Assay of methimazole by n.m.r. spectroscopy

HASSAN Y. ABOUL-ENEIN, *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Riyadh University, Riyadh, Saudia Arabia*

An n.m.r. procedure is described by which methimazole (1-methylimidazole-2-thiol) is determined in pure and tablet formulation. The method is rapid, accurate, precise (s.d. = 0·95%), and also provides a specific identification of methimazole.

Materials. Methimazole (1-methylmirazole-2-thiol) as well as formulated tablets of this drug were obtained from Eli Lilly & Co., Indianapolis, Indiana; methylene chloride and carbon tetrachloride (spectroanalysed grade) were obtained from Fischer Scientific and Co., Fair Lawn, N.J.

Method. Weigh and finely powder not less than 20 methimazole tablets. Dry the powdered tablets over phosphorous pentoxide (45 °C; 8 h). Weigh accurately a portion of the powder, equivalent to a specific amount of methimazole, and place in 50 ml stoppered flask. Use a measured amount of carbon tetrachloride containing 10% methylene chloride so that the final concentration of methimazole will be about 20 mg ml^{-1}. Add an accurately weighed amount of internal standard (benzoic acid) to the sample solution. Stopper the flask and shake (10 min). Filter via a cotton pledget, then transfer about 0·4 ml of the clear solution to an analytical n.m.r. tube and add TMS. Determine the absorption spectrum* integrating the peaks of interest (the N–CH_3 protons of methimazole at 3·56 δ and the aromatic protons of benzoic acid at 7·5 and 8·13 δ); record the mean of five integrations. The amount of methimazole may be calculated as follows:

$$\text{mg of methimazole} = \frac{A_1}{A_{11}} \times \frac{EW_1}{EW_{11}} \times W_{11}$$

A_1 = integral value of the N–CH_3 signal (methimazole); A_{11} = integral value of the aromatic protons (benzoic acid); EW_1 molecular weight of methimazole/3 = 38·06; EW_{11} molecular weight of benzoic acid/5 = 24·42; W_{11} weight (mg) of benzoic acid.

*A Varian T-60 n.m.r. spectrometer was used.

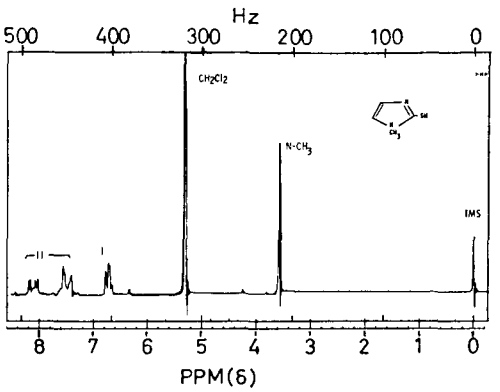

FIG. 1. n.m.r. spectrum of methimazole(I) and bezoic acid(II) in carbon tetrachloride containing 10% methylene chloride.

Samples of pure methimazole in the range 40–75 mg were analysed (benzoic acid in approximately the same amount was added to each tube as an internal standard). The mean recovery in nine separate experiments was 99·12% (s.d. 0·96 relative s.d. 0·0097).

The use of 10% methylene chloride is dictated by the fact that methimazole is very soluble in this solvent but only slightly soluble in CCl_4. The methylene resonance appears at 5·3 δ clear of the peaks of interest. Results of the assay of 5 mg tablets of the drug gave a mean of 99·62 (s.d. 0·945) % $n = 8$ samples of 40 mg. The method is rapid and does not require the manipulation necessary in other methods. There is no evidence in the tablets examined of excipient interference though this may be a problem with other formulations.

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