Determination of Some Mercurials *via* Acetolysis and Nonaqueous Acidimetric Titration

By KENNETH A. CONNORS and DAVID R. SWANSON

An analytical method for certain mercurials is based upon their solvolysis in acetic acid to yield either mercuric acetate or a monosubstituted mercuric acetate. When an excess of methylamine hydrochloride is added, an amount of strong base is released which is equivalent to the mercury-bound acetate. The solution is titrated with standard acetous perchloric acid to complete the analysis. The method is applicable to many mercurials containing a mercury-nitrogen, mercury-oxygen, or mercury-sulfur bond.

MOST ANALYTICAL procedures for mercurials involve release of the mercury by drastic oxidative or reductive treatment and ultimate conversion to mercuric ion, which is then determined by classical methods. The analysis of mercurials has recently been reviewed by Medwick (1).

Two general disadvantages may be associated with these conventional analytical methods; they may be laborious and time consuming, and they lack specificity. This paper reports a simple and rapid titration procedure suitable for the analysis of many mercurials of pharmaceutical interest.

Principle of Method.—The mercurials used in pharmacy can in most cases be represented by the general structure R—Hg—R′, in which one but not both of the bonds may be a carbon-mercury bond. These compounds undergo solvolysis in acetic acid according to Eqs. 1 and 2. The reaction conditions and the nature of the R group determine whether the reaction is essentially stopped with the formation of the monosubstituted mercuric acetate (Eq. 1) or proceeds to yield mercuric acetate (Eq. 2). If an excess of a halide salt of a base is added to the solvolysis reaction mixture, a quantity of strong base will be released which is equivalent to the acetate bound to mercury (Eqs. 3 and 4).

$$R—Hg—R' + HOAc \rightleftarrows R—Hg—OAc + R'H \quad \text{(Eq. 1)}$$

$$R—Hg—OAc + HOAc \rightleftarrows Hg(OAc)_2 + RH \quad \text{(Eq. 2)}$$

$$R—Hg—OAc + BX \rightarrow R—Hg—X + BOAc \quad \text{(Eq. 3)}$$

$$Hg(OAc)_2 + 2BX \rightarrow HgX_2 + 2BOAc \quad \text{(Eq. 4)}$$

The base which is released can be accurately titrated with standard acetous perchloric acid to give a measure of the original mercurial compound. This procedure is seen to utilize a reversal of the Pifer-Wollish method for the titration of amine salts, in which an excess of mercuric acetate is added and the base which is freed may be titrated with perchloric acid (2). It cannot be expected to be suitable for the analysis of mercuric halides, for their acetolysis is essentially the reverse of the reaction upon which the titration is based.

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EXPERIMENTAL

Materials.—Methylamine hydrochloride (Eastman Kodak) was recrystallized from absolute ethanol; *p*-naphtholbenzein and quinaldine red were used directly; glacial acetic acid (reagent grade) was used directly; mercurial samples were dried under reduced pressure before use.

Reagents.—Perchloric acid (0.1 *N*) was prepared by adding 11.0 ml. of 60% perchloric acid and 36.0 ml. of acetic anhydride to several hundred milliliters of glacial acetic acid and diluting to 1 L. with acetic acid; it was standardized against potassium biphthalate using *p*-naphtholbenzein as a visual indicator; 0.1 *M* methylamine hydrochloride was prepared by dissolving about 675 mg. of recrystallized methylamine hydrochloride in enough glacial acetic acid to make 100 ml.; 0.1 *N* aqueous ammonium thiocyanate was standardized against silver nitrate using ferric ammonium sulfate as an indicator. *p*-Naphtholbenzein (0.4%) in glacial acetic acid and a saturated solution of quinaldine red in glacial acetic acid were also employed.

Potentiometric Titration.—A Beckman model H-2 meter was employed for potentiometric titrations. A general purpose glass electrode served as the indicator electrode, and a fiber-type calomel electrode, modified by replacing the aqueous potassium chloride solution with 0.1 *M* lithium perchlorate in glacial acetic acid, was the reference.

Analytical Procedures.—Some variation in the basic procedure is necessary for certain compounds. The procedures recommended are described, and their applicability will be discussed in the following sections.

Procedure A.—A sample corresponding to 0.5 to 0.8 meq. of mercurial is accurately weighed into a flask and is dissolved in glacial acetic acid. Several drops of indicator solution are added, and the solution is titrated to the end point with standard 0.1 *N* perchloric acid; a 10-ml. buret is used. A small

TABLE I.—COMPARISON OF ASSAY RESULTS BY ACETOLYSIS AND THIOCYANATE PROCEDURES

Mercurial	Acetolysis n[a]	Acetolysis Recovery, %	Acetolysis S.D.[b]	Thiocyanate n[a]	Thiocyanate Recovery, %	Thiocyanate S.D.[b]
Mercuric acetate	6	98.8	0.1	4	99.9	0.3
Red mercuric oxide	6	100.5	0.4	7	100.2	0.5
Yellow mercuric oxide	5	99.9	0.5	4	100.0	0.2
Mercuric succinimide	5	98.3	0.3	6	98.6	0.1
Nitromersol	7	97.9	0.3	3	99.1	0.8

[a] Number of determinations. [b] Standard deviation = $\sqrt{\Sigma(x_i - \bar{X})^2/n - 1}$.

(1–2 ml.) excess of 0.1 *M* methylamine hydrochloride solution is added, whereupon the indicator will revert to its basic color. The titration is continued to the end point. The volume of acid consumed between the two end points is equivalent to the mercurial in the sample. If a smaller buret is used, the sample may be reduced to 0.1 meq.

Procedure B.—The weighed sample is dissolved in glacial acetic acid. Indicator and a small excess of methylamine hydrochloride solution are added, and the solution is titrated to the end point with 0.1 *N* perchloric acid. The volume of acid consumed is equivalent to the mercurial plus any strongly basic component in the sample.

Some compounds do not yield satisfactory visual end points and must be titrated potentiometrically (see *Discussion*).

RESULTS

To assess the validity of the proposed method, several mercurials, both inorganic and organic, were analyzed by the acetolysis procedure and by conventional thiocyanate titration (3–5). A comparison of the results, shown in Table I, indicates that the acetolysis method gives assay values which are, within the reproducibilities of the two independent procedures, essentially identical with those of the thiocyanate method. (In certain instances the methods may be expected to yield different results; see below.) Table II lists all of the titration results obtained by the acetolysis procedure, the molecular and equivalent weights for the mercurials, and the procedure employed in each case.

DISCUSSION

Analytical Procedure.—The selection of *Procedure A* or *B* depends upon the structure of the mercurial. It will be noted, from a comparison of the molecular and equivalent weights listed in Table II, that if either or both of the bonds to mercury is a mercury-oxygen or mercury-nitrogen bond that *Procedure A* is usually satisfactory. Such bonds are easily cleaved at room temperature according to Eqs. 1 and 2. *Procedure A* is the more desirable one, for the preliminary titration (before addition of the methylamine hydrochloride) corrects for any basic groups present in the mercurial or in another component of the sample and renders the method quite specific for the mercurial. Figure 1, for example, shows the analysis of both components of a mixture of sodium and mercuric acetates.

Procedure B is necessary for samples which yield a sharp final end point, representing all strongly basic functions in the sample, but would not permit accurate location of the first end point. Thimerosal is such a substance. The acetolysis of this compound gives a thiol (sodium thiosalicylate) and ethyl mercuric acetate. If *Procedure A* is used to analyze this compound, the first end point (representing the titration of the carboxylate group) is obscured by a further consumption of acid for some unknown reason but perhaps is associated with the presence of the thiol group. *Procedure B* must also be employed if the sample contains a weakly basic component, such as theophylline. *Procedure A* in this case would result in two poorly defined end points, each actually representing the titration of the weak base. [In the case of theophylline the first end point is somewhat sharper than the second because mercuric acetate tends to increase the apparent base strength of theophylline (6).] By using *Procedure B* one is able to titrate the strong base component of the mixture, which is a measure of the mercurial present plus any other strong base in the sample.

If the organomercurial contains a carbon-mercury bond which must be cleaved (as in an alkyl or aryl mercuric chloride) neither of these procedures is suitable. More drastic reaction conditions are necessary to solvolyze such a compound. Experiments using perchloric acid as a catalyst under reflux conditions led to nearly quantitative recovery of 0.6 meq. samples of *o*-hydroxyphenyl mercuric chloride in most trials. It was found that an excess of methylamine hydrochloride was required during the reflux, perhaps to shift the equilibrium toward the solvolysis products. The results were observed to be sensitive to the concentration of perchloric acid and to the time of reflux in an irregular manner, and it is believed that side reactions may occur which may lead to nonquantitative recoveries. The acetolysis procedure under reflux conditions is not recommended.

TABLE II.—ANALYSIS OF MERCURIALS BY ACETOLYSIS PROCEDURE

Mercurial	Procedure	Recovery, %	S.D.	Molecular Wt.	Equivalent Wt.	Bond type
Red mercuric oxide	A	100.5	0.4	216.6	108.3	Hg═O
Yellow mercuric oxide	A	99.9	0.5	216.6	108.3	Hg═O
Mercuric succinimide	A	98.3	0.3	396.8	198.4	2 Hg—N
Nitromersol	A	97.9	0.3	351.7	351.7	Hg—O, Hg—C
Phenyl mercuric acetate	A	100.3	0.2	336.8	336.8	Hg—O, Hg—C
Thimerosal	B	100.1	0.2	404.8	202.4	Hg—S, Hg—C
Mercuric nitrate	A[a]	100.5	0.2	324.6	162.3	2 Hg—O
Phenyl mercuric nitrate	A[a]	99.3	0.8	653	327[b]	Hg—O, Hg—C
Meralluride	B[a]	104.9	1.5	611.0	611.0	Hg—N, Hg—C
Mercuric acetate				318.7	159.4	2 Hg—O
(Without theophylline)	A	101.0	0.2			
(With theophylline)	B[a]	100.8	0.5			

[a] Potentiometric titration. [b] *Phenyl mercuric nitrate* is a mixture of phenyl mercuric nitrate and phenyl mercuric hydroxide.

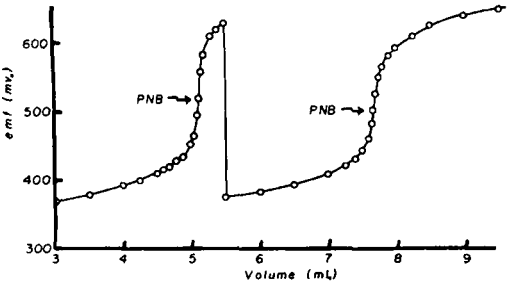

Fig. 1.—Analysis of a mixture of sodium acetate and mercuric acetate by *Procedure A*. Excess methylamine hydrochloride was added at 5.50 ml. The *p*-naphtholbenzein visual end points are indicated.

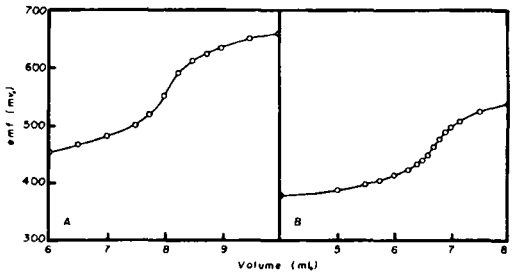

Fig. 2.—(*A*) Potentiometric titration of phenylmercuric nitrate. (*B*) Potentiometric titration of mercuric acetate in the presence of theophylline.

End Point Detection.—Most of the titrations were carried out with visual detection of the end point, using *p*-naphtholbenzein as the indicator. The color change is from yellow (in the basic form) to green (acid form) and is quite sharp. If a large excess of of methylamine hydrochloride is added, the color change becomes rather diffuse due to consumption of perchloric acid by the excess amine salt—hence the direction (see *Experimental*) to keep the excess small. This effect of a large excess of the amine salt is not so noticeable when using quinaldine red as the indicator, probably because quinaldine red is a stronger base than is *p*-naphtholbenzein in the acetic acid system (7, 8).

Mercuric nitrates do not yield accurate visual end points, probably because nitric acid is strong enough in the acetic acid system to compete with perchloric acid. These substances can be successfully analyzed by potentiometric titration (Fig. 2*A*). Potentiometric location of the end point is also necessary if the sample contains theophylline or another very weak base. To demonstrate that the presence of theophylline does not affect determination of the end point, a mixture of mercuric acetate and theophylline was assayed by *Procedure B* with potentiometric titration (Fig. 2*B*); the recovery was essentially identical with that observed in the absence of theophylline (see Table II). Since meralluride contains theophylline, this procedure was employed in its analysis.

Choice of Halide.—Several salts were used in the titration before methylamine hydrochloride was selected as the most suitable one. The quaternary compounds, tetraethylammonium bromide and tetramethylammonium chloride may be employed, but their use always leads to the formation of a precipitate which tends to obscure the indicator color change. Ammonium chloride and potassium chloride are useful salts, but they are relatively insoluble in acetic acid; they were added in the crystalline form. Lithium chloride is soluble in acetic acid, but it appears to be sufficiently ionized in this solvent to be useless for the present purpose. Methylamine hydrochloride is quite satisfactory. It is soluble in acetic acid and is readily purified by recrystallization. If a modest excess is used, sharp end points are observed. It should be recrystallized before use, for its ability to consume a small amount of perchloric acid precludes preliminary neutralization of any free base that may be present as an impurity.

Applicability of Method.—It has been observed with some samples that the proposed acetolysis procedure may give lower results than the thiocyanate titration. This is probably an advantage of the method, for this difference is the result of decomposition of the mercurial, which is not detected by thiocyanate titration. Thus, when a sample of red mercuric oxide was exposed to light and periodically analyzed by both methods, the acetolysis procedure showed a progressive decrease in purity, while the thiocyanate method did not detect this degradation.

Several mercurials cannot be analyzed by the acetolysis method. Mercuric halides and alkyl and aryl mercuric halides have already been discussed. Merbromin, mercuric sulfide, and mercuric sulfate are not soluble in acetic acid. In the analysis of merethoxylline fading end points were noted, though very slow titration eventually led to quantitative recovery, with the equivalent weight equal to one-half the molecular weight. It may be that a slow solvolysis of the amide bond occurs, with consumption of the titrant acid by the product amine.

Differences in solubilities and solvolytic reactivities may permit the analysis of certain mixtures of mercurials by this method.

The acetolysis procedure described in this paper is not of general applicability to the analysis of mercurials. Consideration of the structures of the mercurials listed in Table II will indicate the types of compounds which can be successfully determined. The method possesses the advantages of speed and simplicity for such compounds.

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