

THE PURITY OF CHLOROFORM B.P.

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The "chloro-compound", isolated during previous work on a source of error in the assay of strychnine salts and preparations¹, has been identified as strychnine chloromethobromide. Its identity has been established by the preparation of authentic strychnine chloromethobromide and the corresponding nitrate and iodide. Chlorobromomethane occurs in chloroform B.P. used for extraction of strychnine during the assay. The presence of this impurity in chloroform has been confirmed by gas chromatography which also revealed the presence of methylene dichloride as an additional impurity.

At the Dublin meeting of the British Pharmaceutical Conference we presented a paper on a source of error in the assay of strychnine salts and preparations containing strychnine¹. It was concluded that the chloroform, used for extraction of the strychnine during the assay, reacted with some of the alkaloid and caused an error in both gravimetric and volumetric estimations. A chloro-compound, assumed to be formed by combination of chloroform and strychnine, was isolated but although samples gave consistent figures when subjected to ultimate analysis we were unable to suggest a formula in harmony with the accepted structure of strychnine. Moreover, our analytical figures were not in agreement with those reported by Klemperer and Warren² for a similar compound claimed to be strychnine dichloromethochloride.

To investigate the chloro-compound further sufficient was prepared for a full examination. For this purpose strychnine was dissolved in chloroform and the solution boiled continuously under a reflux condenser, it being expected that the chloro-compound, which commenced to separate from the solution after about one hour, would continue to be formed and the procedure would afford a simple means of preparation. It was found, however, that although the chloro-compound continued to separate from the boiling solution its rate of formation decreased and practically ceased after several days boiling. If the chloroform were recovered from the solution at this stage and used for a repetition of the experiment very little, if any, chloro-compound was obtained. This evidence suggested that the formation of the chloro-compound was due to reaction between strychnine and an impurity present in the chloroform.

To investigate the purity of the chloroform B.P. used in our work it was arranged for samples, before and after treatment with strychnine, to be examined by gas chromatography in the Department of the Government Chemist. Evidence of the presence of methylene dichloride was obtained. On reacting methylene dichloride with strychnine a crystalline addition compound was formed which, however, was not identical with the compound isolated during our work.

THE PURITY OF CHLOROFORM B.P.

More careful examination of our compound revealed that it contained both chlorine and bromine, the latter being the ionisable halogen. Analytical figures were in complete agreement with the compound being strychnine chloromethobromide, $C_{22}H_{24}O_2N_2ClBr$, presumably formed by reaction between strychnine and chlorobromomethane. By interaction between strychnine and authentic chlorobromomethane a crystalline compound was readily obtained and this had the characteristics of our "chloro-compound" and appeared identical with it in all respects although, owing to the substances decomposing on heating, it was not possible to carry out a mixed melting point determination. The presence of chlorobromomethane in chloroform B.P. was confirmed by gas chromatography.

EXPERIMENTAL

Chlorobromomethane. The preparation of chlorobromomethane was analogous to that used by Dougherty³ for dichlorobromomethane.

Methylene dichloride (127 ml.) was mixed with ethyl bromide (148 ml.) and finely powdered anhydrous aluminium chloride (10 g.) added. Most of the solid matter dissolved and the reaction mixture assumed a pale brown colour. After standing at room temperature for 48 hours the mixture was shaken successively with 5 per cent hydrochloric acid (100 ml.), water (100 ml.), 5 per cent sodium hydroxide solution (100 ml.) and two portions (100 ml.) of water. The product was dried over anhydrous calcium chloride and distilled, the fraction boiling between 66° and 71° being collected. By redistillation a portion boiling at 68–69° was obtained. Yield 25 g. Found: total halogen, estimated gravimetrically and calculated as chlorine, 63.0, CH_2ClBr requires 63.3 per cent.

Chloro-compound from strychnine. Strychnine (10 g.) was dissolved in chloroform B.P. (500 ml.) and the solution boiled under a reflux condenser for 10 hours. The chloro-compound which separated from the solution was filtered off, washed with several portions of chloroform and dried at 105°. The yield varied with the sample of chloroform B.P. but was usually about 2 g. and could be increased by continued boiling of the reaction mixture. After recrystallisation from water the compound was obtained as colourless needles which had no definite melting point; at 270° it darkened in colour and at about 300° decomposed. Found on material dried at 105°: C, 57.2; H, 5.35; N, 6.46; Cl, 7.75; Br, 17.4; ionisable Br, 17.1 per cent. $[\alpha]_D^{20} = +14.4^\circ$ (c, 2.0 in water).

Strychnine chloromethobromide. Strychnine (3 g.) was added to chlorobromomethane (10 ml.) and the mixture stirred. The alkaloid began to dissolve but before solution was complete the reaction product began to separate from the mixture which soon became a solid mass. Methanol (50 ml.) was added and the mixture boiled under a reflux condenser for 2 hours, after which the insoluble matter was filtered off and washed with several portions of methanol. After recrystallisation from water 1.8 g. of colourless needles was obtained. Found, on material dried at 105°: C, 56.7; H, 5.4; N, 6.6; Cl, 7.56; Br, 17.4; ionisable Br, 17.1. $[\alpha]_D^{20} = +15.2^\circ$ (c, 2.0 in water). $C_{22}H_{24}O_2N_2Cl.Br$ requires C, 57.0; H, 5.22; N, 6.04; Cl, 7.65; Br, 17.23; ionisable Br, 17.23 per cent.

Strychnine chloromethochloride. Strychnine (3 g.) was dissolved in methylene dichloride (30 ml.) and the solution boiled under a reflux condenser for 10 hours. The insoluble matter was removed by filtration, washed with a small amount of chloroform and dried at 105°. Yield 1.8 g. Recrystallisation from aqueous acetone afforded colourless needles. Found on material dried at 105°: C, 62.6; H, 5.94; N, 7.01; Cl, 16.5; $C_{22}H_{24}O_2N_2Cl_2$ requires C, 63.0; H, 5.77; N, 6.68; Cl, 16.9 per cent.

Strychnine chloromethonitrate. Strychnine chloromethobromide (2 g.) was dissolved in hot water (100 ml.) and, after cooling, concentrated nitric acid (1 ml.) was added with stirring. After standing for 2 hours the precipitate was collected, washed with a little water and recrystallised from water. 1.2 g. of colourless or pale yellow needles was obtained.

Found on material dried at 105°: C, 59.4; H, 5.64; N, 9.95; Cl, 7.83; $C_{22}H_{24}O_5N_3Cl$ requires C, 59.2; H, 5.42; N, 9.4; Cl, 7.95 per cent.

The nitrate prepared in the same way from the strychnine chloro-compound and nitric acid gave the following analytical results. Found: C, 59.6; H, 5.98; N, 9.86; Cl, 7.92 per cent.

Strychnine chloromethiodide. Strychnine chloromethobromide (3 g.) was dissolved in water (60 ml.) by warming and to the hot solution 10 per cent potassium iodide solution (25 ml.) was added with stirring. A precipitate formed almost immediately and, after cooling the mixture, was separated and recrystallised from water. The salt obtained as crystalline needles, contained three molecules of water of crystallisation which were removed by drying *in vacuo* over phosphorus pentoxide. It melted with decomposition at about 260°. Yield 3.5 g. Found, on anhydrous material: C, 51.0; H, 5.14; N, 5.80; total halogen (as Cl), 18.2; I, 24.6; $C_{22}H_{24}O_2N_2ClI$ requires C, 51.7; H, 4.73; N, 5.49; total halogen (as Cl), 18.3; I, 24.8 per cent.

The iodide prepared similarly from the strychnine chloro-compound gave the following results. Found: C, 51.5; H, 5.15; N, 5.78; total halogen (as Cl), 18.1; I, 24.6 per cent. It melted with decomposition at about 260°.

Ultra-violet Absorption

A critical comparison of the strychnine chloro-compound with strychnine chloromethobromide was made by measurement of their ultra-violet absorption with a "Uvispek" spectrophotometer using 0.002 per cent w/v solutions of the compounds in water. The results are shown in Figure 1, which also includes the corresponding absorption curve of strychnine.

Gas Chromatography

Samples of chloroform B.P. and of chloroform, prepared by boiling a solution of strychnine in chloroform B.P. until no more chloro-compound separated and recovering the solvent, were subjected to examination by gas chromatography. This work was carried out by Dr. B. A. Rose and Mr. A. J. Blake, A.R.I.C., at the Government Laboratory, and we are very much indebted to their department for permission to include their

THE PURITY OF CHLOROFORM B.P.

results in the present paper. The apparatus employed was similar to that described by Scott⁴ using a flame detector.

Detection of Methylene Dichloride in Chloroform

The samples were examined by gas chromatography on columns filled with (a) polyethylene glycol 400, (b) liquid paraffin and (c) cetyl alcohol, all operating at 100°; there was no significant difference between the chromatograms obtained from the two samples.

It was decided to attempt to concentrate any trace impurity by fractionation to facilitate its detection. Accordingly 25 ml. of each sample was distilled through an air-jacketed twelve-plate column and the distillate collected at a speed of one drop in approximately 5 seconds. Fractions consisting of a few drops each were collected in weighed receivers and examined chromatographically on the cetyl alcohol column at laboratory temperature; the lower temperature was chosen to retard the passage of the volatile samples through the column and improve the separation.

In all cases, a peak was obtained indicating the presence of an impurity with a lower retention volume than chloroform; this peak became smaller in successive fractions and was also smaller in the fractions from the strychnine-treated chloroform than in the corresponding fractions from the untreated samples.

Identification of impurity. The impurity had a retention volume corresponding to methylene dichloride; no other substance has been found to have the same retention volume on cetyl alcohol and also on liquid paraffin, on which our diagnosis was checked.

Estimation of the amount of impurity (CH₂Cl₂). Mixtures of methylene dichloride and chloroform in varying ratios were prepared and examined

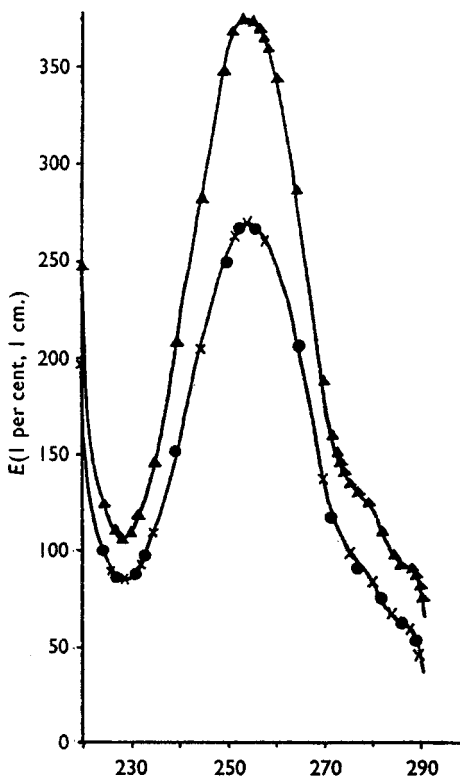


FIG. 1. Ultra-violet absorption curves.

- ▲ = 0.002 per cent strychnine in 0.001N HCl.
- × = 0.002 per cent "chloro-compound" in water.
- = 0.002 per cent strychnine chloromethobromide in water.

on the cetyl alcohol column at laboratory temperature and the ratio of the peak heights CHCl_3 : CH_2Cl_2 measured. From these figures the concentration of methylene dichloride in the weighed distillation fractions was calculated and hence the methylene dichloride content of the samples.

The figures obtained from measuring peak heights on the chromatograms are set out in Tables I—standard mixtures ($\text{CH}_2\text{Cl}_2/\text{CHCl}_3$), II—"untreated" CHCl_3 , III—strychnine treated CHCl_3 .

TABLE I
CHROMATOGRAPHIC DATA: STANDARD MIXTURES, CH_2Cl_2 AND CHCl_3

Per cent CH_2Cl_2 v/v	CHCl_3 Peak height	CH_2Cl_2 Peak height	Peak height ratio CHCl_3 : CH_2Cl_2
1	3.30 in.	0.2 in.	16.5
3	2.12 "	0.35 "	6.06
5	2.08 "	0.58 "	3.60
10	1.80 "	0.80 "	2.25
15	1.90 "	1.24 "	1.53
20	1.75 "	1.60 "	1.09

Some of the chromatograms obtained are also shown in Figure 2.

The chloroform B.P. contains 1–2 per cent of ethanol. Using cetyl alcohol as the fixed phase the ethanol was to be expected to have a longer retention time than the chloroform. In fact there were indications of the ethanol to the right of the chloroform peak.

The fractional distillation and chromatographic examination of the fractions was repeated using portions of the samples which had been washed four times with water and dried with sodium sulphate. The purpose was to ensure that the alcohol (1–2 per cent) contained in Chloroform B.P. was not causing any interference. The figures for methylene chloride content of the washed samples are lower than for the unwashed samples presumably because methylene dichloride has a higher solubility than chloroform in water.

The figures obtained are set out in Tables IV and V.

Detection of Chlorobromomethane in Chloroform

50 ml. of the liquid with a small addition of *p*-xylene was slowly fractionated through a column (25 theoretical plates) over more than 1 working day. Towards the end 16 small separate fractions (each of 0.1–0.2 ml.) were collected between the point where the b.p. showed a slight sign of rising and the final point of rise towards *p*-xylene. Several of these small fractions were then examined by gas chromatography. Fractions 13, 14 and 15 gave chromatograms (in duplicate) showing a small but distinct shoulder near the bottom of the right-hand slope of the chloroform peak. Made up mixtures of pure chloroform with $\frac{1}{2}$ –1 per cent of chlorobromomethane gave closely similar graphs and the comparison indicates the presence of between 0.5 and 1 per cent by volume of the bromo-compound in these small fractions. An approximate estimate is that 0.004 ml. of the bromide was present in the 3 small fractions 13, 14 and 15 which totalled *c.* 0.5 ml.

Figure 3 shows chromatograms obtained during these experiments.

THE PURITY OF CHLOROFORM B.P.

DISCUSSION

The object of the work was the determination of the chemical structure of the "chloro-compound" isolated during our investigations on the assay of strychnine salts¹. The compound is shown to consist of strychnine chloromethobromide. The unexpected detection of bromine made it essential to obtain confirmatory evidence. Accordingly, an authentic specimen of strychnine chloromethobromide was prepared by reaction between strychnine and chlorobromomethane. Both the "chloro-compound" and strychnine chloromethobromide melt with decomposition and, on this account, their identity could not be established by a mixed melting point. Their ultimate analyses and ultra-violet absorption spectra were, however, identical and their corresponding nitrates and iodides possessed respectively identical characteristics. The ultra-violet absorption curve of our "chloro-compound" is similar in shape to that of strychnine and practically identical with it if calculated in terms of molecular extinction instead of $E(1 \text{ per cent, } 1 \text{ cm.})$, as in Figure 1. This evidence supports the view that the strychnine structure remains intact in the molecule and that the "chloro-compound" is, in fact, strychnine chloromethobromide.

The substance isolated by Klemperer and Warren² during their work on *Strychnos henningsii* and described by them as strychnine dichloromethochloride has again engaged our attention. The analytical figures given by these authors for carbon, hydrogen and nitrogen are in good agreement with our own but without knowing how their halogen determinations were carried out it is not possible to comment upon their published figures for total and ionisable chlorine.

The formation of strychnine chloromethobromide when strychnine is dissolved in chloroform led to an investigation of the purity of this solvent. The gas chromatograms reproduced in Figures 2 and 3 afford evidence of the presence of both methylene dichloride and chlorobromomethane in the sample of chloroform B.P. examined. These impurities were much reduced in chloroform, which had been recovered from a solution of strychnine in chloroform previously boiled for some hours.

It must be accepted that the bromine present as chlorobromomethane arises from the chlorine, used directly or indirectly, in the manufacture

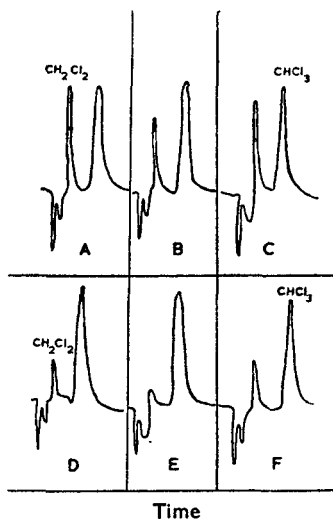


FIG. 2. Chromatograms on cetyl alcohol column at laboratory temperature.

- A, Chloroform B.P. fraction 1.
- B, Chloroform B.P. fraction 2.
- C, 20 per cent CH_2Cl_2 -80 per cent CHCl_3 .
- D, Chloroform, strychnine treated fraction 1.
- E, Chloroform, strychnine treated fraction 2.
- F, 10 per cent CH_2Cl_2 -90 per cent CHCl_3 .

TABLE II

CHROMATOGRAPHIC DATA: DISTILLATION FRACTIONS FROM "UNTREATED" CHCl_3 (25 ML.)

Fraction No.	Wt. (g.)	Vol. (ml.)*	Peak height ratio $\text{CHCl}_3/\text{CH}_2\text{Cl}_2$	Per cent v/v CH_2Cl_2	Vol. CH_2Cl_2 (ml.)
1	0.067	0.044	1.00	20	0.009
2	0.095	0.063	1.52	12	0.0075
3	0.102	0.085	2.80	6	0.005
4 to 6	0.345	0.23	8.04	2	0.004

Total $\text{CH}_2\text{Cl}_2 = 0.0255$ ml. = 0.1 per cent v/v in original sample approx.

* Assuming specific gravity of 1.5.

TABLE III

CHROMATOGRAPHIC DATA: DISTILLATION FRACTIONS FROM STRYCHNINE-TREATED CHCl_3 (25 ML.)

Fraction No.	Wt. (g.)	Vol. (ml.)*	Peak height ratio $\text{CHCl}_3/\text{CH}_2\text{Cl}_2$	Per cent v/v CH_2Cl_2	Vol. CH_2Cl_2 (ml.)
1	0.084	0.056	2.79	6	0.0034
2	0.097	0.064	7.96	2	0.0013
3	0.107	0.070	10.8	1	0.0007

Total $\text{CH}_2\text{Cl}_2 = 0.0054$ ml. approx. = 0.02 per cent in original sample approx.

* Assuming specific gravity of 1.5.

TABLE IV

CHROMATOGRAPHIC DATA: DISTILLATION FRACTIONS FROM "UNTREATED" WASHED CHCl_3 (14 ML.)

Fraction No.	Wt. (g.)	Vol. (ml.)*	Peak height ratio $\text{CHCl}_3/\text{CH}_2\text{Cl}_2$	Per cent v/v CH_2Cl_2	Vol. CH_2Cl_2 (ml.)
1	0.076	0.05	2.14	10	0.005
2	0.083	0.055	3.38	5.3	0.003
3	0.105	0.07	6.6	2.5	0.002
4	0.097	0.065	13.4	1.5	0.001

Total $\text{CH}_2\text{Cl}_2 = 0.011$ ml. = 0.08 per cent on washed sample approx.

* Assuming specific gravity of 1.5.

TABLE V

CHROMATOGRAPHIC DATA: DISTILLATION FRACTIONS FROM STRYCHNINE TREATED, WASHED CHCl_3 (18 ML.)

Fraction	Wt. (g.)	Vol. (ml.)*	Peak height ratio $\text{CHCl}_3/\text{CH}_2\text{Cl}_2$	Per cent v/v CH_2Cl_2	Vol. CH_2Cl_2 (ml.)
1	0.073	0.048	6.38	2.75	0.0013
2	0.087	0.058	8.8	2	0.0011
3	0.074	0.05	20	1	negligible

Total $\text{CH}_2\text{Cl}_2 = 0.0024$ ml. = 0.013 per cent on washed sample approx.

* Assuming specific gravity of 1.5.

of the chloroform. Very little analytical information is available regarding the purity of commercial chlorine and, as far as we are aware, no international specification is available for this product. It has been stated that impurities totalling 0.2 per cent occur in chlorine⁵ and that these consist of hexachlorethane, carbon tetrachloride, chloroform, bromine and ferric chloride, while carbon dioxide, hydrogen chloride, oxygen, carbon monoxide, nitrogen and hydrogen have also been reported.

THE PURITY OF CHLOROFORM B.P.

Chlorinated hydrocarbons may rise from reaction between chlorine gas and lubricants used on valves, etc., and these together with some other impurities may be removed by liquefaction and subsequent distillation of the chlorine. This procedure, however, cannot be relied upon to remove bromine.

Chloroform may be made by treatment of alcohol, acetaldehyde or acetone with bleaching powder, and also by chlorination of methane or reduction of carbon tetrachloride⁶. Most chloroform, we believe, is manufactured in this country today by the acetone-bleaching powder process although chlorination of methane may also be used. The latter process gives rise to a mixture of methylchloride, methylene dichloride, chloroform and carbon tetrachloride which are then separated by fractionation and chloroform, so produced, may contain traces of methylene dichloride. There is also no doubt that brominated products would result when chloroform is made from acetone and bleaching powder, containing bromine, but we have insufficient knowledge to indicate the course of the reaction. We believe that most impurities would be removed by distillation during the final stages of the manufacture of commercial chloroform but that chlorobromomethane, with a boiling point similar to chloroform, would be difficult to eliminate. Although we have carried out no accurate quantitative work, it seems, from the yields of strychnine chloromethobromide, that up to 0.5 per cent may be present in chloroform B.P. Samples of chloroform B.P. from four British manufacturers have been examined and chlorobromomethane detected in all by the strychnine reaction.

There remains the problem of preparing chloroform suitable for alkaloidal assays. From our experiments, the presence of methylene dichloride and chlorobromomethane will give rise to error in strychnine assays¹. Chloroform, purified by strychnine treatment, gave a substantially smaller analytical error in strychnine determinations but the error was not entirely eliminated and we are unable to state, at this stage,

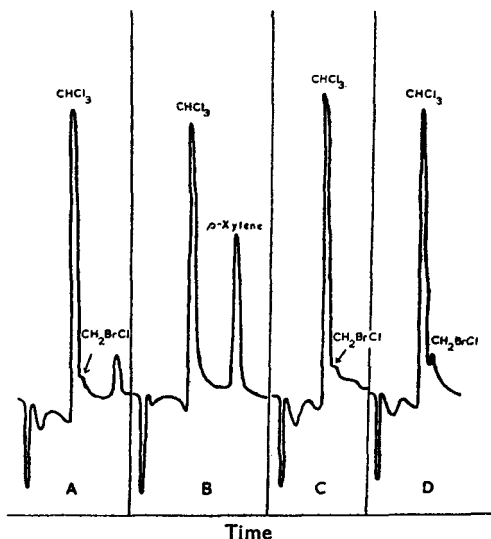


FIG. 3. Chromatograms on polyethylene glycol 400 column at 100°.

- A, Chloroform B.P. fraction 14.
- B, Chloroform, strychnine treated, fraction K.
- C, 1 per cent CH₂BrCl in CHCl₃.
- D, 2 per cent CH₂BrCl in CHCl₃.

whether or not reaction occurs between strychnine and pure chloroform. We hope, in due course, to describe how chloroform suitable for analytical purposes may be prepared.

We wish to thank the Government Chemist, Dr. G. M. Bennett, F.R.S., for his interest in this work and for providing facilities for gas chromatography in his department. We are also indebted to Mr. F. J. McMurray for the micro analyses.

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DISCUSSION

The paper was presented by MR. A. C. CAWS.

MR. C. A. JOHNSON (Nottingham). The gas chromatographic evidence indicated that chlorobromomethane was present, but in much smaller amount than methylene dichloride. Strychnine was shown to form additional compounds with both methylene dichloride and chlorobromomethane, yet the analytical figures agreed closely with those for strychnine chloromethobromide. With different samples of chloroform containing varying amounts of impurities, some variation in the analytical figures for the precipitate would be expected.

MR. S. G. E. STEVENS (London) thought there would be little difference between the spectra of strychnine chloromethochloride and chloromethobromide. Had the chloroform which had been refluxed for some time been examined for decomposition?

DR. W. MITCHELL (London). How much methylene dichloride was present in the chloroform examined? Since methylene dichloride reacted readily with strychnine, the reaction products could be assumed to contain both derivatives. Was the preparation of Klemperer and Warren a mixture of the two derivatives?

DR. J. B. STENLAKE (Glasgow). What was the stability and toxicity of chlorobromomethane?

DR. N. J. HARPER (London). Had any attempt been made to titrate the compounds in non-aqueous media? High purity chloroform could be obtained from chloral hydrate.

DR. D. C. GARRATT (Nottingham). An indication of the error which could arise in strychnine determinations would be helpful.

MR. H. E. BROOKES (Nottingham). Were the impurities found in chloroform consistent from sample to sample?

THE PURITY OF CHLOROFORM B.P.

DR. R. E. STUCKEY (London). Had any attempt been made to find an alternative solvent to chloroform?

MR. A. G. FISHBURN (Rochdale). Were any of the samples of chloroform supplied as suitable for anaesthesia?

MR. D. J. DRAIN (Ware). Had the authors tried reacting chloroform with a less complex but possibly more reactive tertiary base than strychnine?

The AUTHORS in reply said that no great accuracy was claimed for the results obtained by gas chromatography. The precipitate obtained was contaminated with a substance containing chloride ions, as yet not isolated. The analytical figures were consistent because the precipitate was recrystallised from water, so separating the chlorobromide compound from the methylene dichloride compound. The molecular absorption of the two compounds would be the same, but the *E* (1 per cent, 1 cm.) would be different. The figure for content of methylene dichloride in chloroform given by gas chromatography was 0.1 per cent. The reaction between that concentration of methylene dichloride and strychnine was very slow; chlorobromomethane reacted much more readily. Klemperer and Warren stated that their substance was recrystallised from water, so it seemed unlikely that it was a mixture. They had no information about the toxicity of chlorobromomethane, but it seemed to be stable. The compounds had not been titrated in non-aqueous solvents. Experiments had been carried out using chloroform B.P. and chloroform previously treated with strychnine; by evaporation without the addition of alcohol the error was reduced from just over 1 per cent to about 0.5 per cent. The amounts of impurity in chloroform were not consistent. Some samples contained as much as 0.4 to 0.5 per cent and others were nearer 0.1 per cent. An alternative solvent would be welcome, but strychnine was not an easy substance to dissolve. One of the four samples examined was labelled "Chloroform for Anaesthesia". Another sample from the same manufacturer labelled "Chloroform B.P." contained about the same amount of bromo compound. Only one tertiary base had been tried, and that was dimethylaniline. It appeared to react more slowly than strychnine, and did not give a solid derivative.