

After the final evaporation steps with sodium hydroxide, the above products can be tested according to the method given.

SUMMARY.

A test is described for diethylphthalate detection in alcohol and spirituous products. False positives and negative blanks are obviated where previously, with the U. S. P. X test, such false reactions could not be entirely excluded. After completion of the test, results can be read in fifteen minutes or less. The host of organic substances giving false positives are eliminated by the ethyl-ether shake-out of the acid resorcinol mixture, retaining only the fluorescence dye formed. This new modification is offered for review by the Revision Committee of the U. S. Pharmacopœia.

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PHENYLMERCURY NITRATE AND SOME OTHER PHENYLMERCURY SALTS.*

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Phenylmercury nitrate was first prepared by Otto in 1870 (1). Renewed interest has been aroused recently by Weed and Ecker (2, 3, 4), who have studied its use as a non-toxic, non-irritating germicide.

The authors of the above papers have all assumed that the compound was of the normal constitution $C_6H_5HgNO_3$. Studies in these laboratories begun early in 1932 showed that this could not be correct. The average of eighteen analyses for mercury was 63.6%, with 64.1% as the upper, and 63.0% the lower, limit. This result suggested a basic phenylmercury nitrate, $C_6H_5.HgOH.C_6H_5.HgNO_3$, which requires 63.3% mercury. The compound is not, however, a basic salt analogous to bismuth subnitrate, for example. Not only is the composition unaffected by boiling tenth-normal nitric acid but the p_H of an aqueous solution is 4.3. Confirmation of the basic formula for phenylmercury nitrate was obtained by the behavior of phenylmercury hydroxide on titration. The hydroxide behaves as a moderately strong base toward acetic, lactic, hydroxybutyric, and the halogen acids yielding normal salts but behaves as a semi-acid base toward nitric, sulphuric, gluconic and phenol sulphonic acids, yielding basic salts. The remaining hydroxy group in the basic salts cannot therefore be ionized but must be firmly bound in a complex radicle such as $[C_6H_5.HgOH.C_6H_5.Hg.]^+$. Even assuming the presence of a complex ion in aqueous solutions of phenyl mercury nitrate certain anomalies still confront us.

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Thus the solubility of phenylmercury nitrate is increased by dilute alkali. This cannot depend upon an acid ionization of the remaining hydroxyl group, for the solubility of phenylmercury hydroxide is less in dilute alkali than in pure water, due to the common hydroxyl ion. Evidently the stability of the complex ion is affected by the other ions present, but our studies have not yet yielded a satisfactory explanation for the reactions involved.

Our conclusions regarding the basic formula for phenylmercury nitrate have recently been confirmed by Pyman and Stevenson (5). These authors conclusively demonstrated that the basic formula was correct. They prepared true phenylmercury nitrate by the method of Bamberger (6), avoiding aqueous solvents throughout. The compound melted at 132° C. whereas the ordinary "phenylmercury nitrate" melts at 187–190° C. The compound, melting point 132° C., is unstable and is converted to the stable basic form, melting point 187–190° C., on recrystallization from dilute alcohol.

It has been observed that, although the phenylmercury radicle does not exhibit the residual valence of mercury itself, it does possess affinity for various types of bases. For example, the solubility of phenylmercury nitrate in water is diminished by sodium nitrate, due to the common ion effect, and hot concentrated potassium iodide does not dissolve phenylmercury iodide appreciably. On the other hand, mono-ethanolamine increases the solubility of phenylmercury nitrate presumably by the formation of a more soluble complex. In addition, a compound $C_6H_5HgNO_3 \cdot C_6H_5N$ is formed when phenylmercury acetate reacts with sodium nitrate in the presence of pyridine. In this case the organic base replaces the C_6H_5HgOH in the complex ion.

The analyses were carried out by decomposing the compounds with fuming sulphuric acid and hydrogen peroxide, followed either by titration with thiocyanate or by weighing the mercury as sulphide. Halogen compounds were analyzed by the method of Kharasch and Flenner (7).

None of the many preparations of phenylmercury nitrate made in this laboratory have shown the high germicidal potency which we had expected on a basis of literature reports; this was the case particularly when the tests were made in the presence of tissue and other organic matter. Transfer tests, as described by Leonard (8), have shown that much of the activity is bacteriostatic rather than truly germicidal. This transfer test is made after the phenol coefficient test by the Hygienic Laboratory method has been completed. A loopful is transplanted from each dilution of the fifteen-minute bouillon planted tubes into fresh medium. This is done to dilute the germicide which is carried over by the original loopful. If growth appears in this extra transfer tube when there was no growth in the original tube, then the substance being tested is bacteriostatic and not truly germicidal. A true germicide shows no growth in either tube.

Some evidence has been found that the aqueous solution is not entirely non-irritating. The irritating properties were not diminished by further purification.

The aqueous solution is not completely stable, for we have observed a slight, but continuously increasing deposition of sediment when a saturated aqueous solution is allowed to stand for some weeks.

Preparation of Phenylmercury Nitrate.—We have prepared the material used in this work by double decomposition of phenylmercury acetate and sodium nitrate.

Very pure phenylmercury acetate was prepared in small quantities by the method described in the experimental part. For larger quantities it was found more convenient to follow German Patent 553,280 in preparing the acetate.

When purified phenylmercury acetate is treated with a ten-fold excess of sodium nitrate, the yield of the nitrate is 90-92% of the theoretical. The mercury remaining in the mother liquor is not obtainable as phenylmercury nitrate, but is accounted for by the solubility effect of sodium acetate and acetic acid on phenylmercury nitrate. We have found that one mol of sodium acetate even in the presence of ten mols of sodium nitrate increases the solubility to 0.158%, and that in the presence of tenth-normal acetic acid the solubility is 0.3%.

EXPERIMENTAL.

Preparation of Phenylmercury Acetate.—The general procedure for the preparation of phenylmercury acetate is given by the following typical experiment: 22.5 Gm. of mercuric acetate was dissolved in 22.5 Gm. of glacial acetic acid and poured into 100 cc. of thiophene-free benzene. The resulting mushy reaction mixture was heated, with constant agitation, for two hours at 100° C. A colorless homogeneous solution was formed within twenty minutes.

The reaction product was allowed to stand at room temperature over night. Only mono-acetoxy mercuri-benzene remained in solution, but the crystals consisted of a mixture of the mono- and diacetoxy derivatives. Separation was effected by cold thiophene-free benzene. Evaporation of the benzene solutions gave 17.46 Gm. of crude phenylmercury acetate. 1.15 Gm. of benzene-insoluble material, chiefly di-acetoxy mercury benzene, was isolated, and 4.27 Gm. of mercuric acetate was recovered. This accounts for 97.75% of the mercuric acetate used, 2.25% having been lost mechanically.

Recrystallization: 17.46 Gm. gave 12.9 Gm. of satisfactory phenylmercury acetate; melting point 146-147.5° C; analysis gave mercury 59.48 and 59.53%; theoretical 59.6%. The benzene insoluble material was recrystallized from alcohol. The resulting nacreous scales gave mercury 67.6%. $C_6H_4(HgOCOCH_3)_2$ requires 67.4%.

We have found it unprofitable to attempt further recovery of phenylmercury acetate from the aqueous mother liquor. It is best to evaporate to dryness and recover mercury by dry distillation when a sufficient quantity of the solid material has accumulated.

Preparation of Phenylmercury Nitrate.—5.83 Gm. of recrystallized phenylmercury acetate was dissolved in 1000 cc. of boiling water and treated with a hot solution of 22 Gm. of sodium nitrate in 100 cc. of water. The reaction mixture was digested at 90-95° C. for fifteen minutes and allowed to stand over night. The first crop weighed 4.17 Gm.; melting point 186.5-188° C. with decomposition; 63.8% mercury. The second crop, obtained by concentration of the mother liquor, weighed 0.923 Gm.; melting point 188-189° C. with decomposition; 63.3% mercury. Total yield 5.093 Gm.; 92.7% of the theoretical. An aliquot of the filtrate (135 cc.) was analyzed and the total filtrate found to contain 0.178 Gm. mercury or 0.281 Gm. calculated as basic phenylmercury nitrate. This is a concentration of 0.208% which obviously compares favorably with the solubility of phenylmercury nitrate in the presence of sodium acetate, acetic acid and sodium nitrate.

Recrystallization of Phenylmercury Nitrate.—Extensive crystallization experiments were carried out in the effort to account for the irritating properties of the aqueous solutions. Starting with 20 Gm. of phenylmercury nitrate, 2.87 Gm. of what appeared to be the purest specimen of the compound ever isolated was obtained by extraction with hot alcohol; it crystallized in pearly lustrous scales and melted at 191-192.5° C. with decomposition. Analysis gave 63.0% mercury. Its aqueous solution, however, gave p_H 4.3 identical with the p_H of the crude nitrate. Also its irritating properties were not diminished.

Preparation of Phenylmercury Nitrate in the Presence of Pyridine.—Two grams of phenylmercury acetate was dissolved in 6 cc. of pyridine, the solution diluted to 40 cc. with water and filtered. It was treated in the cold with a concentrated aqueous solution containing 7.5 Gm. of

sodium nitrate. A white very slightly gelatinous precipitate formed at once; nitric acid was added until faintly acid to congo. Yield 1.24 Gm.; melting point 182–183° C., but when mixed with known phenylmercury nitrate a depression to 169–172° C. occurred. Analysis gave 47.5% and 47.4% mercury. $C_6H_5HgNO_3 \cdot C_6H_5N$ requires 47.9% mercury.

The low yield (50% of the theoretical) shows the solubility of this pyridine addition product to be far greater than that of phenylmercury nitrate. Inasmuch as 1.23 Gm. remained in approximately 50 cc. of the mother liquor, the solubility of the complex in this solvent is 2.4%.

Preparation of Phenylmercury Hydroxide.—Thirteen grams of pure phenylmercury chloride melting at 250–251° C. was dissolved in 2200 cc. of alcohol and 500 cc. of water and treated with continuous stirring with 10% excess of freshly prepared silver oxide. After two hours' stirring at the boiling point the chloride test was negative and the product was isolated by concentrating the filtrate under diminished pressure. Two crops of phenylmercury hydroxide were obtained: (1) 4.6 Gm. melting at 207–210° C. and (2) 5.47 Gm. melting at 224–225° C. Crop (1) was contaminated with a small proportion of mercury diphenyl which was readily removed by recrystallization from water in which mercury diphenyl is insoluble. Analysis of crop (2) gave mercury 68.26%; C_6H_5HgOH requires 68.10%.

Preparation of Phenylmercury Lactate.—One hundred cubic centimeters of a 1% aqueous solution of phenylmercury hydroxide were treated with a 7.5% aqueous solution of lactic acid until faintly acid to litmus. The reaction mixture was concentrated *in vacuo* to the point of crystallization. A salt was obtained in pure white leaflets melting at 160–161° C. Analysis gave mercury 54.43%; $C_6H_5Hg \cdot C_3H_5O_3$ requires 54.7%. The solubility of phenylmercury lactate in water is 0.5%.

Preparation of Phenylmercury Gluconate.—One hundred cubic centimeters of a 1% aqueous solution of phenylmercury hydroxide was treated with a 10% aqueous solution of gluconic acid until just acid to litmus. The reaction product was isolated as described for the lactate. The salt crystallized in radiate clusters of stout prisms. Two crops were obtained: (1) 1.15 Gm. melting at 171–172° C. with decomposition, and (2) 0.159 Gm. melting at the same point. Analysis gave mercury 54.6%. Neutral phenylmercury gluconate requires 42.42% mercury. The basic salt $C_6H_5Hg \cdot C_6H_{11}O_7 \cdot C_6H_5HgOH$ requires 52.3% mercury. The solubility of basic phenylmercury gluconate is 1.06% at 27° C.

Preparation of Phenylmercury Phenol Sulphonate.—Two grams of phenylmercury hydroxide were dissolved in 110 cc. of hot water and the solution treated with 20% aqueous phenol sulphonic acid until just acid to litmus. A slightly sticky product was precipitated at once; this was discarded. The clear filtrate deposited a powdery precipitate on cooling. Recrystallization from water gave nacreous leaflets with a slight pink coloration. Yield 1.147 Gm. Melting point 162–164° C. with effervescence; this point was not raised by another crystallization. Analysis gave 54.95% mercury. $C_6H_5HgOSO_2 \cdot C_6H_4OH \cdot C_6H_5HgOH$ requires 53.9%.

Preparation of Phenylmercury Hydroxy Butyrate.—This salt was prepared exactly as described for the lactate. It melted at 149–149.5° C. and gave 54.0% mercury as compared with the theoretical value of 52.7%. The solubility in water is 0.6% at 27° C.

Titration of Phenylmercury Hydroxide with Tenth-Normal Nitric Acid.—0.4222 Gm. of phenylmercury hydroxide was dissolved in 50 cc. of hot water and titrated with tenth-normal nitric acid until neutral to methyl orange. (This indicator was chosen because its end-point is closest to the p_H of aqueous phenylmercury nitrate, 4.3) 8.3 cc. was required which is 58% of 14.3 cc. theoretically required for the formation of neutral phenylmercury nitrate. The crystals separating from this reaction melted sharply at 181–182° C. with decomposition. Yield 0.38 Gm. or 84% of the theoretical. Obviously phenylmercury hydroxide behaves as a semi-acid base toward nitric acid.

Titration of Phenylmercury Hydroxide with Normal Hydrochloric Acid.—0.4635 Gm. phenylmercury hydroxide was dissolved in 50 cc. of hot water and titrated with normal hydrochloric acid. 1.49 cc. was required (methyl orange indicator). The theoretical volume required is 1.42 cc., which shows that phenylmercury hydroxide behaves "normally," *i. e.*, as a mono-acid base toward hydrochloric acid.

The germicidal and irritation tests on the compounds reported herein were made in the Biological Research Laboratories of E. R. Squibb and Sons and we gratefully acknowledge their assistance.

SUMMARY.

The composition of phenylmercury nitrate has been studied and evidence which confirms the basic formula $C_6H_5.HgOH.C_6H_5.HgNO_3$ obtained. Some other phenylmercury salts have also been described.

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SOME OBSERVATIONS ON THE PREPARATION OF INTRAVENOUS SOLUTIONS IN THE HOSPITAL PHARMACY.*

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Since the inception of intravenous medication, it has been the practice of many hospitals, at one time or another, to prepare some of the products used for this purpose. Their experience in a large number of cases has been unsatisfactory due to untoward reactions ranging in intensity from mild febrile manifestations and chills to severe reactions with high fever and even death. Many theories have been advanced as to the causes of these undesirable results, with little elimination of them. Some of the causes have been listed by the various investigators as follows:

1. Faulty technique in preparation and administration.
 - (a) Improperly cleaned apparatus.
 - (b) Rate of injection.
 - (c) Temperature of the solution.
2. Personal factors.
 - (a) Idiosyncrasies.
 - (b) Individual resistances.
3. Hæmolytic factor.
4. H-ion concentration.
5. Use of impure chemicals.
6. Bacterial proteins.

In reviewing the possible cause or causes of these unfavorable results, it was found that Factors 1, 2 and 3 could be eliminated since unusual conditions were not encountered when commercially prepared solutions were used. (4) The H-ion of "reaction producing" solutions was found to coincide within the limits of those solutions not producing such reactions. These values were obtained by the colorimetric method. (5) The theory of the use of impure chemicals was discarded in the belief that if these were the source of contamination, all solutions made from the same lot of chemicals should give unsatisfactory results. This was not the case

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