Short Communication

DETERMINATION OF TRICHLOROETHYL PHOSPHATE IN PHARMACEUTICAL PREPARATIONS

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Introduction of the monophosphoric ester of trichloroethanol as a hypnotic made it necessary to develop analytical methods for determining the ester in the presence of its decomposition products. These may arise by ester hydrolysis to yield trichloroethanol followed (or preceded) by other changes due for example to attack on the trichloromethyl part of the molecule. As would be expected, aqueous solutions which have decomposed as a result of prolonged or unsatisfactory storage contain chloride and phosphate ions. The presence of formaldehyde has been demonstrated in autoclaved aqueous solutions.

Published methods for determining trichloroethanol and closely related compounds were examined (Marshall and Owens, 1954; Seto and Schultze, 1956; Rehm and Mader, 1957; Friedman and Cooper, 1958; Archer and Haugas, 1960). None was found suitable for the esterified alcohol.

Enzymatic hydrolysis of the phosphate link (Boon, 1960) worked satisfactorily and the liberated trichloroethanol was isolated by steam distillation, then estimated by the method of Marshall and Owens (1954). Although satisfactory, this procedure was rather cumbersome for routine use. Halogenated compounds have been determined by alkaline hydrolysis followed by titration of the chloride ion thus produced. Application of this method was facilitated by the observation that trichloroethyl phosphate could be extracted by amyl alcohol from acidified aqueous solutions. The combined chlorine proved somewhat resistant to hydrolysis, and required treatment with 2N alcoholic potassium hydroxide for 2 hr. at 120°.

Proposed Volumetric Method

Transfer to a 100 ml. separator, sufficient sample to contain about 120 mg. of trichloroethyl phosphate. Add water (15 ml.) and swirl to dissolve. Adjust to about pH 9 with N sodium hydroxide, add ether (15 ml.), stopper, shake for 1 min., and set aside for 2 min. Transfer the lower aqueous layer to a second separator. Wash the ether with water (1 ml.). Add the washings to the aqueous phase, and reject the ether. Any free trichloroethanol is thus removed from the sample. Add dilute sulphuric acid (B.P. reagent) (2·5 ml.) and amyl alcohol (10 ml.) to the aqueous phase. Stopper, shake for 1 min. and set aside until the phases separate. Transfer the lower aqueous layer to a second separator, and extract with three further 10 ml. portions of amyl alcohol. Combine the amyl alcohol extracts; reject any aqueous phase present. Transfer

to a dry 50 ml. volumetric flask, dilute to 50 ml. with amyl alcohol, and mix. Place a 10·0 ml. aliquot in a 20 ml. ampoule. Add 2N alcoholic potassium hydroxide (10 ml.) to the ampoule, and seal. Autoclave the ampoule for 2 hr. at 15 lb. per sq. in. Cool, and transfer the contents to

TABLE I

COMPARISON OF VOLUMETRIC AND ENZYMATIC METHODS

Autoclaving time min.	Trichloroethyl phosphate content per cent w/v	
	Proposed method	Enzyme method
0	4·13	4·3
8	3·55	3·5
18	2·63	2·7
30	1·31	1·4

a 100 ml. conical flask, washing in with dilute nitric acid (B.P. reagent) (20 ml.). Add ferric ammonium sulphate solution (B.P. reagent) (4 ml.) and 0·1N silver nitrate (5·00 ml.). Titrate with 0·2N ammonium thiocyanate solution.

TABLE II

RESULTS OBTAINED BY THE VOLUMETRIC METHOD

Preparation	Trichloroethyl phosphate	
	Calculated	Found
Syrup	7·0 per cent w/v	6·9 per cent w/v
Syrup	14·0 per cent w/v	13·8 per cent w/v
Tablet	500 mg.	493 mg.
Effervescent tablet ..	500 mg.	490 mg.

1·0 ml. of 0·02N silver nitrate is equivalent to 1·676 mg. of trichloroethyl monosodium phosphate.

The determination of solid trichloroethyl monosodium phosphate by this method gave values within 1 per cent of those obtained by sodium carbonate fusion.

The recommended method determines chlorine-containing materials which can be extracted from acid solution by amyl alcohol. Whilst it eliminates at least 95 per cent of free trichloroethanol and sodium chloride, other possible decomposition products such as trichloroacetic acid and dichloroacetaldehyde are not removed in the course of the assay, and lead to high halogen values. As a check on whether the assay does indeed accurately define the content of trichloroethanol monosodium phosphate the determination was repeated using an alkaline phosphatase hydrolysis (Boon, 1960). Free trichloroethanol was then assayed by the more specific method of Marshall and Owens (1954).

When applied to substrates of 0·1 and 0·2 mg. of monosodium trichloroethyl phosphate, recoveries of trichloroethanol of 98·5 and 95·3 per cent respectively, resulted.

Aqueous solutions of the ester, deliberately decomposed to different extents by autoclaving, were assayed by both methods, and Table I

shows the results obtained. The agreement between the two is taken as confirmation that the recommended method is satisfactorily specific.

Some results obtained by the method are shown in Table II. Aqueous preparations were freshly prepared from accurately weighed quantities of trichloroethyl phosphate (monosodium salt).

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