Quantitative Determination of Some Synthetic Antiparkinsonism Agents

By L. G. CHATTEN and W. J. RACZ

Nonaqueous titrimetry was employed to estimate quantitatively some of the compounds which are useful in treating Parkinsonism. The method was applied to both the crystalline material and their dosage forms. This technique was found to yield results which agreed well with those obtained by either the official procedures or by methods submitted by the manufacturer. Several solvent systems were employed for the analysis of the various compounds, but either chloroform alone or a phenol–chloroform mixture was found to be almost universally applicable. Indicators were found for all the medicinal agents investigated in both of the aforementioned major solvent systems. As an additional means of quantitative assay, the amine salts were precipitated as their tetraphenylborates and the resulting derivative was then determined quantitatively by nonaqueous titrimetry.

IN THE past decade, several synthetic anticholinergic compounds have been found to be useful in controlling the symptoms of Parkinsonism. These compounds are potent systemic pharmacological agents and, therefore, accurate methods of estimating both the crystalline materials and their dosage forms must be available.

A survey of the literature revealed a complete lack of methods for quantitatively determining some of these compounds. Furthermore, although procedures have been published for some of these organic medicinals, in general, they are long and tedious.

For biperiden hydrochloride, no method of quantitative estimation could be found in the literature. On the other hand, the "National Formulary" (1) describes a procedure for cycrimine hydrochloride tablets which is based upon the infrared absorbance of a chloroform solution. The major limitation of this procedure is the large number of extractions which must be performed to ensure complete removal of the drug. The pure drug is assayed by visual nonaqueous titrimetry in glacial acetic acid.

Chafetz (2) devised a method of quantitative estimation for phenyramidol hydrochloride which was based on periodate oxidation followed by ultraviolet spectrophotometric measurement of the resulting araldehyde.

The "British Pharmacopoeia" (3) presents a method for both pure procyclidine hydrochloride and the pharmaceutical dosage forms. It is based on extraction of the liberated base and its estimation by residual titrimetry, but the technique suffers from the same limitations as the NF method for cycrimine HCl tablets. Rogers (4) described an ultraviolet absorption method for procyclidine HCl which required special slit width adjustments, whereas Pellerin and coworkers (5) employed a technique which involved sodium lauryl sulfate as titrant. *Drug Standards* (6) contains a monograph which outlines a nonaqueous titrimetric procedure for the closely related compound, tricyclamol chloride. A mixed solvent system of chloroform and glacial acetic acid is utilized and the end point determined either potentiometrically or visually. The analysis of the capsules was carried out directly on the powdered substance. However, for tricyclamol chloride tablets, the active ingredient was extracted with methanol prior to estimation.

The "United States Pharmacopeia" (7) utilizes a nonaqueous titration in chloroform to assay pure trihexyphenidyl hydrochloride whereas the same compendium describes a colorimetric extraction procedure for the dosage forms. The BP (3) employs methods similar to those described in the USP (7). Kráčmar, Blazek, and Stejskal (8) devised a polarographic procedure for the quantitative estimation of trihexiphenidyl, and Bozsai and Vastogh utilized a similar technique (9). However, since this substance does not contain a functional group which can be readily oxidized or reduced under an applied potential, a suitable group must be introduced. This process may be lengthy and the reactions involved must be quantitative.

It is the purpose of this investigation to develop rapid and accurate analytical procedures which can be employed in routine quality control of these medicinal agents both as raw materials and in pharmaceutical dosage forms.

Received March 13, 1967, from the Faculty of Pharmacy, University of Alberta, Edmonton, Alberta, Canada.

Accepted for publication August 29, 1967.

W. J. Racz is indebted to the Canadian Foundation for the Advancement of Pharmacy and the National Research Council of Canada for financial assistance during the course of this investigation.

The organic medicinals and their dosage forms were generously supplied by the following pharmaceutical companies: Burroughs Wellcome & Co. (Canada) Ltd., procyclidine HCl and Kemadrin 5 mg. tablets); Eli Lilly and Co. (Canada) Ltd., cycrimine HCl, Pagitane 1.25 and 2.50 mg. tablets, tricyclamol chloride and Elorine 50 mg. capsules; Knoll Pharmaceutical Co., diperiden HCl and Akineton 2 mg. tablets; Mead Johnson Laboratories, Analexin 400 mg. capsules; Neisler Laboratories Ltd., phenyramidol HCl; Cyanamid of Canada Ltd., trihexyphenidyl HCl, Artane 2 and 5 mg. tablets.

EXPERIMENTAL

Apparatus

Metrohm Potentiograph model E.336 equipped with a glass-calomel electrode pair, Beckman Zeromatic II pH meter fitted with a glass-calomel electrode system, magnetic stirring apparatus, conventional laboratory glassware, sintered-glass funnels of medium porosity, sintered-glass crucibles of fine porosity, microburet graduated to 0.01 ml.

Reagents and Solutions

Acetone; chloroform; *N,N*-dimethylformamide; glacial acetic acid; phenol; sodium acetate; sodium tetraphenylboron; acetate buffer solution, pH 4.6; crystal violet T.S. USP; 0.1 *N* HCl; 0.05 *N* HCl; 2 *N* HCl; mercuric acetate T.S. USP; 0.5% methyl red in methanol; methyl red solution BP; 0.05 *N* perchloric acid in dioxane (standardized against primary standard potassium acid phthalate); 5% sodium tetraphenylboron solution in water (filtered through a sintered-glass funnel of medium porosity); thymol blue in *N,N*-dimethylformamide USP; 0.25% tropaeolin 00 in methanol.

All chemicals employed in this investigation were either A.C.S. or reagent grade quality.

The antiparkinsonism compounds and their commercial products studied in this investigation are as follows: biperiden HCl (2 mg.),[1] cycrimine HCl (2.5 and 1.25 mg.),[2] phenyramidol HCl (400 mg.),[3] procyclidine HCl (5 mg.),[4] tricyclamol chloride (50 mg.),[5] trihexyphenidyl HCl (5 and 2 mg.).[6]

Procedures for Crystalline Materials

The purity of trihexyphenidyl HCl was determined by the procedure of the USP (7). Procyclidine HCl was estimated by the BP (3) method and cycrimine HCl by the NF (1) procedure.

General Nonaqueous Procedure

Approximately 50 mg. of the material under investigation was accurately weighed into a 150-ml. beaker and dissolved in 50 ml. of the solvent of choice with the aid of magnetic stirring. Mercuric acetate T.S. (1.5 ml.) was then added and the titration followed potentiometrically using 0.05 *N* perchloric acid in dioxane as titrant.

Since official methods were not available for biperiden HCl, tricyclamol chloride, and phenyramidol HCl, the purity of these compounds was determined by the foregoing nonaqueous technique when glacial acetic acid was utilized as solvent system.

Modification 1—Chloroform was employed as the solvent for cycrimine HCl, procyclidine HCl, trihexyphendyl HCl, and tricyclamol chloride. In addition to the potentiometric determinations, visual titrations were also carried out using 3 drops of a saturated solution of methyl red in methanol as indicator. The end point was found to be purplish red in color.

Modification 2—A solvent system comprising equal parts of chloroform and *N,N*-dimethylformamide was employed for the same 4 substances mentioned under *Modification 1*. The end point was detected potentiometrically.

Modification 3—In this instance, the solvent system was similar to that employed by Chatten (10) for the titration of various nitrate and sulfate salts of organic bases. Methyl red was found to be the indicator of choice for biperiden HCl, whereas tropaeolin 00 in anhydrous methanol was employed for phenyramidol HCl. The end point for the latter was orange-brown in color.

For the general procedure as well as all modifications, a blank was performed on the solvent system. Where applicable, the appropriate indicator was included. Corrections were made of all titrant volumes.

Sodium Tetraphenylborate Procedure

This technique was a combination and a modification of the methods of Smith, Worrell, and Sinsheimer (11) and Chatten, Pernarowski, and Levi (12).

A sample (25 to 50 mg.) of the drug was accurately weighed into a 150-ml. beaker and 50 ml. of acetate buffer (pH 4.6) was added. The mixture was stirred magnetically until the drug had dissolved. An excess of the 5% solution of sodium tetraphenylboron was added and the mixture stirred for an additional 20 min. The precipitate was removed with the aid of suction filtration through a sintered-glass crucible of fine porosity. The beaker and the tetraphenylborate were washed with 200 ml. of water. Then the crucible and tetraphenylborate were dried for a period of not less than 18 hr. in a vacuum desiccator over phosphorus pentoxide. The magnetic stirring bar was washed with a small quantity of acetone, the acetone retained in the beaker, and the beaker also dried in a vacuum desiccator over calcium chloride.

Ten milliliters of acetone was added to the crucible containing the tetraphenylborate and the mixture was stirred to dissolve the compound. The solution was then filtered into the dried beaker in which the compound had been prepared. The crucible was washed with an additional 10 ml. of acetone and the filtrate collected in the beaker. Positive pressure was used to facilitate the filtration process. To the filtrate, 30 ml. of glacial acetic acid, 1.5 ml. of mercuric acetate T.S., and 1 drop of crystal violet T.S. were added and the mixture titrated to a blue end point (13) with perchloric acid in dioxane as titrant. A titration light was used to facilitate detection of the end point. A blank titration was performed on the solvent system.

All six antiparkinsonism agents were assayed by this method.

The tetraphenylborate of tricyclamol was prepared, purified, and the equivalent weight determined by the method of Chatten and Doan (13). The adduct was submitted for elemental analysis and the results were as follows: tricyclamol tetraphenylborate, m.p. 197–199°; purity by nonaqueous titrimetry, 99.5%.

Anal.—Calcd. for $C_{44}H_{52}BNO$: C, 84.93; H, 8.43; N, 2.25. Found: C, 84.78; H, 8.26; N, 2.11.

Procedures for Pharmaceutical Dosage Forms

All dosage forms were analyzed by pharmacopeial

[1] Trademarked as Akineton.
[2] Trademarked as Pagitane.
[3] Trademarked as Analexin.
[4] Trademarked as Kemadrin.
[5] Trademarked as Elorine.
[6] Trademarked as Artane.

procedures or by methods supplied by manufacturers, wherever this was possible.

Trihexyphenidyl HCl tablets, cycrimine HCl tablets, and procyclidine HCl tablets were assayed by the procedures of the USP (7), NF (1), and the BP (3), respectively.

Capsules of tricyclamol chloride and phenyramidol HCl were analyzed by methods provided by the respective manufacturers.

A published procedure was not available for the analysis of biperiden HCl tablets.

General Nonaqueous Procedure

A sample of the powdered tablet or capsule material was accurately weighed into a 150-ml. beaker and 25 ml. of chloroform was added. The mixture was stirred magnetically for 40 min. and the solution then filtered through a sintered-glass funnel of medium porosity. The beaker and funnel were washed with an additional 25 ml. of chloroform. A slight excess of mercuric acetate solution was added and the titration followed potentiometrically using perchloric acid in dioxane as titrant. The end point was also detected visually by employing methyl red as indicator. A blank titration was performed on the solvent system and the appropriate correction made.

This method was employed to analyze the dosage forms of the following compounds: cycrimine HCl, procyclidine HCl, and trihexyphenidyl HCl. Tricyclamol chloride capsules were also determined by the above procedure but the samples were not filtered prior to titration.

Tricyclamol chloride capsules were also titrated by a modification in which a 1:1 mixture of dimethylformamide–chloroform was used as solvent. The end point was detected potentiometrically.

Biperiden HCl tablets were assayed by another modification in which the solvent system was 2.5% phenol in chloroform. The same solvent system with a stirring time of 30 min. was employed for phenyramidol capsules. The end point was determined either potentiometrically or visually using tropaeolin 00 as indicator. The end point was found to be orange-brown in color. A blank was determined on the solvent system and capsule excipients prior to the addition of mercuric acetate.

Sodium Tetraphenylborate Method

The pharmaceutical dosage forms were also assayed by the tetraphenylborate method, with the introduction of certain modifications. The finely ground tablet or capsule material was accurately weighed into a 150-ml. beaker and about 2 ml. of acetate buffer was added. The powder was triturated with buffer solution until a smooth paste resulted. The remainder of the 50 ml. of buffer was added and the mixture stirred magnetically for 40 min., and the general procedure was followed beginning with the words "An excess of a 5% solution of sodium tetraphenylboron ...."

The commercial products of biperiden HCl, phenyramidol HCl, procyclidine HCl, tricyclamol chloride, and trihexyphenidyl HCl were determined by this method.

RESULTS AND DISCUSSION

Glacial acetic acid was chosen as the solvent system for determining the purity of those compounds for which no published or accepted procedures existed. It has been extensively used for the analysis of crystalline pharmaceutical substances (3, 7) because of its excellent solvent properties for organic medicinal agents. The potentiometric break obtained in glacial acetic acid was well-defined and thus the end point could be determined accurately. However, this solvent is not suitable for the nonaqueous titration of pharmaceutical dosage forms, because a large number of interfering excipients are soluble in it (14). As noted from Table I, the results obtained in this solvent are in excellent agreement with the theoretical values.

In order to select a suitable titration medium, the solubility of each compound was determined in a variety of solvents which could also be applied to the dosage forms. Trihexyphenidyl HCl, procyclidine HCl, cycrimine HCl, and tricyclamol chloride were found to be soluble in chloroform and 2-propanol. While compounds with the exception of tricyclamol chloride were readily soluble in chloroform, dissolution was slow in 2-propanol.

The potentiometric titration of trihexyphenidyl HCl was attempted in 2-propanol but the inflection point was not well-defined and hence the end point was difficult to determine. On the other hand, in chloroform, the potentiometric break was well-defined and the end point easily detected. Clair and Chatten (14) reported that very few tablet excipients interfere with nonaqueous titrations which are performed in chloroform and hence it was the solvent of choice for the aforementioned materials as it possessed many desirable attributes.

The four antiparkinsonism agents were also titrated in chloroform and the end point was detected with methyl red in anhydrous methanol. Thymol blue can also be utilized as an indicator for the titration of these substances and, in fact, is recommended by the USP (7) for the assay of trihexyphenidyl HCl. However, the former indicator was selected because its color change appeared to be more distinct than that of thymol blue.

In Fig. 1, curve A depicts the potentiometric curve for the titration of procyclidine HCl in chloroform, whereas curve B illustrates the titration of tricyclamol chloride in chloroform. The color changes of methyl red are illustrated on the same figure. Curve C shows the titration of procyclidine HCl in chloroform with thymol blue as indicator.

Tricyclamol chloride was found to be only slowly soluble in chloroform. Therefore, a more suitable solvent, *N,N*-dimethylformamide, was selected. In addition, this solvent was observed to possess excellent solubilizing properties for the hydrochlorides of trihexyphenidyl, cycrimine, procyclidine, and phenyramidol. However, titration of tricyclamol chloride in *N,N*-dimethylformamide resulted in a depressed and poorly defined end point. Investigation of mixed solvent systems resulted in a mixture of chloroform and *N,N*-dimethylformamide (1:1) which gave sharp end points and yet retained excellent solvent powers for the compounds previously mentioned. Unfortunately, a suitable indicator could not be found for the chloroform–*N,N*-dimethylformamide solvent system.

Phenyramidol HCl could not be titrated in *N,N*-dimethylformamide–chloroform as the potentio-

TABLE I—SUMMARY OF DATA FOR ANALYSIS OF CRYSTALLINE COMPOUNDS EXPRESSED AS PERCENT RECOVERY ± STANDARD DEVIATION

Compd.	Official Method	Potentiometric Titration in Glacial Acetic Acid	Potentiometric Titration in Chloroform	Visual Titration in Chloroform	Potentiometric Titration in DMF–$CHCl_3$	Potentiometric Titration in Phenol–$CHCl_3$	Visual Titration in Phenol–$CHCl_3$	Tetraphenylborate
Trihexyphenidyl hydrochloride	100.0 ±0.54	...	...	99.6 ±0.25	100.1 ±0.36	...	...	97.9 ±1.12
Procyclidine hydrochloride	98.7 ±1.96	...	99.9 ±0.45	99.9 ±0.42	100.1 ±0.62	...	...	97.5 ±1.58
Cycrimine hydrochloride	99.5 ±0.58	...	100.0 ±0.43	99.3 ±0.32	100.1 ±0.64	...	...	98.6 ±1.49
Biperiden hydrochloride		99.9 ±0.89	...	...	...	100.2 ±0.71	99.9 ±0.41	98.5 ±.94
Phenyramidol hydrochloride		100.1 ±0.38	...	...	...	100.2 ±0.37	99.9 ±0.40	98.8 ±1.91
Tricyclamol chloride		99.8 ±0.53	99.4 ±0.25	99.5 ±0.32	99.9 ±0.49	...	...	95.1 ±0.66

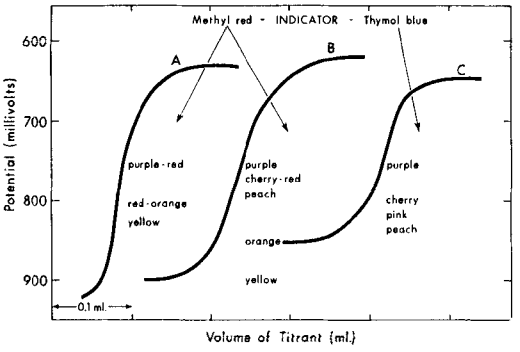

Fig. 1—Titrations in chloroform. Key: A, *procyclidine HCl;* B, *tricyclamol chloride;* C, *procyclidine HCl.*

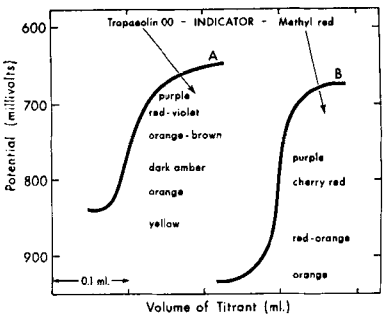

Fig. 2—Titrations in phenol–chloroform. Key: A, *phenyramidol HCl;* B, *biperiden HCl.*

metric break was very poorly defined. In addition, biperiden HCl was found to possess a low solubility in chloroform and hence a combination of the two factors created the need for another solvent system for these two compounds. The present investigation showed that biperiden HCl and phenyramidol HCl were soluble in a system containing 2.5% phenol in chloroform and these substances were readily titratable in this solvent system. The weak acidity of the solvent system may enhance the weak basicity of phenyramidol HCl whereas *N,N*-dimethylformamide would have the opposite effect upon the antiparkinsonism agent.

Tropaeolin 00 in methanol was the indicator of choice for phenyramidol HCl in the phenol–chloroform system and Fig. 2, curve A depicts the titration curve together with the indicator changes. Methyl red can also be used and was, in fact, selected for biperiden HCl. Curve B illustrates the titration curve and indicator changes for that substance.

Tetraphenylborate Method

Sodium tetraphenylboron has been used for the characterization and determination of organic medicinal agents containing basic nitrogen functional groups. Smith, Worrell, and Sinsheimer (11) have titrated some sympathomimetic amines with sodium tetraphenylboron and detected the end point amperometrically.

In a previous report, Chatten and Doan (13) prepared in excellent yields the tetraphenylborates of the compounds under study in this project. It was of interest, therefore, to attempt to modify their procedure in order to obtain quantitative results.

An acidic pH in the range of 4 to 6 has been reported to be suitable for the preparation of the tetraphenylborates of organic bases (11). It was found that buffered solutions in the pH range of 4 to 5.6 gave reasonable analytical results, while in a more acid system, the tetraphenylborates of the substances in this investigation exhibited increased solubility. Hence, the acetate–acetic acid buffer pair (pH 4.6) was selected for solvent power and convenience

One disadvantage of the tetraphenylborate method is the difficulty encountered in removing the precipitate from the vessel in which it was prepared. To overcome this problem, the beaker was allowed to dry and the acetone solution of the tetraphenylborate filtered into it.

The end point of the titration was found to appear very slowly and false end points occurred prior to the stoichiometric end point. The addition of mercuric acetate T.S. to the tetraphenylborate solution allowed the stoichiometric end point to be reached in a shorter space of time because the premature end points were few and very short-lived.

Examination of Table I reveals the various nonaqueous methods which were developed in this

investigation for the hydrochlorides of trihexyphenidyl, procyclidine, and cycrimine gave excellent agreement with the official procedures. No official methods were available for biperiden HCl, phenyramidol HCl, and tricyclamol HCl. Because of their widespread utility, however, potentiometric titrations in glacial acetic acid were accepted as standards and all other techniques were compared to them. For reasons of solubility, which have been already explained, the hydrochlorides of biperiden and phenyramidol were titrated in a phenol–chloroform solvent system. The results obtained are in excellent agreement with those in glacial acetic acid. For tricyclamol chloride, all nonaqueous techniques gave virtually identical results. Although the results by the tetraphenylborate method were slightly lower in almost every instance than those obtained with all other techniques, the values were believed to be within experimental error between two methods. In general, the recoveries were considered to be acceptable.

The results obtained from the analysis of the pharmaceutical dosage forms are listed in Table II. No official or manufacturers' procedure was available for biperiden HCl tablets. In addition, quantitative recoveries could not be obtained for this preparation by the tetraphenylborate method.

The analysis of phenyramidol HCl capsules was carried out by four methods: (*a*) and (*b*) potentiometric and visual nonaqueous titration in the phenol–chloroform solvent system, (*c*) preparation and titration of the tetraphenylborate, and (*d*) the manufacturers' procedure. Excellent agreement was obtained by the four methods of assay applied to this dosage form.

For trihexyphenidyl HCl, the four methods of analysis gave very good agreement, as shown by Table II, for the 5-mg. tablet. Small but not significant anomalies occurred with the 2-mg. product. For both nonaqueous procedures, it was necessary to remove interfering excipients by filtration, prior to titration.

The results of the nonaqueous assays for tricyclamol chloride in chloroform were below those obtained by the manufacturers' method. This may be caused by the slow solubility of the drug in chloroform. The higher recoveries in a mixed solvent system of *N,N*-dimethylformamide–chloroform are probably due to the enhanced solubility of tricyclamol chloride in that system. The low recoveries obtained by the tetraphenylborate procedure may be attributed to the suggestion that the quaternary ammonium compound does not form tetraphenylborates as readily as the other substances do.

As noted from Table II, the results obtained by the nonaqueous methods for procyclidine HCl are in good agreement with the official procedure of the BP (3). Filtration of the chloroform solutions prior to carrying out the titrations was found to be necessary as undissolved excipients interfered with the end points. It is noted that the tetraphenylborate method yielded values which appear to be higher than those obtained by the official procedure. This discrepancy is probably due to excipient interference.

For cycrimine HCl the results with the nonaqueous procedures agreed well with the NF (1) method for the 2.5-mg. tablet. However, for the 1.25-mg. product, the results by the nonaqueous techniques were much too low. No satisfactory explanation can be offered for this anomaly, since increasing the extraction time did not increase the percent recovery.

The tetraphenylborate method could not be applied to cycrimine HCl tablets as the recoveries obtained were much above the theoretical values. It would appear that these tablets contain an excipient which is capable of reacting with sodium tetraphenylboron and this results in overestimation.

It is worthy of mention that analysis of procyclidine HCl 5 mg., trihexyphenidyl HCl 5 mg., and cycrimine HCl 2.5-mg. tablets was attempted in the *N,N*-dimethylformamide–chloroform mixture but gross overestimation occurred in all three instances. This would seem to indicate that a titratable excipient which is soluble in dimethylformamide but not in chloroform must be present in the tablet formulations.

TABLE II—SUMMARY OF DATA FOR ANALYSIS OF DOSAGE FORMS BY VARIOUS PROCEDURES EXPRESSED AS PERCENT POTENCY ± STANDARD DEVIATION

Compd.	Official or Manufacturers' Procedure	Potentiometric Titration in Chloroform	Visual Titration in Chloroform	Potentiometric Titration in DMF–$CHCl_3$	Potentiometric Titration in Phenol–$CHCl_3$	Visual Titration in Phenol–$CHCl_3$	Tetraphenylborate
Biperiden HCl, 2 mg.	...	...	...	...	94.9	95.8	No result
	...	...	...	...	±0.72	±0.90	
Phenyramidol HCl, 400 mg.	93.9	...	...	...	92.2	91.7	92.7
	±0.29	...	...	...	±0.98	±0.18	±0.67
Trihexyphenidyl HCl, 5 mg.	97.3	96.6	96.2	...	...	...	97.1
	±1.65	±1.58	±0.27	...	...	...	±2.32
Trihexyphenidyl HCl, 2 mg.	106.9	104.6	106.9	...	...	...	104.9
	±0.89	±1.39	±0.40	...	...	...	±2.20
Tricyclamol chloride, 50 mg.	101.0	98.5	98.6	99.4	...	...	94.7
	±0.56	±1.15	±0.91	±0.70	...	...	±2.63
Procyclidine HCl, 5 mg.	94.5	94.6	94.2	...	...	...	97.7
	±3.08	±0.71	±0.53	...	...	...	±1.62
Cycrimine HCl, 2.5 mg.	94.5	93.8	92.2	...	...	...	No result
	±5.69	±1.23	±0.23	...	...	...	
Cycrimine HCl, 1.25 mg.	95.2	80.7	80.4	...	...	...	No result
	±1.53	±1.20	±1.39	...	...	...	

SUMMARY

A nonaqueous method of analysis utilizing chloroform as solvent has been developed for four compounds and their dosage forms. The results obtained are in excellent agreement with those obtained by the official or manufacturers' methods, but the nonaqueous procedure is much more rapid.

Phenol–chloroform mixture was employed with good results as solvent for the analysis of two of the organic medicinal agents investigated.

N,N-Dimethylformamide–chloroform mixture was successfully utilized as a solvent system for the nonaqueous titration of four of the crystalline salts. However, the solvent could be applied only to one dosage form.

A method based on precipitation of the amine as the tetraphenylborate and then estimating the tetraphenylborate by nonaqueous titrimetry was developed. This procedure does not have as wide an application as does direct nonaqueous titrimetry, but good analytical data were obtained for five of the dosage forms. This method would appear to be susceptible to excipient interference.

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Keyphrases

Antiparkinsonism agents, synthetic
Titrimetry, nonaqueous-quantitative analysis
Tetraphenylborate salt formation
Perchloric acid in dioxane titrant
Mercuric acetate T.S. and mercuric acetate plus crystal violet T.S. indicators
Methyl red and methyl red plus crystal violet T.S. indicators
Tropaeolin 00—indicator
Colorimetric end point determination
Potentiometric end point determination

Gas Chromatographic Determination of Trisulfapyrimidines in Tablets

By JOHN W. TURCZAN

A procedure for the quantitative determination of individual sulfapyrimidines in mixtures has been developed. Analyses of known mixtures show an accuracy of 1–2 percent. The method is based on acid hydrolysis of the trisulfapyrimidines to sulfanilic acid and their respective heterocyclic amines, followed by the separation and determination of the amines by gas chromatography.

THE SEPARATION and quantitative determination of the three sulfapyrimidines, which are frequently dispensed together, is a difficult problem. In the usual methods of analysis the aromatic primary amino group or the acidic hydrogen (1) is determined. These procedures are therefore not specific and cannot determine individual sulfapyrimidines in a multi-sulfapyrimidine mixture. A paper chromatographic procedure (2) has been developed which identifies and quantitates mixtures of sulfapyrimidines and other sulfonamides.

An alternative method proposed here is based on gas chromatography after an acid hydrolysis (3, 4) of the sulfapyrimidines to sulfanilic acid and their respective heterocyclic amines. A study was made to determine optimum conditions for the hydrolysis. The following procedure was then used to analyze known mixtures and commercial tablets.

Received June 21, 1967, from the New York District Laboratories, U. S. Department of Health, Education, and Welfare, Food and Drug Administration, Brooklyn, NY 11232

Accepted for publication August 21, 1967.

The author acknowledges the assistance of Evelyn Sarnoff, Dr. R. Ginell, and Gertrude Lowell, in the preparation of this report, and Anthony Romano, Jr., Minneapolis District, Anthony C. Celeste, Kansas City District, and Martin Goldstein, New Orleans District.