In order to substantiate the method of preparing the standard curve for the recovery study, the standards were determined according to the exact procedure employed for the talc samples (heating, filtering). There was no significant change in the least square line as compared to a standard curve prepared without the heating and filtering steps. This indicated that any loss of antimony in the spiked samples probably involves the presence of talc.

An experiment, similar in design to the foregoing procedure, was performed with a final concentration of 3 *M* hydrochloric acid instead of the 1.5 *M* hydrochloric acid as in the preceding method. In this procedure, the concentration of acid was kept constant throughout the method. The major advantage of the modified method is the elimination of adding 71 ml. of water before extraction with the isopropyl ether. This particular step is not desirable because of the possible increase in rate of hydrolysis of antimony (V) to a nonreactive form, antimony (IV). In the original procedure, the volume of aqueous phase was 121 ml. up to the ether extraction step as compared to 65 ml. in the modified method. Thus, the latter procedure should create a more favorable environment for a higher partition coefficient.

A recovery study was performed at the 4 levels of antimony previously mentioned. The recoveries were similar to those obtained in the original method. These results seem to indicate that the partition coefficient is the same for both methods even though the ratio of organic to aqueous phase is different.

Several authors have indicated with their systems that the rhodamine B–antimony complex is fairly stable. However, the stability of the complex in isopropyl ether has been found to vary between authors. Ward and Lakin (13) state that the color is stable up to 6.5 hr., while Van Aman (14) indicates the color fades 1.2% in 1.5 hr. or 30% in 18 hr. However, Maren (8) mentions that the color is not stable, and the absorbance readings must be made within 30 min. of the extraction. We have found that there was a decrease in the absorbance readings of the color complex with time when water was used in the reference cell. A study of absorbance *versus* time for three levels of antimony and a blank was performed at 5-min. intervals for 35 min. The results obtained show that the initial absorbance readings decreased continuously for 20 min. The difference between the initial reading and those taken at 20 min. ranged from 0.017–0.027 absorbance units with 1–4 mcg. of antimony, respectively, and in most cases much less for the blank. However, from 25–35 min. the absorbance readings for the antimony complex remained almost constant (0.004 maximum difference). Subtraction of the blank absorbance reading from the antimony complex absorbance reading at the same respective time yielded a nearly constant absorbance for 35 min. In effect, absorbance readings can be made any time during the first 35 min. after the extraction step for the samples as long as the blank is prepared and read at the same time as the sample.

In conclusion, the methods show that the antimony content found in the talcs tested is considerably lower than the 2 p.p.m. level which may be required by the Food and Drug Administration.

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Determination of Meprobamate in Tablets by NMR

By JOHN W. TURCZAN and THEODORE C. KRAM

A rapid NMR procedure was developed for the analysis of meprobamate tablets with malonic acid as internal standard. An average error of 0.9 percent was obtained on seven synthetic mixtures. The NMR spectrum, in addition, provided a very specific means of identification for meprobamate.

THE CURRENT development of more complex drugs and drug mixtures, and the necessity for the analysis of many more samples has led to the need for rapid and simple methods of analysis. We have successfully analyzed many high-dosage-form pharmaceuticals by extracting them with a suitable solvent and obtaining their NMR spectra with the aid of an internal standard. The recorded spectrum from the NMR spectrometer provides an identification of the active ingredient, which contributes to the specificity of the procedure. Meprobamate has been determined by this technique, using acetone as solvent and

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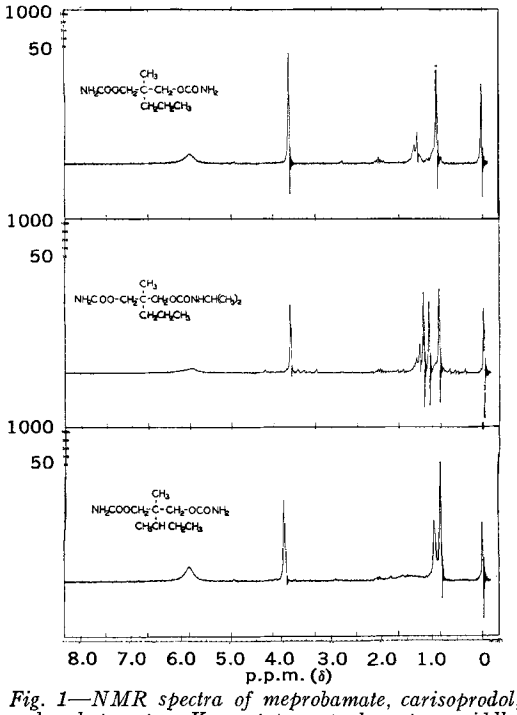

Fig. 1—NMR spectra of meprobamate, carisoprodol, and mebutamate. Key: top, meprobamate; middle, carisoprodol; bottom, mebutamate.

malonic acid as internal standard (Fig. 1). Two drugs closely related in structure and use, carisoprodol[1] and mebutamate, show distinct differences in their spectra from that of meprobamate and also can be analyzed by the same procedure.

Meprobamate is usually determined by the NF XII method (1) which involves an acidic solvolysis followed by a titration with sodium hydroxide in the presence of formaldehyde. This method is more time consuming and less specific than the proposed NMR method. Other published procedures are based on alkaline hydrolysis of the carbamate group followed by steam distillation (2), color reactions (3, 4), and infrared spectroscopy (5, 6). A near infrared method recently developed in this laboratory appears to be promising (7). The chief advantages of the NMR method over these other methods is rapidity and specificity.

PROCEDURE

Weigh and finely powder not less than 20 tablets. Then weigh accurately a portion of the powder, equivalent to about 400 mg. of meprobamate, in a glass-stoppered centrifuge tube and add about 400 mg. of malonic acid. Shake with 5 ml. of acetone for 2 min. and centrifuge. Transfer approximately 0.4 ml. of the clear supernatant to an analytical NMR tube, place in an NMR spectrometer (60 MHz), and obtain the spectrum, adjusting the spin rate so that no spinning sidebands occur between 3.1 and 4.0 p.p.m. The peaks of interest are integrated several times in each direction.

[1] Soma. Wallace Laboratories, Cranbury, N. J.

RESULTS AND DISCUSSION

The 60-MHz spectrum of meprobamate (Fig. 1) shows a peak at 3.8 p.p.m., representing 2 equivalent methylene groups. It was chosen for quantitative analysis and compared with the peak produced by the two methylene protons of malonic acid at 3.3 p.p.m. The clusters appearing at 0.8–1.4 p.p.m. confirm the meprobamate identity. Since acetone's carbon-13 satellite at 3.1 p.p.m. does not interfere with the upfield portion of the meprobamate spectrum, it is unnecessary to use the deuterated solvent for routine work.

The amount of meprobamate per tablet may be calculated as follows:

$$\frac{\text{mg. meprobamate}}{\text{tablet}} = \frac{A_{\text{mep.}}}{A_{\text{mal.}}} \times \frac{EW_{\text{mep.}}}{EW_{\text{mal.}}} \times \text{mg. mal.} \times \frac{\text{wt. 1 tablet}}{\text{wt. sample}}$$

$A_{\text{mep.}}$ = integral value of the singlet at 3.8 p.p.m.
$A_{\text{mal.}}$ = integral value of the singlet at 3.3 p.p.m.
$EW_{\text{mep.}}$ = formula weight of meprobamate/4 = 54.56.
$EW_{\text{mal.}}$ = formula weight of malonic acid/2 = 52.03.

The average deviation obtained for 7 standard preparations was 0.9% (Table I). The proportion of malonic acid to meprobamate appears to have no significant bearing on the accuracy of the determination for the range of proportions shown in the table.

TABLE I—DETERMINATION OF MEPROBAMATE IN SYNTHETIC SAMPLES BY NMR

Synthetic Sample	Malonic Acid Internal Std., mg. Added/ml.	Meprobamate, mg./ml. Added	Found	Deviation, %
1	87.3	99.7	98.0	1.7
2	87.5	98.1	99.9	1.8
3	85.1	100.1	99.0	1.1
4	87.6	100.3	99.7	0.6
5	67.5	73.5	73.3	0.3
6	129.8	74.6	74.4	0.3
7	70.7	91.5	91.7	0.2

TABLE II—DETERMINATION OF MEPROBAMATE IN COMMERCIAL SAMPLES BY NMR

Commercial Tablet	Malonic Acid Internal Std., mg. Added/ml.	Declared mg./ Tablet	Found, mg./Tablet NMR	NF XII
1	76.1	400	393	391
2	78.8	400	398	396
3	75.1	400	413	397
4	72.9	400	399	402

Since this method was developed, approximately 30 commercial preparations of meprobamate have been analyzed by NMR. Four of these samples have also been analyzed by the NF XII method as well (1). Results obtained by both methods are shown in Table II.

Tablets have been marketed in which meprobamate was combined with other active ingredients. The following substances have been examined and found to produce no interference in the determination of meprobamate: amphetamine sulfate, hydrochlorothiazide, dexamethasone, pentaerythritol tetranitrate, benactyzine hydrochloride, and aspirin.

Carisoprodol and mebutamate were analyzed by the same procedure. Their NMR spectra are also shown in Fig. 1. Unlike meprobamate, two peaks are produced at 3.8 p.p.m. Further differences may be noted in the area of 0.8 to 1.4 p.p.m. Preliminary work shows the accuracy to be of the same order as for meprobamate.

The speed, accuracy, and specificity of the NMR method make it useful as a rapid procedure that can provide both a quick and conclusive identification and an assay having an accuracy of about 1–2%.

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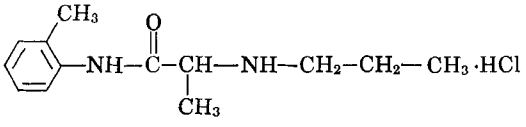
Qualitative and Quantitative Tests for Prilocaine Hydrochloride

By EDWARD F. SALIM* and BERTIL ÖRTENBLAD†

Provisional, unofficial monographs are developed by the Drug Standards Laboratory, in cooperation with the manufacturers of the drug concerned, for publication in the *Journal of Pharmaceutical Sciences*. The ready availability of this information affords discriminating medical and pharmaceutical practitioners with an added basis for confidence in the quality of new drug products generally, and of those covered by the monographs particularly. Such monographs will appear on drugs representing new chemical entities for which suitable identity tests and assay procedures are not available in the published literature. The purity and assay limits reported for the drugs and their dosage forms are based on observations made on samples representative of commercial production and are considered to be reasonable within expected analytical and manufacturing variation.

2-(PROPYLAMINO) - *o* - PROPIONOTOLUIDIDE HYDROCHLORIDE; $C_{13}H_{20}N_2O \cdot HCl$; mol. wt. 256.78. The structural formula of prilocaine hydrochloride may be represented as:



Physical Properties—Prilocaine hydrochloride occurs as a white, odorless crystalline powder with a bitter taste, m.p. 166–169° (USP class I). It is freely soluble in water and in alcohol, slightly soluble in chloroform, very slightly soluble in acetone, and practically insoluble in ether.

Identity Tests—The infrared spectrum of a 0.5% dispersion of prilocaine hydrochloride in potassium bromide, in a disk of about 0.82 mm. thickness, is shown in Fig. 1.

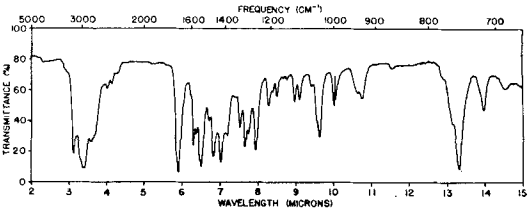


Fig. 1—Infrared spectrum of prilocaine hydrochloride in potassium bromide disk (0.5%); Perkin-Elmer model 21 spectrophotometer, sodium chloride prism.

Dissolve about 100 mg. of prilocaine hydrochloride in about 3 ml. of water, add ammonia T.S. until basic, and filter. Acidify the filtrate with diluted nitric acid, and add 1 ml. of silver nitrate T.S.: a white precipitate forms, which is insoluble in diluted nitric acid, but soluble in ammonia T.S. (presence of chloride).

Transfer about 300 mg. of prilocaine hydrochloride to a separator and dissolve in 5 ml. of water. Add 4 ml. of ammonia T.S. and extract with four 15-ml. portions of chloroform, filtering the extracts through paper. Evaporate the combined

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