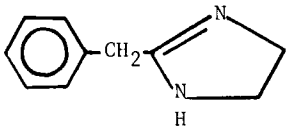
The method reported in this study is simple and rapid. Also it gives accurate and reproducible results; 99.58 ± 1.32% for authentic tolazoline HCl and 100.06 ± 2.66 for tolazoline HCl tablets (Priscol®). In addition, the PMR spectrum obtained helps in confirming the identity and purity of the drug.

INTRODUCTION

Tolazoline (4,5-dihydro-2-phenylmethyl-1H-imidazole), an alpha-adrenergic blocking agent, has the structure shown below. It is official in B.P. 1973 as its hydrochloride salt. The assay method for the pure substance and its tablet involves titration in glacial acetic acid medium using solvent blue 19 as indicator and acetous perchloric acid as titrant[2]. On the other hand, the B.P. 1968 method of tolazoline or its tablets is through extraction of the base in alkaline medium by chloroform followed by removal of



solvent, addition of known excess of standard hydrochloric acid and back titration against standard sodium hydroxide solution using methyl red as indicator[3]. Tolazoline can be determined gravimetrically through precipitation by Reinecke's salt or tungstosilicic acid[4]. A non-aqueous titration method similar to B.P. 1973 has been reported by Bayer and Posgay[5]. Indirect complexometric

titration methods were reported where tolazoline is precipitated by potassium idobismuthate reagent[6] or by cupric picrate[7]. In both cases the remaining metal ion is determined complexometrically by titration against EDTA. Many authors reported different methods, for the estimation of tolazoline in its pharmaceutical preparations, which depend on the its UV absorption spectral properties[8-10]. As other imidazoline derivatives tolazoline undergoes Laubies color test; this is the basis of a colorimetric procedure developed by Slack and Mader[11]. Also Bogs and Daerr described a colormetric method for its assay making use of the color picrate method of Howorka[12,13]. Thin layer and gas chromatographic methods have been used for the isolation and identification of tolazoline[14-15]. Boon and Sudds[17] developed a gas chromatographic procedure for its quantitation in its pharmaceutical preparations.

This communication describes a new method, involving the application of PMR spectrometry, for the assay of tolazoline and its tablets.

EXPERIMENTAL

A Varian T60-A NMR Spectrometer was used throughout the study. The internal standard, hexamethylcyclotrisilazane, was purchased from ICN K&K Labs, Plainview, N.Y., U.S.A. Carbon tetrachloride, spectral grade, was used. Authentic tolazoline hydrochlorides and tolazoline hydrochloride tablets (Priscol ^{R}) were obtained from Ciba-Geigy Ltd., Basle, Switzerland.

PROCEDURE

For Authentic Tolazoline HCl: Place a weighed aliquot of tolazoline HCl, in the range of 200 mg, in a 10 ml stoppered flask. Add 5.0 ml of water and 500 mg of sodium bicarbonate and mix well. Add 5.0 ml of carbon tetrachloride containing the internal standard; the concentration of internal standard is about 10 mg/ml. Stopper the flask and place it in a shaker for 10 minutes to affect extraction of tolazoline. Filter, using cotton pledget, then transfer 0.4 ml of the clear carbon tetrachloride solution to an NMR tube.

Run the PMR spectrum of the solution adjusting the spin rate to eliminate side bands as much as possible. Measure the integrals of the singlets at 0.00 and 3.37 ppm, for the internal standard and tolazoline respectively, three times and get the average of each. Calculate the weight of tolazoline using the following equation:

$$W_t = \frac{H_s M_t}{H_t M_s} \times \frac{I_t W_s}{I_s} = \frac{18 \times 160.2}{6 \times 222.3} \frac{I_t W_s}{I_s}$$

$$= 2.162 \times \frac{I_t W_s}{I_s}$$

Where I = integral of signal (mm)

H = Number of protons within the signal.

M = Molecular weight

W = Weight (mg)

The subscripts "s" and "t" stand for the internal standard and tolazoline respectively.

For Tolazoline HCl Tablets (Priscol^{R}):

Each tablet is claimed to contain 25.00 mg of tolazoline HCl i.e. equivalent to 20.364 mg of tolazoline base.

Place 5 tablets in a 10 ml stoppered flask to which add 5.0 ml of water and 500 mg of sodium bicarbonate. Disentegrate the tablets and mix well. Add 5.0 ml of carbon tetrachloride containing the internal standard solution (about 10 mg/ml). Stopper the flask and continue extraction as previously mentioned under authentic tolazoline HCl.

The final carbon tetrachloride solution would contain 101.82 of tolazoline base. Transfer about 0.4 ml. of the clear carbon tetrachloride solution and run its PMR spectrum and proceed as previously described.

Results and Discussion:

The method described in this communication involves firstly the extraction of tolazoline base liberated by alkalinizing the aqueous solution of tolazoline hydrochloride. The PMR spectrum of tolazoline extracted by carbon tetrachloride containing known amount of hexamethylcyclotrisilazane, is then secondly recorded on Varian T60-A NMR Spectrometer. This standard was chosen in this study as it has been previously recommended and used[1,18-20].

The PMR spectrum of the carbon tetrachloride solution of tolazoline, using hexamethylcyclotrisilazane as internal standard, is shown in Figure 1.

The tolazoline signals, measured in δ-scale, are referenced to hexamethylcyclotrisilazane whose singlet was positioned at 0.00 ppm. Those signals are : a singlet at 3.37 ppm for the $-CH_2-CH_2-$ of the imidazoline moiety as well as the $-CH_2-$ portion of the benzyl group, and another singlet at 7.13 ppm for the monosubstituted phenyl ring. Either signal could be chosen for quantitative determination by comparing its integral to that of the sharp singlet of a known amount of the internal standard. In this study the singlet at 3.37 ppm was chosen.

The -NH- proton shows up as broad band in the range 4.0 - 6.00 ppm depending on the concentration of tolazoline, however, it does not interfere with the measurement of the integral of either singlet.

Table 1 shows the percent recoveries obtained when this method is used for the assay of authentic tolazoline HCl (data are calculated in terms of tolazoline base). The results demonstrate good precision (average recovery is 99.58 $\pm$ 1.32%). On the other hand, when the method is used for the assay of tolazoline HCl tablets (Priscol ^{R}) it gives reasonable results as indicated in Table 2 (average recovery is 100.06 $\pm$ 2.66 %).

The percent recoveries obtained by this method comply with the requirements cited by B.P. 1973 for tolazoline HCl powder (99 - 101%)

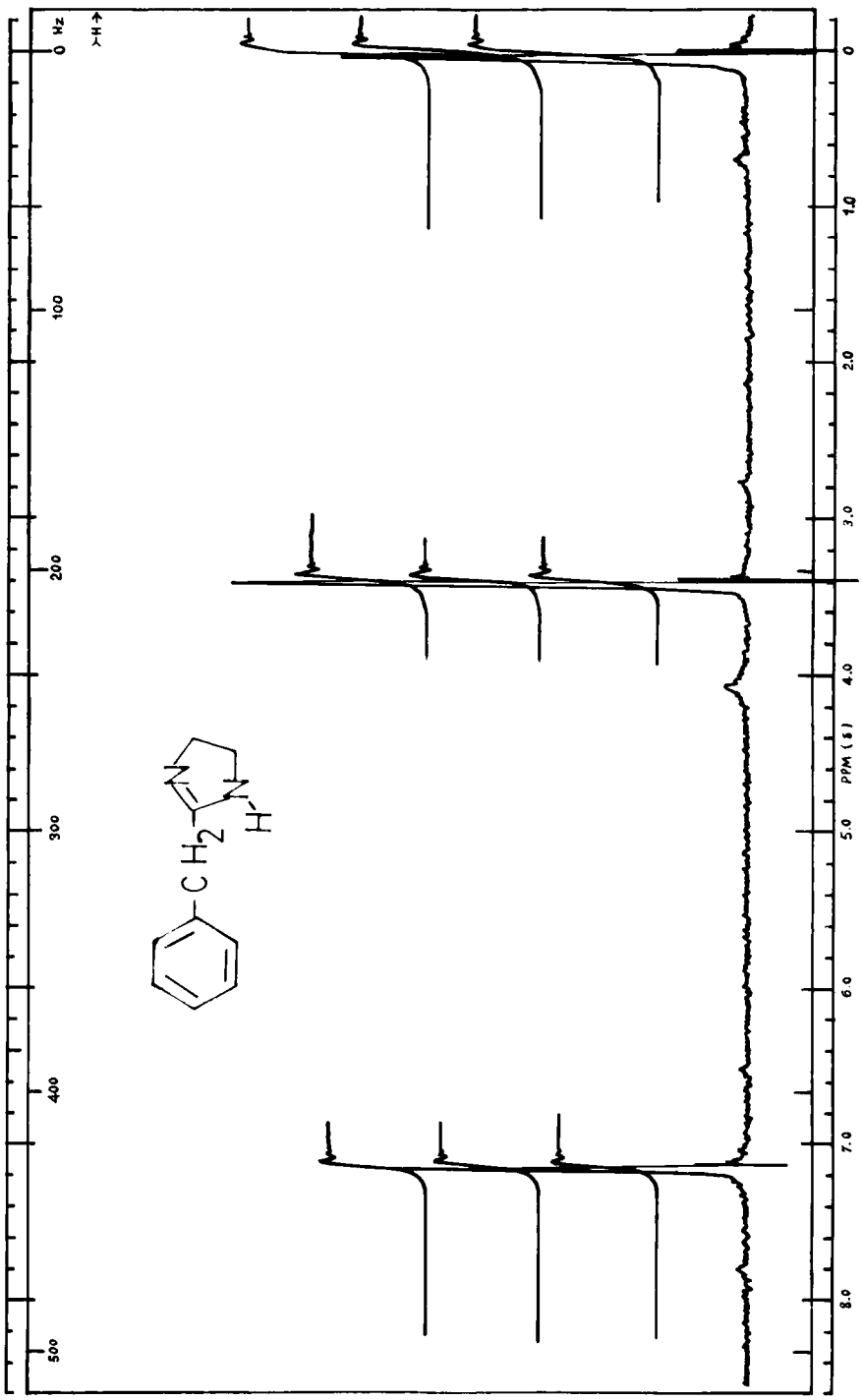


Figure 1. - PMR spectrum of tolazoline and hexamethylcyclotrisilazane in carbon tetrachloride.

Table I. - The Percentage Recoveries of Authentic Tolazoline Hydrochloride.

Sample No.[a]	Tolazoline HCl Taken (mg)	Tolazoline[b]		% Recovery
		Taken (mg)	Found (mg)	
1	197.00	160.30	155.17	96.80
2	196.00	160.00	163.20	102.00
3	196.10	160.08	158.16	98.80
4	196.50	160.20	161.16	100.60
5	196.60	160.40	159.04	99.15
6	196.90	160.70	161.80	100.68
7	196.70	160.40	160.00	99.75
8	196.60	160.40	158.60	98.88
			Average % Recovery = 99.58 $\pm$ 1.32[c]	

[a] The concentration of hexamethylcyclotrisilazane in all solutions is 49.65 mg.

[b] Each gm of Tolazoline HCl is equivalent to 0.8138 gm of Tolazoline base.

[c] Standard deviation.

Table II. - The Percentage Recoveries of Tolazoline Hydrochloride Tablets (Priscol[R]).

Sample No.[a]	Tolazoline Base in five Tablets		% Recovery
	Claimed (mg)[b]	Found (mg)	
1	101.82	99.78	98.00
2	101.82	99.78	98.00
3	101.82	102.58	100.75
4	101.82	103.67	101.82
5	101.82	99.44	97.66
6	101.82	105.83	103.94
7	101.82	101.51	99.70
8	101.82	102.54	100.71
Average % Recovery = 100.06 ± 2.66[c]			

a The concentration of hexamethylcyclotrisilazane in all solutions is 49.65 mg.

b Each tablet is claimed to contain 25.00 mg tolazoline HCl which is equivalent to 20.364 mg of tolazoline base.

c Standard deviation.

and for tolazoline HCl tablets (92.5 - 107.5%). However, it should be pointed out that both methods, described by B.P. 1973 and B.P. 1968, involve titration of tolazoline base by standard acid and thus they are nonspecific for tolazoline. On the contrary, the proposed method is specific for tolazoline and there was no evidence for interfernece from excipients when the method is used for tolazoline HCl tablets. In addition, the method is simple and rapid. It provides the PMR spectrum of the drug which helps in its identification and checking its purity.

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