

ment of the mercury atom and make it a more effective electron-pair acceptor (15).

If the antibacterial activity changes with the electronic effect of the halogen and the trifluoromethyl groups, substitution in the *ortho* and *para* positions would affect the electronic environment of the mercury atom more than substitution in the *meta* position, and the activity of former compounds would be greater than the latter chemical. This was observed with the high concentrations.

It might be postulated that with very dilute samples certain factors such as the dispersion of the drug, the media, or the dilution factor might overshadow or interfere in some manner with the electronic effect of the trifluoromethyl group. Perhaps other testing techniques which are more sensitive should be employed to test the antibacterial activity of the very dilute samples.

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Colorimetric Determination of Chlorpheniramine Maleate

By JOSEPH HUDANICK

A sensitive colorimetric method has been developed for determining chlorpheniramine maleate in various pharmaceutical preparations. The method is especially suitable as a rapid control method.

CHLORPHENIRAMINE MALEATE, a pyridine derived antihistamine, is presently marketed in a variety of pharmaceutical preparations. Its determination is especially difficult when present in small amounts and in combination with certain other antihistamines and related compounds. Ordinary methods (1-3) such as ultraviolet, chromatographic, and gravimetric techniques, are time consuming and relatively nonselective. Jones and Brady (4) describe a general colorimetric method for determining pyridine derived antihistamines which is a modification of the Koenig reaction (5, 6). This method in its present form is of low sensitivity and unsuitable for mixtures of antihistamines. By changing the reaction conditions and using sulfanilic acid instead of aniline and an acetate buffer instead of phthalate, chlorpheniramine formed a very intense transient yellow suitable for quantitative analysis. The intensity of the color (absorption peak at 480 $m\mu$) is approximately 40 times that obtained by the Jones and Brady method and about three times as sensitive as the ultraviolet method. In addition, the color is very reproducible (standard deviation 0.4%) and unaffected by the presence of methapyrilene HCl and pyrilamine maleate, two pyridine derived antihistamines which are commonly associated with chlorpheniramine in many preparations. The very closely related compounds, pheniramine maleate and brompheniramine maleate, react the same as chlorpheniramine maleate. The method has been found suitable for determining

chlorpheniramine in many varied tablet combinations and timed release pellets.

EXPERIMENTAL

Buffered Sulfanilic Acid Solution.—Dissolve 2.5 Gm. of sulfanilic acid and 4.00 Gm. of anhydrous

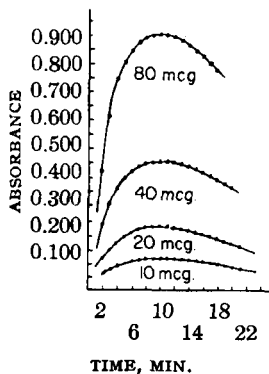


Fig. 1.—Plot of absorbance vs. time for specific concentrations of chlorpheniramine maleate.

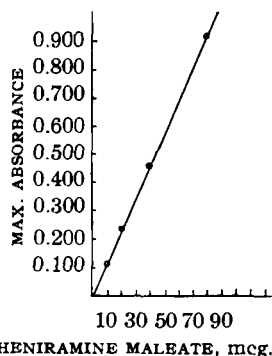


Fig. 2.—Plot of maximum absorbance of developed color vs. concentration.

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TABLE I.—EFFECT OF DIVERSE AMINE COMPOUNDS ON ABSORBANCE

40 mcg. Chlorpheniramine Maleate +	Compd. Added, mcg.	Absorbance
+ 800	Methapyrilene HCl	0.461, 0.460
+ 800	Pyrilamine maleate	0.461, 0.459
+2000	Phenylpropanolamine HCl	0.463, 0.459
+2000	Phenylephrine HCl	0.464, 0.460
+2000	Racephedrine HCl	0.458, 0.461
+2000	Dextromethorphan HBr	0.460, 0.459

sodium acetate into 40 ml. water and dilute to 175 ml. with 95% ethanol.

Aqueous Hydrochloric Acid 0.25 N.—The normality was adjusted to $\pm 2.0\%$.

Cyanogen Bromide Solution.—Dissolve 2.0 Gm. cyanogen bromide into 50 ml. water and keep under refrigeration.

Stock Standard Solution.—This is a solution of chlorpheniramine maleate in 0.25 N HCl, concentration = 1.00 mg./ml. Prepare solutions containing 0.01, 0.02, 0.04, and 0.08 mg./ml. chlorpheniramine maleate in 0.25 N HCl from this solution.

Pipet 7.0 ml. of buffered sulfanilic acid solution into each of five 50-ml. glass-stoppered Erlenmeyer flasks. Pipet 1.0 ml. of the serial dilutions into the flasks; pipet 1 ml. of 0.25 N HCl for a reagent blank into one flask. Add 3.0 ml. cold cyanogen bromide solution to each with swirling. Determine the absorbance of the solutions relative to the reagent blank at 1-minute intervals at 480 $m\mu$ on a Beckman DU spectrophotometer. A plot of absorbance versus time is shown in Fig. 1; a plot of maximum absorbance versus concentration is shown in Fig. 2. The maximum absorbance is linear with respect to concentration.

Interference from Other Amines

To determine the interference from certain other amines, solutions of chlorpheniramine maleate (concentration = 0.040 mg./ml. in 0.25 N HCl) were prepared containing added amounts of the various

compounds. As previously described 1 ml. of each solution was used for the color reaction and the maximum absorbance recorded. The results of duplicate runs are shown in Table I. No significant interference was observed at the stated concentrations. Normal tablet excipients and compounds such as aspirin, phenacetin, caffeine, and ascorbic acid do not cause interference.

Chromatographic Identification

A paper chromatographic separation is used to ascertain which of the three similarly reacting antihistamines (pheniramine, brompheniramine, or chlorpheniramine maleate) is present in a sample. The sample and control spots (pipeted as ether extracts from aqueous alkaline solutions) are chromatographed using an ascending technique on Whatman No. 1 paper which has been pretreated by soaking in 2.0% aqueous ammonium sulfate and thoroughly air drying. The developing solvent is made by shaking 100 ml. of *n*-butanol with 100 ml. aqueous 6.0% citric acid. After separation of the phases, the butanol layer is used as the mobile solvent and the aqueous layer as the immobile solvent. After chromatographing for 15 hours, the paper is air dried and dipped into Dragendorff's reagent (2) to locate the spots. The R_f values for pheniramine, brompheniramine, and chlorpheniramine are 0.25, 0.58, and 0.53, respectively.

SUMMARY

A colorimetric method based upon the Koenig reaction has been described for determining chlorpheniramine maleate in certain pharmaceutical preparations. The method requires very little time to perform and has very good precision. (Standard deviation is 0.4%.)

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Solubility and Dissolution Rates in Reactive Media

By W. I. HIGUCHI, EINO NELSON†, and J. G. WAGNER‡

The relationship between the diffusion-controlled dissolution rate of a substance in a reactive medium and the solubility of the substance in the medium has been analyzed. The results reconcile the total solubility method and the simultaneous diffusion and chemical reaction method of interpreting data on dissolution rates.

THE PROBLEM OF dissolution rates of solids in reactive solutions has been recently examined

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by the total solubility method (1-3) and by the simultaneous chemical reaction and diffusion (SCRD) method (4). Because of the differences between the two concepts and because the problem is important, it appears that a clarification of the data is necessary.

Both theories are based on the diffusion layer (or film) model; therefore, they both assume that the dissolution rate is controlled by diffusion rates of the important species through this layer. The model assumed in the SCR method takes into account simultaneous rapid reversible chemical reaction and diffusion of all the important species. The resulting equations for dissolution rate, G , in this case are relatively complicated. On the other