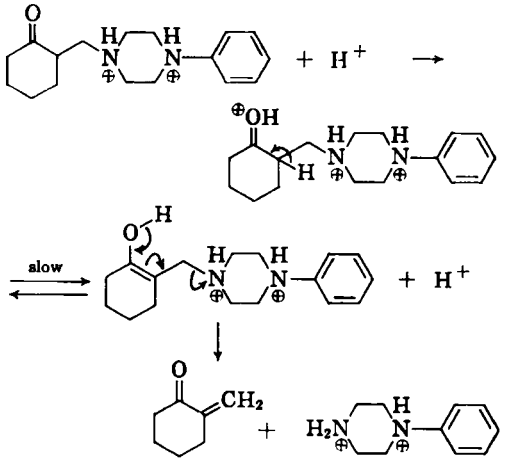

Scheme III

The 2-methylenecyclohexanone shown in the postulated reactions appears to dimerize and rearrange according to the pathway suggested by Warnhoff and Johnson (5).

Pharmaceutical Consideration.—The immediate practical application of this study was in the elimination or control of factors affecting the rate of breakdown of a parenteral preparation for clinical pharmacological work. The pH of an aqueous solution of compound MA1050 is 5.0. The kinetic data indicated that a solution at this pH could not be sterilized by autoclaving, nor could a sterile solution be prepared aseptically and stored even at refrigeration temperature for reasonable lengths of time without appreciable breakdown. Formulation considerations were therefore directed to the prepasation of a sterile lyophilized powder.

SUMMARY

A Mannich base, 2-(4-phenyl-1-piperazinylmethyl) cyclohexanone, was susceptible to hydrolytic attack at its methylene-nitrogen linkage. The breakdown products were isolated and characterized as *N*-phenylpiperazine and the hydrated dimer of 2-methylenecyclohexanone.

A kinetic study of the hydrolysis reaction in buffer solutions of pH 1.1 to 5.5 and factors influencing it are reported. The hydrolysis was pseudo first order in nature and was specific acid and general base catalyzed. The pH profile showed the compound to have maximum stability in solution at pH 2. At pH values other than 2, ionic concentration of the medium affected the rate. The energy of activation for the hydrolysis in buffered aqueous solutions, uncorrected for the heat of ionization of water, was 27.3 Kcal./mole. In view of the uncertainty of the hydrogen or hydroxyl ion dependency, no rate equation is given. However, two probable pathways for the hydrolysis are suggested.

Knowledge from the evaluation of stability factors influencing compound MA1050 was applied to pharmaceutical considerations with the development of a lyophilized product as the most stable dosage form.

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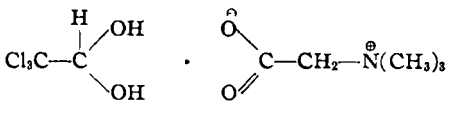
Drug Standards

Qualitative and Quantitative Tests for Chloral Betaine

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.

CHLORAL HYDRATE-betaine adduct; $C_7H_{14}Cl_3NO_4$; mol. wt. 282.55. The structural formula of chloral betaine may be represented as



Physical Properties.—Chloral betaine occurs as a white, crystalline powder having a faint aromatic,

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Mead Johnson and Co., Evansville, Ind., has cooperated by furnishing samples and data to aid in the development and preparation of this monograph.

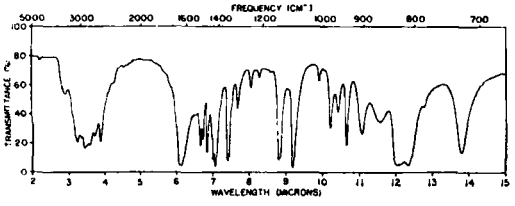

Fig. 1.— Infrared spectrum of chloral betaine in potassium bromide disk (0.5%). Perkin-Elmer model 21 spectrophotometer; sodium chloride prism.

penetrating, slightly acrid odor characteristic of chloral hydrate and a slightly bitter taste, m.p. 122–124.5°, U.S.P. XVI Class Ia. It is very soluble in water, freely soluble in alcohol, and very slightly soluble in chloroform.

Identity Tests.—Warm chloral betaine with a few drops of aniline and of sodium hydroxide T.S.: the mixture has the intensely disagreeable odor of phenyl isocyanide. (*Caution:* poisonous.)

The infrared spectrum of a 0.5% dispersion of chloral betaine in potassium bromide, in a disk of about 0.82 mm. thickness, is shown in Fig. 1.

Purity Tests.—Char about 1 Gm. of chloral betaine, accurately weighed, cool the residue, add 1 ml. of sulfuric acid, heat cautiously until evolution of sulfur trioxide ceases, ignite, cool, and weigh: the residue does not exceed 0.2%. Retain the residue for the heavy metals test.

Dissolve the sulfated ash obtained from 1 Gm. of chloral betaine in a small volume of hot nitric acid and evaporate to dryness on a steam bath. Dissolve the residue in 2 ml. of diluted acetic acid, dilute to 25 ml. with water, and determine the heavy metals content of this solution by the U.S.P. XVI heavy metals test, method I: the heavy metals limit for chloral betaine is 20 p.p.m.

Determine the water content of chloral betaine by the titrimetric (Karl Fischer) method: chloral betaine contains not less than 5.85% and not more than 7.35% water.

Assay.—*Betaine.*—Transfer about 200 mg. of chloral betaine, accurately weighed, to a 200-ml. tall-form beaker and dissolve in 50 ml. of glacial acetic acid. Add 5 ml. of acetic anhydride, 1.5 to 2 ml. of a 1 in 5000 solution of *p*-naphtholbenzein in glacial acetic acid, and titrate with 0.1 *N* acetous perchloric acid. Perform a blank titration and make any necessary correction. Each milliliter of 0.1 *N* perchloric acid is equivalent to 11.72 mg. of $C_5H_{11}NO_2$. The amount of betaine found is not less than 40% and not more than 44%.

Chloral Hydrate.—Transfer about 500 mg. of chloral betaine, accurately weighed, to a 125-ml. conical flask and dissolve in 25 ml. of water. Add 25.0 ml. of 0.1 *N* sodium hydroxide, swirl to mix, and allow the mixture to stand for 2 minutes. Add phenolphthalein T.S. and titrate the residual alkali at once with 0.1 *N* hydrochloric acid. Each milliliter of 0.1 *N* sodium hydroxide is equivalent to 16.54 mg. of $C_2H_3Cl_3O_2$. The amount of chloral hydrate found is not less than 56% and not more than 59.5%.

DOSAGE FORMS OF CHLORAL BETAINE

Chloral Betaine Tablets

Identity Tests.—Remove the film coating from one chloral betaine tablet by cutting with a sharp blade or by shaking with chloroform for about 1 hour and triturate the tablet to a fine powder. The infrared spectrum of a 0.5% dispersion of the powdered tablet in potassium bromide, in a disk of about 0.82 mm. thickness, corresponds to that of chloral betaine (Fig. 1).

Assay.—Transfer 10 whole tablets to a 200-ml. volumetric flask, add 160 ml. of water, and shake mechanically for 45 minutes or until tablet disintegration is complete. Add water to volume and mix. Filter, rejecting the first portion of filtrate. Pipet a portion of the filtrate, equivalent to about 250 mg. of chloral hydrate, into a 125-ml. conical flask. Add 20.0 ml. of 0.1 *N* sodium hydroxide and allow the mixture to stand for 2 minutes. Add phenolphthalein T.S. and titrate the residual alkali at once with 0.1 *N* hydrochloric acid. Each milliliter of 0.1 *N* sodium hydroxide is equivalent to 16.54 mg. of $C_2H_3Cl_3O_2$. The amount of chloral hydrate found is not less than 95% and not more than 110% of the labeled amount.

DISCUSSION

U.S.P. and N.F. terminology for solubility, melting range, reagents, etc., have been used wherever feasible.

Chloral betaine,[1] a chemical complex of chloral hydrate and betaine, is an oral sedative and hypnotic compound.

Quantitative Methods.—The quantitative methods provided are simple to perform and possess sufficient accuracy and precision for their intended purposes. Titrimetric determination of the water content gave an average value of 6.34 ± 0.10%.[2] Nonaqueous titration of this compound with acetous perchloric acid gave an average value equivalent to 41.2 ± 0.1% betaine. Acidimetric determination of the chloral hydrate content gave an average value of 58.8 ± 0.1%. Analysis of commercial tablets gave an average value of 102.3 ± 0.03% based on the chloral hydrate content.

[1] Marketed as Beta-Chlor by Mead Johnson and Co., Evansville, Ind.

[2] Maximum deviation from the mean value.