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Keyphrases

3-Substituted-2-benzoxazolinones—synthesis
2-Amino-5-trifluoromethylbenzoxazole—synthesis
5-Trifluoromethyl-2-benzoxazolinone—synthesis
Pharmacological screening—3-substituted-2-benzoxazoles
IR spectrophotometry—structure
NMR spectroscopy—structure

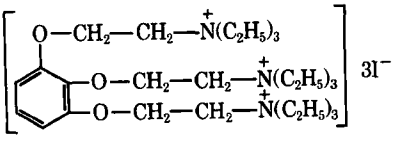
Drug Standards

Quantitative Determination of Gallamine Triethiodide

By PETER P. ASCIONE, JOHN B. ZAGAR, and GEORGE P. CHREKIAN

A nonaqueous method for the determination of crystalline gallamine triethiodide was developed. The titration utilized a mixture of *N,N*-dimethylformamide (DMF)–*p*-dioxane as the solvent, bromophenol blue as an indicator, and 0.1 *N* perchloric acid as the titrant. Also a colorimetric acid-dye extraction was developed for the determination of gallamine triethiodide in the injectable dosage form. This technique involved the extraction of an acid-dye complex, gallamine triethiodide and bromocresol green buffered to pH 5.3, with chloroform.

A SURVEY of literature revealed that gallamine triethiodide (I), a muscle relaxant, was synthesized and introduced in 1946 by Bovet (1). Its structure, although much simpler, was based on that of *d*-tubocurarine, and it owes its high potency as a relaxant to the three triethylammonium groups of its molecule (2).



I

Pharmaceutical dosage form and the crystalline powder are currently being assayed by the procedure outlined in the NF XII (3). This procedure is based on the Volhard volumetric titration of the iodide present in the molecule. However this procedure is capable of measuring halogens other than the iodide portion of the molecule, thereby lacking specificity for gallamine. A spectrophotometric determination was investigated but it was found to be a function of the iodide portion of the molecule rather than the active triethylammonium groups.

The purpose of this investigation was to develop a rapid and more specific procedure which could be employed in quality control laboratories for analyzing gallamine triethiodide both in

Received May 6, 1968, from the Department of Analytical Development, Quality Control Section, Lederle Laboratories, Pearl River, NY 10965
Accepted for publication July 11, 1968.

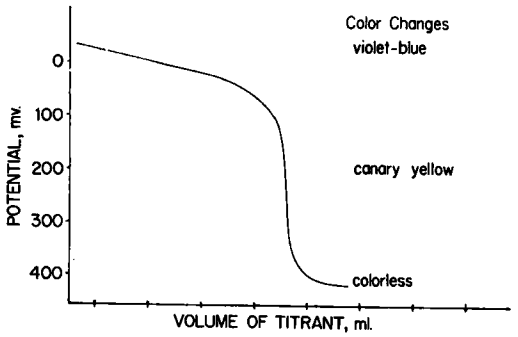


Fig. 1—Titration of gallamine triethiodide showing potentiometric inflection and color change of bromophenol blue indicator.

pharmaceutical dosage form and as a crystalline powder.

EXPERIMENTAL

Apparatus—Precision-Dow Recordomatic titrimeter equipped with a glass electrode and a sleeve-type calomel electrode. The calomel electrode was modified by replacing the aqueous saturated solution of potassium chloride in the bridge with saturated solution of potassium chloride in methanol.

Reagents and Solutions—Chloroform; *p*-dioxane, *N,N*-dimethylformamide (DMF); glacial acetic acid; 1% bromophenol blue in DMF; 6% mercuric acetate in glacial acetic acid; 0.1 *N* perchloric acid in glacial acetic acid [standardized against primary standard potassium acid phthalate by the procedure of the USP XVII (4)]; phosphate buffer: dissolve 38 g. of monobasic sodium phosphate and 2 g. of anhydrous dibasic sodium phosphate in water to make 1,000 ml.; bromocresol green dye solution: dissolve 200 mg. of bromocresol green in 100 ml. of water by adding 6.4 ml. of 0.1 *N* sodium hydroxide and dilute to 250 ml. with water, wash the solution with five 10-ml. portions of chloroform, and filter; standard preparation: dissolve in water a suitable quantity of gallamine triethiodide reference standard and dilute quantitatively and stepwise to obtain a solution having a concentration of 100 mcg. per ml.

Nonaqueous Method—*Assay Procedure*—Weigh accurately 0.2 g. of gallamine triethiodide into a 250-ml. beaker and dissolve in 10 ml. of DMF. Add 5 ml. of 6% mercuric acetate; then add 150 ml. of *p*-dioxane and mix the solution with the aid of magnetic stirring. The titration is followed potentiometrically using 0.1 *N* perchloric acid in glacial acetic as the titrant. In addition to the potentiometric determination, visual titrations can also be carried out using 6 drops of 1% bromophenol blue in DMF as the indicator, which changes from purple to canary yellow at the stoichiometric end point. Each milliliter of 0.1 *N* perchloric acid is equivalent to 29.72 mg. of gallamine triethiodide.

Colorimetric Acid-Dye Extraction Method—*Assay Preparation*—Pipet an accurately measured volume of gallamine triethiodide injection and dilute quantitatively and stepwise to obtain a solution having a concentration of 100 mcg./ml. in water.

Procedure—Pipet 5 ml. of assay preparation into a 125-ml. separator. To a second 125-ml. separator pipet 5 ml. of standard preparation. To each separator add 10 ml. of phosphate buffer solution and 5 ml. bromocresol green solution. Extract each solution with four 20-ml. portions of chloroform, collecting the chloroform extracts in 100-ml. volumetric flasks. Add chloroform to volume in each flask and mix. Concomitantly determine the absorbances of both solutions in 1-cm. cells at 416 mμ on a suitable spectrophotometer, using chloroform as the blank.

RESULTS AND DISCUSSION

Gallamine triethiodide possesses three quaternary nitrogen groups, each exhibiting basic characteristics in nonaqueous media. These three basic groups are susceptible to titration by perchloric acid. The nonaqueous method specifically and distinctively measures the quaternary nature of this compound.

The solvent of choice for determining the purity of crystalline gallamine triethiodide was *p*-dioxane. However due to the limited solubility of this compound, it was first necessary to effect solution using DMF. Using the ratio of DMF to *p*-dioxane as outlined under *Experimental*, a well-defined potentiometric end point shown in Fig. 1 was obtained when titrated with 0.1 *N* perchloric acid in acetic acid.

The bromophenol blue end point of the titration was found to appear sharply and occurred at the stoichiometric end point. This was determined potentiometrically with the indicator in the system as shown in Fig. 1. To obtain a stoichiometric end point it was necessary to add mercuric acetate to the solution of gallamine triethiodide prior to titration (5).

Noted in Table I are the results obtained by the nonaqueous method and acid-dye extraction procedure on various lots of crystalline powder and batches of dosage form. The methods are rapid, simple, more specific, and provide quantitative results.

The colorimetric acid-dye method is based on the quaternary nitrogen groups each having the basic characteristics in a dye extraction (6). These three basic groups react with bromocresol green at pH 5.3 and are distinguished because of their solubility in chloroform.

TABLE I—SUMMARY OF ANALYTICAL DATA FOR ANALYSIS OF CRYSTALLINE POWDER AND INJECTABLE DOSAGE FORM OF GALLAMINE TRIETHIODIDE

	Method		
	Potentiometric Titration, %	Visual Titration, %	Colorimetric Acid-Dye Extraction, mg./ml.
Crystalline Powder			
Lot 1	100.3	99.7	
Lot 2	99.5	99.6	
Lot 3	99.0	98.7	
Lot 4	98.6	99.3	
Injectable Form 20.6 mg./ml.			
Batch 1			21.1
Batch 2			21.3
Batch 3			20.5
Batch 4			20.1

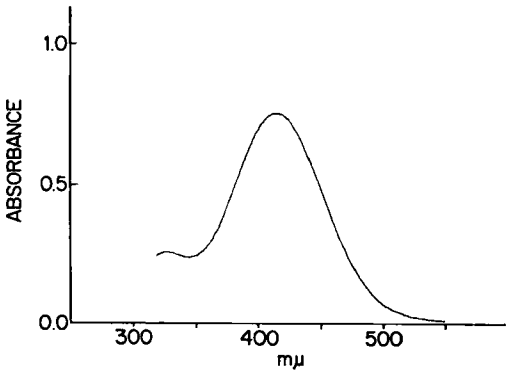


Fig. 2—Spectrum of acid-dye complex of gallamine triethiodide.

The absorption spectrum of the acid-dye chloroform extract was determined on a Cary model II recording spectrophotometer. Figure 2 shows the absorption spectra in the region 550–350 for the gallamine acid-dye extract. The wavelength where maximum absorption occurred was 416 mμ.

Various concentrations of gallamine triethiodide were evaluated by the acid-dye extraction procedure for the purpose of preparing a standard calibration curve. A typical linear Beer's law plot was obtained when the absorbance of the acid-dye extract *versus* concentration of gallamine triethiodide was plotted in the range of 2 to 10 mcg./ml.

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Keyphrases

Gallamine triethiodide—analysis
Titration, nonaqueous—analysis
Bromophenol blue—indicator
Perchloric acid—titrant
Colorimetric analysis—spectrophotometer
Bromocresol green-gallamine triethiodide—complex

Technical Articles

Instrumentation of a Rotary Tablet Machine

By FRANK W. GOODHART, GUSTAVO MAYORGA, MORTIMER N. MILLS, and FRED C. NINGER

The Manesty 45 station Rotapress was instrumented to measure compressional force, ejection force, and lower punch pulldown force. Various positions in the pressure linkage were monitored to determine the optimum location for compressional force measurement. The upper part of the compression column just below the link to the upper roller carriage was chosen for installation of strain gauges for compressional force measurement. Ejection force was measured by installing a force washer beneath the head of the bolt which holds the ejection cam in place. The ejection cam was not modified in any way. Lower punch pulldown force was measured by using a bolt containing internally mounted strain gauges to replace one of the three bolts normally holding the pulldown cam in position. Examples of the results obtained by compressing antacid tablets at various speeds and forces are given. Data collected over a 24-day period on the compression of these tablets under regular production conditions are given.

ROTARY TABLET machine instrumentation has been described by Knoechel (1–3) and Wray (4). Sites for gauging and methodology have been developed for certain types of American-made machines such as the Stokes BB-2, Stokes 541, and other similar presses. It has become apparent that measurement of tableting forces is a helpful tool in the development of tablet formulations and trouble shooting. Furthermore, the use of tablet machine instrumentation makes for better production control thus giving

Received May 22, 1968, from the Pharmaceutical Research and Development Laboratories, Warner-Lambert Research Institute, Morris Plains, NJ 07950
Accepted for publication July 18, 1968.