THE DETERMINATION OF ISONIAZID

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A method for the determination of isoniazid (*iso*nicotinyl hydrazide) by addition of excess of 0·1N iodine solution in the presence of sodium bicarbonate and titration of the excess of iodine has been suggested by Canbäck.[1] Although this method appeared to be satisfactory for the pure hydrazide, erratic results were obtained on tablets of known composition containing lactose and starch as excipients, owing to oxidation of the lactose under these conditions, a fact that was not observed by Canbäck.

Three other volumetric methods have recently been published, and of these the bromimetric assay proposed by Haugas and Mitchell[2] appears to be the most satisfactory, since the two methods suggested by Scott[3] are based on non-stoichiometric reactions involving the use of empirical factors. Before these three methods were published we had examined the possibility of titrating isoniazid with standard potassium iodate solution. Although the method is no more precise than the bromimetric assay, it has been used successfully in these laboratories for several months, and it provides a useful alternative.

Although hydrazine can be determined by titration with iodate under the conditions laid down by Andrews,[4] this technique fails with isoniazid owing to slow liberation of the iodine and absence of a detectable end-point in the solvent layer. *p*-Ethoxychrysoidine has recently been suggested as an internal indicator for use in iodate titrations[5] and titration of isoniazid may be carried out by its means. The colour change of the indicator from red to purple-red, which is reversible, is not satisfactory for the purpose, being largely masked by the yellow colour of the iodine monochloride produced in the reaction, but a satisfactory end-point may be obtained by continuing the titration until the colour of the indicator is irreversibly discharged, involving a change from scarlet to full yellow in titrating the hydrazide.

Neither lactose nor starch interferes with this determination, and the method is particularly useful in the presence of starch, which dissolves readily at the concentrations of hydrochloric acid employed.

Several batches of isoniazid and of tablets have been assayed by both bromimetric and iodate methods. The results are summarised in Table I.

The conditions found satisfactory are embodied in the following procedure:—

Weigh accurately about 0·15 g. of isoniazid and dissolve it in 20 ml. of water in a conical flask. Add 30 ml. of concentrated hydrochloric acid and titrate with 0·05M potassium iodate constantly swirling the contents of the flask during the addition. After adding about 90 per cent. of the expected titre add 12 drops of 0·1 per cent. solution of *p*-ethoxychrysoidine

in ethanol (95 per cent. v/v) and continue titrating slowly. When the indicator colour changes from scarlet to orange add the iodate drop by drop, allowing about 30 seconds after each drop, until the end-point, when the liquid turns from orange to yellow. Carry out a blank determination, titrating until the indicator is practically colourless. 1 ml. of 0·05M potassium iodate ≡ 6·85 mg. of isoniazid.

TABLE I

DETERMINATION OF ISONIAZID

	Bromimetric assay	Iodate assay	Difference
	per cent.	per cent.	per cent.
Isoniazid solid (1)	98·8	98·3	− 0·5
(2)	99·1	98·7	− 0·4
(3)	99·0	99·3	+ 0·3
	mg. per tablet	mg. per tablet	mg. per tablet
Isoniazid tablets (1)	46·5	46·1, 46·3	− 0·3
(2)	47·3	47·8, 48·1	+ 0·65
(3)	48·7	48·8, 48·9	+ 0·15
(4)	47·4	47·5, 47·8	+ 0·25

For the assay of isoniazid tablets, weigh accurately into a conical flask an amount of the powdered tablets containing about 150 mg. of isoniazid. Add 20 ml. of water and, after the powder is dispersed, 30 ml. of concentrated hydrochloric acid. Titrate with 0·05M potassium iodate as described above.

REFERENCES

1. Canbäck, *J. Pharm. Pharmacol.*, 1952, **4**, 407.
2. Haugas and Mitchell, *ibid.*, 1952, **4**, 687.
3. Scott, *ibid.*, 1952, **4**, 681.
4. Andrews, *J. Amer. chem. Soc.* 1903, **25**, 756.
5. Belcher and Clark, *Anal. Chim. Acta*, 1951, **4**, 580.