Ergotamine Tartrate U.S.P.

By G. L. SZENDEY

On the basis of melting point and solubility, ergotamine tartrate U.S.P. is a mixture of ergotamine tartrate and ergotamine bitartrate. Several samples with different properties were studied by means of titrimetric methods in nonaqueous media using 0.05 *N* perchloric acid and 0.1 *N* potassium methoxide. The melting point well indicates the approximate ratio of ergotamine tartrate-bitartrate mixture. Ergotamine tartrate with a melting point of about 180° (decompn.) contains about 83% ergotamine base, equivalent to 94% ergotamine tartrate.

SEVERAL authors reported (1–4) a discrepancy concerning ergotamine tartrate U.S.P. It was stated that requirements for solubility and melting point represent, contrary to the British Pharmacopoeia, a mixture of ergotamine tartrate and ergotamine hydrogen tartrate (ergotamine bitartrate).

Table I lists the differing requirements of the British Pharmacopoeia and the United States Pharmacopeia of ergotamine tartrate.

The present paper reports on quantitative studies of ergotamine tartrate samples with different melting points and discusses questions deriving from the above-mentioned problem.

METHOD

Apparatus.—Microburets, 3 or 5 ml. Melting range apparatus with light paraffin bath and calibrated thermometer (type II, U.S.P. XVI).

Assay of Ergotamine Base in Ergotamine Tartrate

Reagents.—All reagents are analytical grade. *Glacial acetic acid*, Merck. *Anhydrous acetic acid* (1000 ml. of glacial acetic acid mixed with 60 ml. of acetic anhydride). *Crystal violet indicator*, 0.25% in anhydrous acetic acid. *Perchloric acid*, 0.05 *N*, prepared by mixing 5.5 ml. (8.4 Gm.) of perchloric acid (60%, d. 1.54) with 200 ml. of anhydrous acetic acid and 20 ml. of acetic anhydride; cooling the solution, then adding anhydrous acetic acid to make 1000 ml. The normality factor was obtained by titration against sym.-diphenylguanidine (mol. wt. 211.26, m.p. 147–149): approximately 20 mg., accurately weighed, was dissolved in 15 ml. of anhydrous acetic acid, 1–2 drops of crystal violet indicator was added and titrated with the perchloric acid solution until the violet color changed to blue-bluish green. Each 10.56 mg. of sym.-diphenylguanidine is equivalent to 1 ml. of 0.05 *N* perchloric acid.

Procedure.—About 70 mg. of ergotamine tartrate, accurately weighed, was dissolved in 15 ml. of anhydrous acetic acid, 1–2 drops of crystal violet indicator was added and titrated with 0.05 *N* perchloric acid until the violet color changed to blue-bluish green. Each 32.84 mg. of ergotamine tartrate [mol. wt. 1313.46, $(C_{33}H_{35}N_5O_5)_2.C_4H_6O_6$] or each 29.08 mg. of ergotamine base (mol. wt. 581.65, $C_{33}H_{35}N_5O_5$) is equivalent to 1 ml. of 0.05 *N* perchloric acid. Accuracy, ±0.5%.

Assay of Tartaric Acid in Ergotamine Tartrate

Reagents.—All reagents are analytical grade. *Anhydrous methanol. Potassium metal. Benzene*, dried over potassium metal. *Pyridine. Naphtholbenzein* (Merck) indicator, 1% in pyridine. *Potassium methoxide*, 0.1 *N*, prepared as follows: about 4.3 Gm. of freshly cut potassium metal was added, in small portions, to 150 ml. of ice-cooled anhydrous methanol contained in a 1000-ml. volumetric flask. When dissolved, sufficient benzene was added to make 1000 ml. The solution was preserved in a container, well protected from light and moisture. Standardization was made by titration against benzoic acid, Merck (mol. wt. 122.12): approximately 25 mg., accurately weighed, was dissolved in 15 ml. of neutralized pyridine, 1 drop of naphtholbenzein indicator was added and titrated with the potassium methoxide solution until the yellow color changed to green. Each 12.21 mg. of benzoic acid is equivalent to 1 ml. of 0.1 *N* potassium methoxide.

Procedure.—Ergotamine tartrate, 100–150 mg., accurately weighed, was dissolved in 15 ml. of neutralized pyridine, 3 drops of naphtholbenzein indicator was added and titrated with 0.1 *N* potassium methoxide until the yellow color changed to green. Protect the solution from the carbon dioxide of the atmosphere. Each 7.504 mg. of tartaric acid is equivalent to 1 ml. of 0.1 *N* potassium methoxide. Accuracy of the method, ±1.0%.

RESULTS

Analytical data of assays are reported in Table II. Estimation of ergotamine base was carried out in anhydrous acetic acid by using 0.05 *N* perchloric acid. Each value presented is the average of four parallel analyses. Evidently there is a large scale of possibilities between ergotamine tartrate and bitartrate to produce mixtures of both salts, where melting point indicates the approximate ratio.

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TABLE I.—COMPARISON OF REQUIREMENTS, B.P. AND U.S.P.

Properties	B.P. 1953	B.P. 1958	U.S.P. XIV	U.S.P. XV	U.S.P.XVI
Solubility	Soluble in water, forming a solution which is liable to become turbid; the addition of tartaric acid is necessary to maintain a clear solution. Soluble in 500 parts of alcohol (90%).		1 Gm. of ergotamine tartrate dissolves in about 500 ml. of water and in about 500 ml. of alcohol.		
Melting point	Softens at about 187° and decomposes at about 192° without melting.		Melts between 177 and 184° (decompn.)		Melts at about 180° (decompn.)

TABLE II.—PROPERTIES OF ERGOTAMINE TARTRATE SAMPLES

Substance	Solubility	M.P., °C.	Contents of Alkaloid Calcd.,[a] % Ergotamine Base Found	Ergotamine Base Theory	Ergotamine Tartrate Found	Ergotamine Tartrate Theory
Ergotamine tartrate B.P.	As B.P. standard	190–193 (decompn.)	88.08	88.57	99.44	100.00
Ergotamine tartrate U.S.P.	As U.S.P. standard	179–180 (decompn.)	82.02	88.57	93.75	100.00
Ergotamine bitartrate-ergotamine tartrate B.P. (6:4)	As U.S.P. standard, ergotamine tartrate	177–180 (decompn.)	82.68	83.12[b]	93.35	93.85[b]
Ergotamine bitartrate	Soluble in about 500 ml. of water and in about 500 ml. of alcohol (90%)	173–175 (decompn.)	78.38	79.49	88.50[c] 98.60[d]	89.75[c] 100.00[d]

[a] All values are calculated on dried substance (100° *in vacuo*). [b] Based on a mixture of ergotamine bitartrate-ergotamine tartrate (6:4). [c] Calculated on ergotamine tartrate (equivalent wt. = mol. wt./2) = 656.73). [d] Calculated on ergotamine bitartrate (equivalent wt. = mol. wt. = 731.74). 10.25% is the difference between the two equivalent weights. Ergotamine bitartrate was prepared from ergotamine base by precipitation in methanol using a surplus of tartaric acid (about 30% of the base quantity). This salt is official in the "Pharmacopoea Bohemoslovenica," 2nd ed., 1954.

Further data have been obtained by analyzing, on one hand, the contents of ergotamine base, on the other, the contents of tartaric acid of samples with different melting points (Table III). The

TABLE III.—ASSAY OF ERGOTAMINE TARTRATE SAMPLES[a]

M.P., °C.	Ergotamine Base, % Found	Ergotamine Base, % Theory	Tartaric Acid, % Found	Tartaric Acid, % Theory	Total Found, %
178–180 (decompn.)	82.47	88.57	17.38	11.43	99.85
183–184 (decompn.)	84.51	88.57	15.17	11.43	99.68
187–188 (decompn.)	86.63	88.57	12.59	11.43	99.22
189–191 (decompn.)	89.03	88.57	10.49	11.43	99.52

[a] All values are calculated on dried substance (100° *in vacuo*). The present data are average values of three parallel analyses.

assay of tartaric acid in ergotamine tartrate was carried out by a modified titrimetric method of Gyenes and Szász (5), using 0.1 *N* potassium methoxide and naphtholbenzein indicator which gave an exact end point.

All samples were checked for purity by paper chromatograms using a modified Macek method (R_f of ergotamine, about 0.1) (4, 6, 7). No ergotaminine or other alkaloid contaminant was found.

DISCUSSION

As is shown in Table II, ergotamine tartrate U.S.P. contains about 60% ergotamine bitartrate and 40% ergotamine tartrate. On the basis of the found base content, calculated on ergotamine tartrate, there is a deviation of about 6% (in case of ergotamine bitartrate, 10.25%) from 100.00% ergotamine tartrate.

The van Urk colorimetric method (*p*-dimethylaminobenzaldehyde T.S. as reagent) yields an accuracy of about ±4–6% when the U.S.P. XVI directions are followed. Positive errors of estimation reduce the deviation partly or completely, recording a more-or-less pure ergotamine tartrate. Against that, negative errors in the van Urk method and the alleged error in composition (due to presence of bitartrate) together caused a deviation of up to 10 to 12%. Such a variation can be avoided by application of the much more exact perchloric acid method. Furthermore, the use of an exact method is not sufficient to reach the minimal U.S.P. requirement of 97.0%, simultaneously maintaining the requirement for melting point of 180° (decompn.) (see Tables II and III); these two requirements are incompatible.

A good soluble ergotamine salt, *e.g.*, ergotamine bitartrate, is often requested for solutions or injections. In our opinion, the slighter solubility of ergotamine tartrate is not disadvantageous for the use in pharmaceutical preparations, because in the case of tablets, ergotamine (base or tartrate) is absorbed by the stomach in the form of the hydrochloric salt, and in the case of injections or solutions (prescribed pH 3–4, adjusted by tartaric acid), ergotamine tartrate is converted into the bitartrate salt.

SUMMARY

1. Quantitative studies using titrimetric methods in nonaqueous media indicated that ergotamine tartrate U.S.P. with a melting point of 180° (decompn.) contains about 60% ergotamine bitartrate.

2. Melting points between 170–192° (decompn.) indicate the approximate ratio of ergotamine bitartrate-tartrate mixture.

3. Application of the perchloric acid titrimetric method (accuracy, ±0.5%) for the assay of ergotamine tartrate substance yields more exact quantitative data than the official van Urk colorimetric method (accuracy, ±4–6%).

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Notes

Quaternary Ammonium Germicides as Surface Disinfectants

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The quaternary ammonium compounds tested proved to be excellent germicides in the dilutions recommended by the manufacturer for waxed and unwaxed floor coverings. In the case of waxed stainless steel, it was assumed that the wax interfered with the disinfectant action because the unwaxed stainless steel was found to be sterile. Quaternary ammonium germicides were found to be unsatisfactory disinfectants for vinyl tile.

THE PURPOSE of this study is to determine whether the quaternary ammonium germicides are useful as sanitizing agents in preventing the spread of infections caused by the staphylococci organisms.

The quaternary ammonium germicides are odorless, colorless, highly stable, and are relatively nontoxic when used in their recommended germicidal concentrations. In general, the quaternary ammonium germicides have been found to inhibit the oxidation of certain carbohydrates (1) and thereby interfere with respiration and glycolysis of bacteria. They are usually tested by the phenol coefficient method. Since in the United States 5% phenol is accepted as the standard of excellence for general disinfection, Reddish (2) has pointed out that dilutions 20 times the phenol coefficient afford a wide margin of safety. The dilution calculated on this basis is usually of sufficient strength to kill all pathogenic microorganisms which cause epidemics.

Although the phenol coefficient is an excellent *in vitro* test, in light of the increase of staphylococcus infections in hospitals, a practical test is recommended. The phenol coefficient test employs *Salmonella typhosa* which is similar in resistance to most disease-producing microorganisms. There are some organisms that are more resistant to disinfectants than *Salmonella typhosa*, one of which is the nonspore forming *Staphylococcus aureus*.

Of particular importance to this study are the incompatabilities of the quaternary ammonium germicides which occur under normal sanitizing conditions. Domagk (3) in 1935 was the first to call attention to the interfering action of ordinary soap on the quaternary ammonium germicides. Since then, incompatibilities such as the nitrate and benzalkonium chloride incompatibility (4) have been pointed out. It is generally recognized that when surfaces have been washed with ordinary soap and water, the objects must be thoroughly rinsed with water before applying a quaternary ammonium disinfectant for sterilizing purposes. This applies to the disinfection of wounds following the cleansing procedure with soap and water.

EXPERIMENTAL[1]

Roccal 10%[2]—The active ingredient is a mixture of technical grade alkyldimethylbenzyl ammonium chlorides in which the alkyl is a mixture of C_8H_{17} to $C_{18}H_{37}$ groups. The phenol coefficient of Roccal 10% is 25 when tested against *Salmonella typhosa* at 20°. It is used for sanitizing eating and drinking utensils.

Quaternary Ammonium Germicide.—The active

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[1] Tabulated data of the experimental results are available from Dr. C. Lee Huyck, Division of Eaton Laboratories of the Norwich Pharmacal Co., Norwich, N. Y.

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