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PREPARATION OF A SOLUBLE FERRIC ARSENATE.[*]

BY

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It is generally conceded that the Iron Arsenate of the pharmacopœias is a very unsatisfactory preparation for medicinal use, for it is variable in composition, and it also has the disadvantage of being quite insoluble in water. As the analogous Iron Phosphate, although still retained by the British Pharmacopœia under the title of *Ferri Phosphas*, was replaced in the United States Pharmacopœia as long ago as 1880 by a soluble ferric phosphate (*Ferri Phosphas Solubilis*), which is now largely used, the idea suggested itself that a soluble ferric arsenate would likewise present decided advantages over the insoluble compounds which are at present officially recognised. Some experiments were therefore made some years ago for the production of such a soluble salt, by the use of a method precisely analogous to that employed for the preparation of a soluble ferric phosphate—namely, by the combination, in suitable proportions, of ferric citrate and sodium arsenate.[1] The theoretical proportions of the respective

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[1] After completing these experiments it was observed that the 'National Formulary of Unofficial Preparations,' third edition, 1906, has adopted a Syrup of Arsenate of Iron, which is directed to be prepared as follows:—0·40 Gm. of anhydrous sodium arsenate and 0·35 Gm. of ferric citrate (U.S.P.) are dissolved together in 32 C.c. of water, and this solution is then mixed with sufficient syrup (U.S.P.) to make 100 C.c. of finished product. It is stated (*loc. cit.*) that 4 C.c. of this syrup contain about 0·0016 Gm. of ferric arsenate, which would be correct if the prescribed amount of sodium arsenate were completely converted into ferric arsenate, but this is evidently not the case, as may be seen from the following consideration:—0·40 Gm. of anhydrous sodium arsenate would require an amount of ferric citrate corresponding to 0·12 Gm. Fe, and if this amount of iron were contained in 0·35 Gm. of official ferric citrate, it would be equivalent to 34·3 per cent., which is approximately double the percentage of this element usually present in the official salt.

salts required for the reaction may be considered to be those represented by the following equation :—

$$\underset{\substack{186\\(100)}}{\underline{\mathrm{Na_2HAsO_4}}} + \underset{\substack{245\\(131\cdot7)}}{\underline{\mathrm{Fe'''\ C_6H_5O_7}}} = \mathrm{Fe'''\ AsO_4} + \mathrm{Na_2HC_6H_5O_7}.$$

One hundred parts of anhydrous sodium arsenate would thus require such an amount of iron as would correspond to 131·7 parts of anhydrous ferric citrate. It has been found, however, that the scaling of the product is much facilitated if one-tenth more than the calculated amount of ferric citrate is employed, and the proportion of the latter salt would thus be practically 145 parts. It is likewise important that anhydrous sodium arsenate should be used in this process, on account of the variable amount of water contained in the crystallised salt.

The method of procedure is briefly as follows :—

To an amount of solution of ferric citrate corresponding to 145 parts of the anhydrous salt is added 100 parts of anhydrous sodium arsenate, and the mixture gently heated on a water-bath until the latter salt has become completely dissolved. The original brown colour of the liquid will then have changed to a bright green. The liquid is subsequently filtered, evaporated at a gentle heat to a syrupy consistence, and spread on plates of glass, so that, on drying, the salt may be obtained in the form of scales.

Soluble Iron Arsenate[2] (*Ferri Arsenas Solubilis*), as thus prepared, has the following characters, which will serve for its identification.

Thin, bright green, transparent scales, which are readily and completely soluble in water, affording a bright green solu-

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[2] The designation "Soluble Iron Arsenate" has, unfortunately, been adopted by the 'British Pharmaceutical Codex,' p. 427, as a synonym for a preparation to which the same work has given the evidently incorrect title of "Ferri Citro-Arsenias Ammoniatas (Ammoniated Citro-arsenate of Iron)." It is described as follows :—"Ammoniated citro-arsenate of iron is said to be a double salt of ferrous arsenate and ammonium citrate. It occurs in green or yellowish-green deliquescent scales, very soluble in water. It contains from 15 to 18 per cent. of metallic iron, and the equivalent of 1·4 per cent. of arsenious anhydride." A preparation which is stated to contain the amount of iron and arsenious anhydride above indicated, and which evidently corresponds with that described in the B.P.C., has been in use for some time, but it is designated by the manufacturers as "Iron Arsenite with Ammonium Citrate (Ferrous Arsenite with Ammonium Citrate)." The synonym, "Soluble Iron Arsenate," which has been adopted by the 'British Pharmaceutical Codex' for the preparation described in that work is, therefore, evidently a misnomer.

tion; insoluble in alcohol. The aqueous solution of the salt has an acid reaction. On the addition of a solution of ammonia a brown coloration is produced, but no precipitate. With potassium ferrocyanide it gives a blue coloration, which is rendered much deeper in colour, with the formation of a blue precipitate, on the addition of hydrochloric acid. If 0·5 Gm. of the salt be dissolved in 5 C.c. of hot water, and to the solution about 10 C.c. of a 5 per cent. solution of potassium hydroxide be added, a reddish-brown precipitate will be produced. The filtrate from this precipitate, when acidified with hydrochloric acid, then about 5 C.c. of magnesia mixture added, and, finally, a slight excess of solution of ammonia, will yield a white crystalline precipitate. This latter precipitate, when collected on a filter and washed with a little water, affords in contact with a few drops of a solution of silver nitrate a chocolate-brown colour (identification of arsenic acid, and distinction from soluble ferric phosphate). It should be kept protected from the light.

Quantitative Determination of the Arsenic and Iron.

In view of the desirability of adopting some standard for Soluble Iron Arsenate with respect to its arsenic content, the percentage amount of the latter element was determined in a specimen of the salt which had been prepared on a manufacturing scale. For this purpose different methods were employed, in order to ascertain, by a comparison of the results, which of these would be best adapted for a rapid control of the product, while at the same time possessing a degree of accuracy sufficient for technical requirements.

Method I.—This was practically the same as that described in connection with the analysis of the official iron arsenate. About 1 gramme of the salt, accurately weighed, was dissolved in 100 C.c. of water, the solution acidified with hydrochloric acid, and then saturated with sulphur dioxide for the purpose of reducing the arsenic acid to the arsenous state. After removing the excess of sulphur dioxide by heat, the arsenic was precipitated as sulphide, the latter collected, converted by means of fuming nitric acid into arsenic acid, and finally precipitated as ammonio-magnesium arsenate. This, after drying at 100-105° C., was weighed as $Mg(NH_4)AsO_4,\frac{1}{2}H_2O$, of which 100 parts correspond to 74·6 parts H_3AsO_4, or 39·4 parts As. In the filtrate and washings from the arsenous sulphide the iron may be estimated by concentrating the mixed liquids, oxidising with a little nitric acid, and precipitating first with sodium hydroxide, on account of the presence of the organic acid. The ferric hydroxide is then collected, washed, redissolved in hydrochloric acid, finally precipitated by ammonia, and, after ignition, weighed as Fe_2O_3.

Method II.—About 1 gramme of the salt, accurately weighed, was dissolved in 50 C.c. of water, the solution heated to boiling, and then added, with constant stirring, to 15 C.c. of a 10 per cent. solution of sodium hydroxide. After digesting for half-an-hour on a water-bath, the precipitate was collected on a filter, washed with water, then dissolved in hydrochloric acid, and the iron finally precipitated from the hot liquid by ammonia. The resulting ferric hydroxide is washed, dried, and ignited. The filtrate and washings from the first precipitation of the iron were concentrated, acidified with hydrochloric acid, then made slightly alkaline with ammonia, and the arsenic finally precipitated as ammonio-magnesium arsenate. This, after drying at 100-105° C., was weighed as $Mg(NH_4)AsO_4,\frac{1}{2}H_2O$. If the initial step in the above method be reversed, that is, the caustic alkali added to the hot solution of the ferric arsenate, somewhat less accurate results are obtained, owing to the retention of some of the arsenic by the iron precipitate in the form of a basic compound.

Method III.—Since it has recently been shown (Rosenthaler, 'Zeitschrift f. analyt. Chem.,' 1906, 45, 596) that, under well-defined conditions, arsenic acid may be very accurately estimated volumetrically by an iodometric method, it was deemed of interest to ascertain its applicability in the analysis of soluble iron arsenate. This method naturally permits of the indirect estimation of the iron in an analogous manner, by determining the amount of iodine liberated from a solution of potassium iodide. In the case of arsenic acid the reaction is stated to be completely effected in the cold in ten to fifteen minutes, provided a large amount of free hydrochloric acid is present, and may be expressed by the following equation:—

$$H_3AsO_4+2KI+2HCl=H_3AsO_3+I_2+2KCl+H_2O.$$

In employing this method the iron and arsenic were initially separated by both the above described methods, I. and II., in order to compare the results.

(*a*) *Separation of the Iron and Arsenic by Method I.*—The solution of arsenic acid, obtained as described under Method

I., was brought into a glass-stoppered bottle having a capacity of about 100 C.c., and 2 grammes of potassium iodide added, together with such an amount of hydrochloric acid that the liquid would contain about 20 per cent. of HCl. Any slight precipitate that is thus produced is redissolved by the addition of the smallest possible quantity of water. After being allowed to stand for ten minutes at the ordinary temperature, the liberated iodine was titrated with a standardised solution of sodium thiosulphate with the use of a little light petroleum to indicate the end of the reaction. For the estimation of the iron, the filtrate and washings from the precipitate of arsenous sulphide, obtained as described under Method I., were concentrated, and, after oxidation with nitric acid, the iron was precipitated by means of sodium hydroxide. The ferric hydroxide was collected on a filter, washed, dissolved in 10 C.c. of hydrochloric acid, and the solution diluted to the measure of about 50 C.c. This was transferred to a glass-stoppered bottle having a capacity of about 100 C.c., 2 grammes of potassium iodide added, and, after standing for half an hour at a temperature of 40-50° C., the cooled liquid was titrated with a standardised solution of sodium thiosulphate, using starch as an indicator.

(β) *Separation of the Iron and Arsenic by Method II.*—The precipitate of ferric hydroxide obtained by adding a solution of the soluble iron arsenate to a solution of sodium hydroxide was treated in precisely the same manner as described in connection with the corresponding precipitate under (α), the iron being finally estimated indirectly by titrating the liberated iodine with a standardised solution of sodium thiosulphate. For the estimation of the arsenic, the alkaline filtrate and washings from the above-mentioned precipitate of ferric hydroxide were concentrated, neutralised with hydrochloric acid, and subsequently such an amount of the latter added that the liquid would contain about 20 per cent. of free HCl. The process was then conducted in precisely the same manner as described under (α).

The results of these determinations of the arsenic in Soluble Iron Arsenate were as follows :—

Method I.—1·0284 gramme of the salt gave 0·3480 gramme $Mg(NH_4)AsO_4,\frac{1}{2}H_2O$, corresponding to 13·33 per cent. As.

Method II.—0·9449 gramme of the salt gave 0·3188 gramme $Mg(NH_4)AsO_4,\frac{1}{2}H_2O$, corresponding to 13·29 per cent. As

Method III.—Volumetric.

(*α*) The arsenical solution from 0·8922 gramme of the salt liberated an amount of iodine equivalent to 31 C.c. $Na_2S_2O_3$(1 C.c. = 0·0125 I), corresponding to 12·83 per cent. As.

(*β*) The arsenical solution from 0·9970 gramme of the salt liberated an amount of iodine equivalent to 35·2 C.c. $Na_2S_2O_3$(1 C.c. = 0·0125 I), corresponding to 13·04 per cent. As.

From a comparison of these figures it may be concluded that the simple method of assay designated as II. affords results which are sufficiently accurate for technical purposes, and that, when a standardised solution of sodium thiosulphate is available, the assay may be still further expedited by the volumetric determination of the iron and arsenic, as described under Method III. (*β*).

Although the composition of this salt is naturally subject to slight variations, if it be assumed to contain an amount of arsenic ranging from 13 to 13·5 per cent., this would correspond, approximately, to from 34 to 35 per cent. of anhydrous ferric arsenate. The proportion of iron, with consideration of the calculated excess of the latter, would consequently correspond to about 11 per cent., but the adoption of a standard for this element is obviously of very much less importance than the control of the arsenical content of the preparation.

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