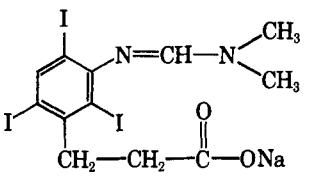
Qualitative and Quantitative Tests for Sodium Ipodate

Provisional, unofficial monographs are developed by the Drug Standards Laboratory, in cooperation with the manufacturers of the drug concerned, for publication in the *Journal of Pharmaceutical Sciences*. The ready availability of this information affords discriminating medical and pharmaceutical practitioners with an added basis for confidence in the quality of new drug products generally, and of those covered by the monographs particularly. Such monographs will appear on drugs representing new chemical entities for which suitable identity tests and assay procedures are not available in the published literature. The purity and assay limits reported for the drugs and their dosage forms are based on observations made on samples representative of commercial production and are considered to be reasonable within expected analytical and manufacturing variation.

SODIUM 3-(dimethylaminomethyleneamino)-2,4,6-triiodohydrocinnamate, $C_{12}H_{12}I_3N_2NaO_2$; mol. wt. 619.94. The structural formula of sodium ipodate may be represented as



Physical Properties.—Sodium ipodate occurs as a white to off-white, odorless, fine crystalline powder. It is very soluble in water, freely soluble in alcohol and in methanol, and very slightly soluble in chloroform.

Identity Tests.—Heat about 500 mg. of sodium ipodate in a porcelain crucible over a free flame: violet vapors of iodine are evolved.

Sodium ipodate responds to the U.S.P. XVI flame test for sodium.

A 1 in 100,000 solution of sodium ipodate in methanol exhibits an ultraviolet absorbance maximum at about 235 mμ [absorptivity (1% 1 cm.) about 600]. The spectrum is shown in Fig. 1.

The infrared spectrum of a 0.5% dispersion of sodium ipodate in potassium bromide, in a disk of about 0.82 mm. thickness, is shown in Fig. 2.

Purity Tests.—Dry about 1 Gm. of sodium ipodate, accurately weighed, in a vacuum oven at 60° for 3 hr.: it loses not more than 0.5% of its weight.

Dissolve about 200 mg. of sodium ipodate in 10 ml. of water. Add 2 ml. of 1 *N* sulfuric acid and 2 ml. of chloroform, and shake vigorously. Allow the layers to separate: the chloroform layer shows no violet color (absence of free iodine).

Determine the heavy metals content of sodium ipodate by the U.S.P. XVI heavy metals test, method II. The heavy metals limit for sodium ipodate is 30 p.p.m.

Assay.—Transfer about 300 mg. of sodium ipodate, accurately weighed, to a glass-stoppered, 250-ml. flask, add 30 ml. of sodium hydroxide solution (1 in 20) and 500 mg. of powdered zinc, connect the flask to a reflux condenser, and reflux the mixture for 30 min. Cool to room temperature, wash the condenser with 20 ml. of water, and filter the mixture. Wash the flask and the filter with small portions of water, adding the washings to the filtrate. Add to the filtrate 5 ml. of glacial acetic acid and 3 drops of eosin Y T.S., and titrate with 0.05 *N* silver nitrate until the entire mixture changes to a permanent

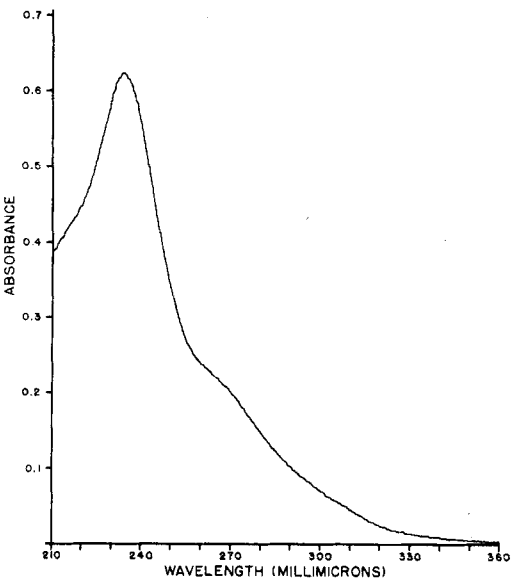


Fig. 1.—Ultraviolet absorption spectrum of sodium ipodate in methanol (10 mcg./ml.); Beckman model DK-2A spectrophotometer.

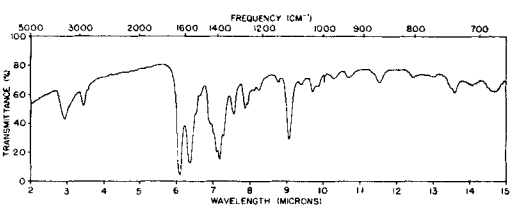


Fig. 2.—Infrared spectrum of sodium ipodate in potassium bromide disk (0.5%); Perkin-Elmer model 21 spectrophotometer, sodium chloride prism.

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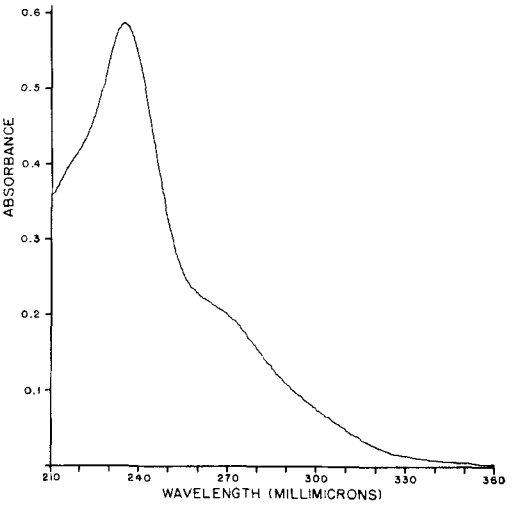

Fig. 3.—Ultraviolet absorption spectrum of 3-(dimethylaminomethyleneamino) - 2,4,6 - triiodohydrocinnamic acid in alcohol (10 mcg./ml.); Beckman model DK-2A spectrophotometer.

pink color. Each milliliter of 0.05 *N* silver nitrate is equivalent to 6.345 mg. of iodine (I) and to 10.33 mg. of $C_{12}H_{12}I_3N_2NaO_2$. The amount of sodium ipodate found, calculated on the anhydrous basis, is not less than 97.5% and not more than 102.5% of the weight of the sample taken.

DOSAGE FORMS OF SODIUM IPODATE

Sodium Ipodate Capsules

Identity Tests.—Transfer the contents of a sufficient number of capsules, equivalent to about 2 Gm. of sodium ipodate, to a 250-ml. separator, add 100 ml. of water and 50 ml. of solvent hexane, and shake. Transfer the aqueous layer to a beaker, add 5 ml. of diluted hydrochloric acid, and mix. Filter, retain the filtrate, and wash the precipitate with several portions of water. Dry the residue of 3-(dimethylaminomethyleneamino) - 2,4,6 - triiodohydrocinnamic acid in a vacuum oven at 60° for 4 hr.: the residue responds to the following tests.

Heat about 500 mg. of the residue in a porcelain crucible over a free flame: violet vapors of iodine are evolved.

A 1:100,000 solution of the residue in alcohol exhibits an ultraviolet absorbance maximum at about 236 mμ [absorptivity (1%, 1 cm.) about 580]. The spectrum is shown in Fig. 3.

The filtrate responds to the U.S.P. XVI flame test for sodium.

Assay.—*Sodium Ipodate.*—Place a number of capsules, equivalent to about 5 Gm. of sodium ipodate, in a 400-ml. beaker, add 200 ml. of sodium hydroxide T.S. and 50 ml. of solvent hexane, and stir mechanically until the capsules have completely disintegrated. Transfer the mixture to a 500-ml. separator, wash the beaker with a total of 25 ml. of sodium hydroxide T.S. in divided portions, and add the washings to the separator. Allow the layers to separate, and transfer the aqueous layer to a 500-ml. volumetric flask. Wash the solvent hexane layer with two 50-ml. portions of sodium hydroxide T.S., add the washings to the volumetric flask, dilute to volume with sodium hydroxide T.S., and mix well. Pipet 25 ml. of the solution, which may be milky in appearance, into a glass-stoppered 250-ml. conical flask, add 500 mg. of powdered zinc and proceed as directed in the assay under sodium ipodate, beginning with ". . . connect the flask to a reflux condenser . . . ." Each milliliter of 0.05 *N* silver nitrate is equivalent to 10.33 mg. of $C_{12}H_{12}I_3N_2NaO_2$. The amount of sodium ipodate found is not less than 90.0% and not more than 110.0% of the labeled amount.

DISCUSSION

Sodium ipodate[1] is an oral radiographic contrast medium for cholangiography and cholecystography.

Identity Tests.—Because similar observations can be made with other radiographic contrast media, identity tests based upon evolution of iodine vapor and comparison of the ultraviolet absorption spectrum with that of a reference standard are not sufficient to identify sodium ipodate. Comparison of the infrared spectrum with that produced by reference material under identical conditions provides a satisfactory test.

Quantitative Methods.—The assay method provided for the bulk drug and dosage form is the usual one employed in the official monographs for iodinated radiopaque compounds. Tetrabromophenolphthalein ethyl ester is the more commonly used adsorption indicator, but in a comparison of this indicator with eosin Y both gave sharp reproducible end points. A disadvantage of tetrabromophenolphthalein ethyl ester is the relative difficulty in sensing the proximity to the green end point against the greenish cast of the bulk solution. With eosin Y, however, the approach of the end point is signaled by the appearance of a transitory pink color at the point of entry of a drop of titrant into the solution being titrated. At the end point, the entire mixture turns pink.

The assay of bulk sodium ipodate gave an average value of 98.9 ± 0.1%,[2] equivalent to 60.7 ± 0.1% iodine (I). Analysis of commercial 0.5 Gm. capsules gave an average value of 100.4 ± 0.1%[2] of the labeled amount of sodium ipodate.

[1] Marketed as Oragrafin Sodium by E. R. Squibb and Sons New York, N. Y.

[2] Maximum deviation from the mean value.