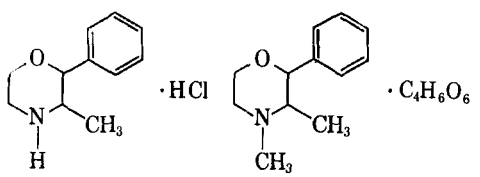
# Identification and Assay of Phenmetrazine and Phendimetrazine in Pharmaceutical Dosage Forms

By W. N. FRENCH and J. F. TRUELOVE

**A simple quantitative method for the determination of phenmetrazine and phendimetrazine in pharmaceutical dosage forms is described. It involves extraction of the base from alkaline solution, followed by conversion to the acetate and titrimetric analysis of the salt by means of perchloric acid. Colorings making conventional assays inapplicable do not interfere with the assay. Specific procedures for the isolation and characterization of these drugs by means of derivative formation are recorded.**

PHENMETRAZINE HYDROCHLORIDE (I) and phendimetrazine bitartrate (II), two anorexigenic agents for the treatment of obesity, are marketed presently in a number of pharmaceutical preparations.



I II

Methods for the identification and determination of phenmetrazine, including microchemical spot tests (1, 2), an ultraviolet spectrophotometric analysis (3), and nonaqueous titrimetric procedures based on the use of perchloric acid (4) or sodium tetraphenylborate (5) have been described in the literature. Comparable data for phendimetrazine have not been published so far.

It is the purpose of this paper to describe the preparation and properties of some hitherto unreported derivatives of these medicinals and present a simple method for characterizing and determining the clinically important drugs in commercial products.

## EXPERIMENTAL

**Formation of Picrate Derivatives.**—Add 15 ml. of a 1.0% aqueous solution of picric acid to 100 mg. of phenmetrazine hydrochloride or phendimetrazine bitartrate dissolved in 2 ml. of water. If the derivative does not precipitate immediately from the cloudy solution in crystalline form but separates as an oil, swirl the flask gently, and scrape the walls of the vessel with a spatula to induce crystallization. Filter off the reaction product after 15 min., wash with distilled water, and dry *in vacuo*. Recrystallize the compound by dissolving in 10 ml. of hot benzene, adding, if necessary, a few drops of ethyl alcohol to aid dissolution. Filter through a small plug of glass wool, and evaporate the filtrate to a volume of about 5 ml. on the steam bath. Allow the solution to cool and crystallize. Remove the solvent by suction filtration, wash the crystals with benzene, and dry the purified derivative *in vacuo*.

Phenmetrazine hydrochloride yields about 160 mg. (84%) of crude picrate, m.p. 198–199°. Recrystallization raises the melting point to 199.5°. [*dl-trans*-Phenmetrazine picrate is reported to melt at 200–202° (6).]

*Anal.*—Calcd. for $C_{11}H_{15}NO \cdot C_6H_3N_3O_7$: mol. wt., 406.4. Found: mol. wt., 404.7 (by nonaqueous titration).

Phendimetrazine bitartrate yields about 100 mg. (82%) of crude picrate, m.p. near 186°. Recrystallization raises the melting point to 187°. [*dl-trans*-Phendimetrazine picrate is reported to melt at 190° (7).]

*Anal.*—Calcd. for $C_{12}H_{17}NO \cdot C_6H_3N_3O_7$: mol. wt., 420.4. Found: mol. wt., 419.6 (by nonaqueous titration).

**Isolation of Picrate Derivatives from Pharmaceutical Dosage Forms.**—*Noncolored Tablets.*—Triturate a sample (equivalent to 25 mg. of phenmetrazine hydrochloride or 35 mg. of phendimetrazine bitartrate) with 2 ml. of distilled water, filter through a small plug of glass wool, and rinse with 1 ml. of water. Add 5 ml. of 1.0% aqueous picric acid reagent to the filtrate and isolate the derivative as described above.

*Colored Tablets.*—Reduce sample to a fine powder and transfer an aliquot equivalent to about 25 mg. of phenmetrazine hydrochloride or 35 mg. of phendimetrazine bitartrate to a small separator. Add 0.5 ml. of 1 *N* NaOH and extract with 5 ml. of ether. Pour the extract through a small plug of glass wool,

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rinsing the separator with an additional 3–5 ml. of solvent. Evaporate the combined filtrates just to dryness, and dissolve the residue in 1 ml. of distilled water containing 3 drops of 1 *N* hydrochloric acid. Add to this solution 5 ml. of the picric acid reagent and proceed to isolate the derivative in accordance with the procedure given.

**Formation of p-Toluenesulfonamide Derivative of Phenmetrazine.**—Add 100 mg. of phenmetrazine hydrochloride to a solution of 200 mg. of *p*-toluenesulfonyl chloride in 2 ml. of dry pyridine and heat on the steam bath for 5 min. Add 2 ml. of distilled water and continue heating until the yellow color is discharged (1–2 min.). Cool the vessel to room temperature, dilute the solution with 20 ml. of water, and shake vigorously to induce crystallization. Filter off the derivative, wash with water, and dry *in vacuo*. The yield of crude product is about 120 mg. (78%), m.p. 135–136°. Recrystallize by dissolving in 10 ml. of ether, filtering through a small plug of glass wool, evaporating the filtrate to a volume of 5 ml., and adding 10 ml. of petroleum ether (b.p. 30–60°). The purified derivative melts at 137.5–138.0°.

*Anal.*—Calcd. for $C_{18}H_{21}NO_3S$: N, 4.23. Found: N, 4.27.

**Isolation of Derivative from Pharmaceutical Dosage Forms.**—Reduce the tablet to a fine powder, transfer the equivalent of about 25 mg. of phenmetrazine hydrochloride into a separator containing 0.5 ml. of 1 *N* NaOH, and extract with 5 ml. of ether. Pass the ether extract through a small plug of glass wool, rinse the separator with another 3–5 ml. of ether, and evaporate the combined filtrates just to dryness. To the residue add 1 ml. of dry pyridine, followed by 50 mg. of *p*-toluenesulfonyl chloride, and isolate the crystalline derivative in accordance with the procedure described above.

**Recovery of Phendimetrazine Bitartrate from Tablets.**—Place a powdered tablet (or the equivalent of about 35 mg. of phendimetrazine bitartrate) into a small separator containing 0.5 ml. of 1 *N* NaOH and extract with 5 ml. of ether. Pour the extract through a small plug of glass wool and rinse the separator with a 3–5 ml. portion of ether. Evaporate the combined filtrates to a volume of about 5 ml. and add a solution of 20 mg. of tartaric acid in 2 ml. of acetone. Crystals of pure phendimetrazine bitartrate, m.p. 186.0°, separate on cooling the solution in ice.

**Determination of Phenmetrazine or Phendimetrazine in Tablets.**—Place an accurately weighed quantity of powdered tablet sample, equivalent to about 75 mg. of phenmetrazine hydrochloride or 100 mg. of phendimetrazine bitartrate, into a 125-ml. separator containing 5 ml. of 1 *N* NaOH. Shake with 40 ml. of chloroform, let layers separate, and draw off the chloroform extract through a small column of glass wool (about 1 × 12 cm.) into a 250-ml. conical flask containing approximately 5 ml. of glacial acetic acid. Repeat the extraction with an additional 30 ml. and two 10-ml. portions of chloroform, passing each extract likewise through the glass wool column. Place the flask containing the combined extracts in a boiling water bath and evaporate the solution to about 35 ml. Cool the vessel to room temperature and titrate the solution with 0.05 *N* perchloric acid in dioxane from a 10-ml. microburet using 2 drops of a 0.5% solution of crystal violet in glacial acetic acid as indicator. Compute the composition of the sample following a blank titration under the same experimental conditions. Each milliliter of 0.05 *N* perchloric acid is equivalent to 10.685 mg. of phenmetrazine hydrochloride or 17.073 mg. of phendimetrazine bitartrate.

## RESULTS AND DISCUSSION

The identification of phenmetrazine or phendimetrazine is accomplished readily *via* formation of the respective picrate derivative. Simple extraction of the base from tablet preparations permits application of the microchemical reaction to pharmaceutical dosage forms. Phenmetrazine may also be characterized as the *p*-toluenesulfonamide derivative, m.p. 137.5–138.0°, while phendimetrazine may be recovered readily as the bitartrate. The derivatives are prepared easily and purified and display sharp and characteristic melting points. Further identifications can be made by comparing their infrared absorption spectra with those of authentic reference standards.

A number of assay procedures were investigated before a modified nonaqueous titration method was found to give satisfactory results. Assay of phenmetrazine hydrochloride by determination of halogen content *via* argentiometric titration, which is at best an indirect assay only, was found to be unsuitable since all pharmaceutical formulations examined contained interfering coloring agents.

Ultraviolet methods of analysis also proved to be unsatisfactory since consistent results could not be obtained. Each compound exhibits typical phenyl absorptions at 266, 262, 260 (sh), 256, and 250 mμ, with a maximum molecular extinction of about 220 occurring at 256 mμ. Thus, relatively concentrated solutions (approximately 40 mg./100 ml.) are required for absorption measurements, and interference by tablet excipients becomes a strong possibility. Coloring agents present in the preparations examined interfered markedly, and the use of charcoal to insure their removal meant also a partial loss of active ingredient. Ion exchange resins were applied for clean-up of aqueous tablet extracts, but results obtained were likewise less precise than those arrived at by the nonaqueous titrimetric method described.

Quantitative recoveries of the pure drugs are realized by titration with perchloric acid in either dioxane or glacial acetic acid using crystal violet as indicator and glacial acetic acid as solvent. Determination of the hydrochloride requires the addition of a slight excess of mercuric acetate (100 mg. per 50 mg. of sample). The analysis of tablets is based upon extraction of the drug from an aqueous alkaline suspension by means of chloroform. Ether proves unsatisfactory for this purpose because phenmetrazine and phendimetrazine are water soluble and hence not removed completely from aqueous solution, even after repeated extractions. Chloroform is a satisfactory solvent for recovering the drugs, provided only a small volume of sodium hydroxide solution is used to liberate the base. Otherwise, troublesome emulsions occur. The chloroform extract is passed through a small glass wool column to remove any water droplets from the solvent system and also to absorb some color from the extract. The eluant is added to glacial acetic

TABLE I.—ANALYSIS OF PHENMETRAZINE AND PHENDIMETRAZINE AND THEIR PHARMACEUTICAL DOSAGE FORMS

| Product | Code No. | Assay, % | S. D.[a] |
|---|---|---|---|
| **Pure Drugs** | | | |
| Phenmetrazine hydrochloride | | 100.0[b] | 0.29 |
| Phendimetrazine bitartrate | | 99.5[b] | 0.20 |
| Phenmetrazine hydrochloride | | 100.1[c] | 0.36[c] |
| Phendimetrazine bitartrate | | 99.7[c] | 0.10[c] |
| **Tablets** | | | |
| Phenmetrazine hydrochloride | A | 100.6 | 0.02 |
| | B | 102.8 | 0.57 |
| | C | 100.2 | 0.45 |
| | D | 100.5 | 0.79 |
| Phendimetrazine bitartrate | E | 95.9 | 1.09 |
| | F | 96.7 | 0.73 |

[a] Based on six assays for each product. [b] By direct titration in acetic acid. [c] Four assays by the method described for tablet assay.

acid to form the acetate of the base before the solution is concentrated. Both phenmetrazine and phendimetrazine are somewhat volatile, and losses occur during evaporation of the solvent if the drugs are not first converted to their salts. Evaporation of the solution is necessary to remove water from the extract by azeotropic distillation as well as to obtain a smaller volume for titrimetric analysis.

Good recoveries of the pure drugs were realized by this procedure and satisfactory results obtained for commercial products marketed in Canada, as shown in Table I. The two lots of phendimetrazine tablets (code No. E and F) assayed 95.9 and 96.7%, respectively. Commercially available phendimetrazine bitartrate was also of similar purity and had to be recrystallized several times to obtain an analytical specimen which could be used as reference standard (99.5% purity). The results show that the pure drug is recovered quantitatively by the method described for the assay of tablets. The low values obtained with the commercial samples are therefore probably due to the use of impure bulk drug.

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# Quantitative Reaction for Pentylenetetrazole

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**The published procedures for pentylenetetetrazole include either a gravimetric determination or a filtration step. The method described allows direct titration with hydrochloric acid following precipitation of a silver–pentylenetetrazole phosphotungstate salt. The precision of the method is established, and the composition of the phosphotungstate salt is characterized.**

THE PROCEDURES described in the literature for the determination of pentylenetetrazole include complexation with mercuric chloride (1, 2), cuprous chloride (3), and cadmium chloride (4). The official compendia, the "United States Pharmacopeia" (5) and the "National Formulary" (6), use an extraction procedure for the analysis of pentylenetetrazole injection. All of these procedures involve a gravimetric determination or a filtration step.

In looking for a more suitable method of analysis, it was found that silver ion forms a complex with pentylenetetrazole; however, it was not sufficiently insoluble to be used as a basis for analysis. The phosphotungstate salt of the silver complex, however, has a low solubility in water. This reaction was made the basis of an analytical procedure for pentylenetetrazole tablets. The stoichiometry of the reaction requires 4 moles of pentylenetetrazole for each 3 moles of silver ion in the formation of the phosphotungstate precipitate. This ratio was found to be constant in the presence of an excess of either pentylenetetrazole or silver ion.

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## EXPERIMENTAL

**Composition of the Precipitate.**—A quantity of the complex phosphotungstate salt was collected and dried *in vacuo* at room temperature. The