A NOTE ON THE ASSAY OF THE METHYL AND PROPYL ESTERS OF *p*-HYDROXYBENZOIC ACID

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According to the Danish Pharmacopœia 1948, methyl *p*-hydroxybenzoate is assayed by treatment with aqueous sodium hydroxide solution on a water bath followed by bromination in acid solution, the excess of bromine being estimated with sodium thiosulphate after the addition of potassium iodide. As six atoms of bromine are absorbed by one molecule of the ester the methanol is presumably oxidised to formaldehyde.

$$HO{\cdot}C_6H_4{\cdot}COOH + CH_3OH + 3Br_2 = HO{\cdot}C_6H_2Br_2{\cdot}COOH + CH_2O + 4HBr$$

It seemed reasonable to suppose that time could be saved by brominating the ester directly without previous hydrolysis when the reaction would be expressed by the following equation:—

$$HO{\cdot}C_6H_4COOCH_3 + 2Br_2 = HO{\cdot}C_6H_2Br_2COOCH_3 + 2HBr\cdot$$

Good results were obtained when the ester was dissolved in sodium hydroxide solution provided that the alkaline solution was brominated with 0·1 N bromine and acidified with hydrochloric acid immediately after the preparation of the solution. Bromination was not complete under 40 minutes. If the alkaline solution of the ester was not brominated and acidified immediately high results were obtained due to slow hydrolysis of the ester by hydroxyl ions and oxidation of the methanol produced thereby (see Table I).

TABLE I

Estimation of methyl *p*-hydroxybenzoate without previous hydrolysis

Age of solution	Time of bromination minutes	per cent.
Fresh	20	99·2, 99·1
,,	30	98·8, 99·1
,,	40	99·5
,,	50	99·4
4 hours	40	101·2
8 hours	40	110·2
48 hours	40	137·4

The method of the Danish Pharmacopœia gave slightly higher figures for the same sample; it was found that the instruction to brominate in the dark was unnecessary as the same figures were obtained when the bottles were left in the light during bromination (see Table II).

A sample of propyl *p*-hydroxybenzoate when assayed without previous hydrolysis gave high figures (>103 per cent.), but two recrystallisations (one from aqueous ethanol and one from benzene) yielded a product assaying at 100·6 per cent. It seemed probable that the high figure

TABLE II

ESTIMATION OF METHYL *p*-HYDROXYBENZOATE AFTER HYDROLYSIS (DANISH PHARMACOPŒIA)

Conditions of bromination	per cent.
In the dark	99·7, 99·7
In the light	99·7, 99·8

TABLE III

ESTIMATION OF PROPYL *p*-HYDROXYBENZOATE

Sample	Time of bromination minutes	Results	
		Method of Danish Pharmacopæia per cent.	Method not involving hydrolysis per cent.
Old sample	20	99·0	102·9
	30	99·2	103·3
	40	99·3	103·2
	50	99·0	103·3
Sample recrystallised twice ..	20		100·6
	30		100·6
	40		100·6
	50		100·7
Sample recrystallised after washing with sodium bicarbonate solution	10	99·2	100·2
	20	99·4	100·2
	30	99·5	100·2
	70	99·6	
	120		100·2

resulted from the presence of free *p*-hydroxybenzoic acid in the sample, this theory being reinforced by the fact that a sample washed with 5 per cent. solution of sodium bicarbonate and then recrystallised from benzene assayed at 100·2 per cent. The last named sample, when assayed by the method of the Danish Pharmacopœia for methyl *p*-hydroxybenzoate gave low figures, even when the bromination was allowed to proceed for over an hour, presumably because the propanol resulting from the hydrolysis of the ester is less readily oxidised, than is the methanol in the case of methyl *p*-hydroxybenzoate.

Finally, the impure sample of propyl *p*-hydroxybenzoate which by the simpler process (i.e., estimation without previous hydrolysis) had assayed at over 103 per cent. when assayed by the method of the Danish Pharmacopœia for methyl *p*-hydroxybenzoate assayed at 99·0 to 99·3 per cent., which suggests that the presence of free acid is more easily detected by the simpler process than by the process involving saponification. Simple calculation supports this suggestion for it can easily be shown that a sample of propyl *p*-hydroxybenzoate containing exactly 10 per cent. of free *p*-hydroxybenzoic acid as impurity would assay at 103 per cent. by the direct bromination process but at 98·7 per cent. by the Danish Pharmacopœia process if it can be assumed that both processes yield a correct picture of the facts. The theoretically calculated figures for the methyl ester containing 10 per cent. of free acid would be 101·03 per cent. by the direct bromination process but 97·32 per cent. by the

Danish Pharmacopœia method, hence for the methyl ester the presence of free acid is more readily detected by the latter process.

All the above figures are calculated on the assumption that although a poor sample of ester might easily contain appreciable quantities of free *p*-hydroxybenzoic acid the equivalent amount of methanol or propanol produced simultaneously would have volatilised. As free *p*-hydroxybenzoic acid is a very likely impurity in any of its esters and as neither assay process readily reveals the presence of small amounts of free acid in either the methyl or the propyl ester, it seems highly desirable that the B.P.C. monograph should contain a separate test for limit of free acid.

Bromination without previous saponification is complete in 20 minutes with propyl *p*-hydroxybenzoate, whereas in the case of the methyl ester 40 minutes is required.

Proposed Method

About 1 g. of ester, accurately weighed, was dissolved in a mixture of 20 per cent. w/v solution of sodium hydroxide (2 ml.) and water (20 ml.) without the aid of heat and the volume made up to 100 ml with water. 20 ml. of this solution was treated immediately in a stoppered bottle with 0·1 N bromine (50·0 ml.) and hydrochloric acid (6 ml.) with shaking. The bottle was stoppered and allowed to stand, with frequent shaking for 40 minutes (methyl ester) or 20 minutes (propyl ester). 10 per cent. w/v solution of potassium iodide (10 ml.) was then added and the liberated iodine titrated with 0·1 N sodium thiosulphate. Each ml. of 0·1 N bromine is equivalent to 0·003802 g. of methyl *p*-hydroxybenzoate, or 0·004505 g. of propyl *p*-hydroxybenzoate.

Summary

1. It is proposed to modify the assay process for methyl *p*-hydroxybenzoate as given in the Danish Pharmacopœia by omitting the preliminary saponification process.

2. Propyl *p*-hydroxybenzoate can be determined in the same manner and gives results more in accordance with the facts than does the bromination of the products of hydrolysis, the presence of free *p*-hydroxybenzoic acid being indicated by a figure greater than 100 per cent.

3. Neither process is sufficiently sensitive to limit small quantities of free acid and a separate limit test for this very likely impurity is desirable.

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