DETERMINATION OF CHLOROFORM.*

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INTRODUCTION.

Several methods are given in the literature for the estimation of chloroform in Chloroform Liniment and in Spirit of Chloroform. Most of these methods involve the use of strong alkali as a hydrolyzing agent and are based on the reaction $CHCl_3 + 4KOH = 3KCl + HCOOK + 2H_2O$.

Andersen (1) used a strong alcoholic alkali solution to decompose the chloroform in Chloroform Liniment, making use of a pressure flask and also refluxing under pressure. Warren (2) permitted the liniment to stand over night in contact with 30 per cent alcoholic potash and then determined the chloride formed. Murray (3) used potassium hydroxide in methyl alcohol to decompose chloroform at room temperature. The results which he obtained were not satisfactory. Morrow (4) recommended the use of alcoholic potash to decompose the chloroform, the reaction taking place in a pressure flask. Meyer (5) and Harrison (6) determined chloroform in Chloroform Liniment by direct distillation. Willzerodt (7) also used alcoholic potash to decompose chloroform in Chloroform Liniment under pressure.

Schlicht and Austen (8) determined the chloroform in admixtures with alcohol by diluting with water and extracting with ether, then determining the specific gravity of the ethereal solution.

In our investigations three methods were used to decompose and determine the chloroform.

(1) Refluxing with strong alcoholic alkali.
(2) Refluxing under pressure.
(3) Heating with strong alcoholic alkali under pressure.

Refluxing with strong alkali and boiling under pressure gave slightly lower results than those obtained by refluxing under pressure. Not one of the three methods gave a 100 per cent recovery.

According to Mossler (9) if the conditions are not regulated the reaction between alkali in alcohol and chloroform can be as follows:

$$CHCl_3 + 3KOH = 3KCl + CO + 2H_2O$$

and it is possible for ethylene to form along with the carbon monoxide. This reaction is prevented by refluxing the chloroform with the alkali or heating under pressure. This reaction, however, should not interfere with the subsequent determination of the chloride ion.

EXPERIMENTAL.

REAGENTS REQUIRED.—*Reagent A*. Alcoholic potassium hydroxide. Dissolve 30 Gm. of reagent potassium hydroxide in 100 cc. of aldehyde free alcohol.

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Reagent B. Dissolve 25 Gm. of sodium in 200 cc. of aldehyde free alcohol.

Reagent C. Dissolve 30 Gm. of reagent potassium hydroxide in 100 cc. of isopropyl alcohol.

Silver nitrate: Tenth-normal solution.

Potassium thiocyanate: Tenth-normal solution.

Nitric acid: U. S. P. Dilute.

Ferric alum indicator: A cold, saturated solution of ferric ammonium sulphate $(NH_4)_2SO_4 . Fe_2(SO_4)_3 . 24H_2O$ to which enough nitric acid had been added to repress the yellow color.

The same pipettes, burettes and flasks were used throughout to avoid errors.

SAMPLES USED.—*Sample A.* Chloroform, U. S. P.

Sample B. Purified chloroform.

One hundred cc. of U. S. P. chloroform was thoroughly washed with three one hundred-cc. portions of 20 per cent sodium bisulphite, then with four 100-cc. portions of distilled water. The chloroform was dried with anhydrous sodium sulphate and then distilled. This procedure was repeated three times.

SPIRIT OF CHLOROFORM.—*Sample A.* 8.8500 Gm. of Chloroform U. S. P. was accurately weighed, dissolved in alcohol and made up to 100 cc. at 25° C.

Sample B. 8.9180 Gm. of purified chloroform was accurately weighed and made up to 100 cc. at 25° C. with aldehyde-free alcohol.

Samples C and D. Spirit of Chloroform U. S. P. prepared, respectively, by Joseph Rosin and John C. Krantz, Jr.

CHLOROFORM LINIMENT.—*Sample A.* 44.200 Gm. of Chloroform U. S. P. was accurately weighed and made up to 100 cc. with Soap Liniment U. S. P. at 25° C.

Sample B. 44.3075 Gm. of purified chloroform was accurately weighed and made up to 100 cc. with Soap Liniment U. S. P. at 25° C.

ASSAY OF CHLOROFORM.—*Method I.* From a weighing burette or by means of a Victor Meyer bulb, weigh out accurately 0.2–0.5 Gm. of chloroform into a 300-cc. Erlenmeyer flask containing 50 cc. of alkali. Connect the flask with a long condenser, well cooled, and reflux on a boiling water-bath for four hours. (The connecting stopper must be wrapped in tin foil.) Cool, transfer to a 500-cc. volumetric flask and make up to volume with distilled water. Place a 100-cc. aliquot in a 250-cc. beaker and evaporate on a water-bath until all the alcohol is removed, add a few drops of phenolphthalein, and acidify with dilute nitric acid. Transfer to a 250-cc. volumetric flask and add 40 cc. of 0.1 normal silver nitrate solution. Shake the stoppered flask until the precipitate coagulates enough to give a clear supernatant liquid. Make up to the mark, mix, and filter through a dry filter, discarding the first 15 cc. of filtrate. Transfer 100 cc. of the filtrate into a beaker, add 2–3 cc. of ferric alum indicator and titrate the excess silver nitrate with tenth-normal potassium thiocyanate. Carry out a blank determination using the same amounts of reagents, and apply a correction for the end-point and the chloride in the reagents. Each cc. of tenth-normal silver nitrate consumed is equivalent to 0.00398 Gm. of chloroform.

Method II. Weigh accurately 0.2–0.5 Gm. of chloroform into a 500-cc. Erlenmeyer flask containing 50 cc. of alkali. Stopper the flask with a foil-covered rubber stopper carrying a U-shaped condenser and wire the stopper securely. To guard against danger from bursting, cover the flask with a towel. Connect the condenser to a cold water supply and heat the flask on a water-bath for three hours. Complete the determination as in Method I.

The U-shaped condenser: A piece of glass tubing with an outside diameter of 7 mm. and 30 cm. long is heated and bent double, the radius of the bend being about one cm. The ends are fire polished and pushed through a two-hole rubber stopper so that the length of the condenser from the top of the rubber stopper to the end of the bend is about 12 cm. The open ends are reheated and bent away from each other.

Method III. This method was the same as Method I except that a pressure bottle of 225 cc. capacity was used in place of the Erlenmeyer flask and condenser.

The chloride formed in the above reactions was also determined gravimetrically according to the usual procedure, filtering through a Gooch crucible and drying the precipitate at 110° C., using 100-cc. aliquots in each determination. The results obtained gravimetrically and volumetrically checked quite well, but the volumetric methods are preferred, due to the shorter time required for the operation.

TABLE I.—DETERMINATION OF CHLOROFORM.

Each Value Given Is the Average of Four Determinations on Aliquot Samples.
(Volumetric Determination of Chloride.)

Sample.	Method.	Reagent.	Weight of Sample.	Gm. Recovered.	Per Cent.
A	I	A	0.5438	0.5353	98.43
A	II	A	0.4108	0.3897	97.27
A	III	B	0.4570	0.4399	96.27
A	I	C	0.3012	0.2945	97.77
A	II	B	0.4562	0.4485	98.32
B	I	A	1.0581	1.0445	98.66
B	I	A	0.3690	0.3670	99.42
B	I	B	0.8333	0.8204	98.45
B	I	B	0.2824	0.2806	99.39
B	I	C	1.8225	1.7498	96.03
B	II	A	2.1106	2.0784	98.57
B	II	A	0.4973	0.4939	99.28
B	II	B	0.3543	0.3515	99.28
B	II	C	0.2980	0.2887	96.71
B	III	A	1.1611	1.1283	97.40
B	III	A	0.3858	0.3818	98.84
B	III	B	0.2933	0.2897	98.70

TABLE II.—DETERMINATION OF CHLOROFORM.

(Gravimetric Determination of Chloride.)

Sample.	Method.	Reagent.	Sample Used.	Weight Recovered.	Per Cent.
B	I	A	1.0581	1.0401	98.39
B	I	B	0.8337	0.8072	96.82
B	I	C	1.6613	1.6107	96.95
B	II	A	1.8067	1.7679	97.28
B	II	B	0.3427	0.3353	97.84
B	II	C	0.2288	0.2211	96.63
B	III	A	1.1604	1.1372	98.00
B	III	B	1.0495	1.0235	97.61
B	III	C	1.1933	1.1648	97.61

CHLOROFORM LINIMENT.—*Method I.* Measure accurately by means of a pipette 5 cc. of chloroform liniment at 25° C. into a 100-cc. volumetric flask containing alcohol. Add enough alcohol to make up to volume at 25° C. and mix thoroughly. By means of a pipette transfer 10 cc. of the diluted sample into a 300-cc. Erlenmeyer flask containing 50 cc. of the alkali solution. Connect the flask with a well-cooled reflux condenser and heat on a water-bath for four hours. Complete the assay as in Method I under chloroform.

Method II. Measure accurately 10 cc. of chloroform liniment at 25° C. into a 100-cc. volumetric flask containing alcohol, make up to volume and mix thoroughly. By means of a pipette transfer 10 cc. of the dilute sample into a large hard glass test-tube containing 20 cc. of distilled water and 5 cc. of sulphuric acid. Connect the tube with a water-cooled condenser and heat gently until about 10 cc. are distilled over into a 300-cc. Erlenmeyer flask containing 50 cc. of alcoholic alkali. Surround the Erlenmeyer flask with an ice-bath during the distillation. All rubber stoppers must be covered with tin foil.

Connect the flask containing the distillate and the alkali with a reflux condenser and heat on a water-bath for four hours. The remainder of the procedure is the same as in Method I under chloroform.

TABLE III.—DETERMINATION OF CHLOROFORM IN CHLOROFORM LINIMENT.

(Average of Four Determinations.)

Sample.	Method.	Reagent.	Gm. Found/100 Cc.	Per Cent Recovery.
B	I	A	43.4180	98.00
B	I	B	43.4420	98.04
B	IA*	A	43.4700	98.10
B	IA	B	43.4620	98.09
B	IB[1]	A	43.4880	98.15
B	IB	B	43.3800	97.90
B	II	A	43.4040	97.96
B	II	B	43.3806	97.91
B	IIA	A	43.5966	98.39
B	IIA	B	43.5788	98.35
B	IIB	A	43.4878	98.15
B	IIB	B	43.5808	98.36
A	I	A	43.0000	97.28
A	I	B	42.4640	96.07
A	IA	A	41.5200	94.00
A	IA	B	41.5060	93.90
A	IB	A	42.8600	96.98
A	IB	B	42.8940	97.04
A	IIA	A	43.4400	98.28
A	IIA	B	43.0800	97.46
A	IIA	A	43.4800	98.37
A	IIA	B	43.3070	97.97
A	IIB	A	43.2400	97.82
A	IIB	B	43.5330	98.50

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* In Methods IA and IIA a pressure bottle was substituted for the flask and reflux condenser.

[1] In Methods IB and IIB a flask containing a U-shaped condenser was used.

TABLE IV.—CHLOROFORM IN SPIRIT OF CHLOROFORM.

(Average of Five Determinations.)

Sample.	Method.	Reagent.	Cc. Sample.	Gm. $CHCl_3$.	Gm./100 Cc.	Per Cent Recovery.
D	I	A	5	0.4221	8.442	.....
C	I	A	5	0.4181	8.362	.....
A	I	A	5	0.4243	8.486	95.84
A	II	A	5	0.4249	8.498	96.02
A	III	A	5	0.4263	8.526	96.39
A	I	C	5	0.4099	8.198	92.64
A	II	C	5	0.4226	8.452	93.90
A	III	C	5	0.4104	8.208	92.77
A	I	B	5	0.4271	8.542	96.52
A	II	B	5	0.4152	8.304	93.80
A	III	B	5	0.4238	8.476	95.77
B	I	A	5	0.4383	8.766	98.32
B	II	A	5	0.4398	8.796	98.63
B	III	A	5	0.4390	8.780	98.45
B	I	C	5	0.4223	8.446	94.72
B	II	C	5	0.4251	8.502	95.35
B	III	C	5	0.4271	8.542	95.55
B	I	B	5	0.4404	8.808	98.79
B	II	B	5	0.4394	8.788	98.28
B	III	B	5	0.4397	8.794	98.73

CHLOROFORM IN SPIRIT OF CHLOROFORM.—The methods used to determine chloroform in Spirit of Chloroform were the same as those used to determine chloroform. Samples of Spirit of Chloroform were taken as follows: Five cc. were transferred accurately with a pipette into the flask containing alkali and hydrolysis effected. The samples were all withdrawn at 25° C.

From our experience, we find that one of the greatest sources of error lies in the sampling of the liniment and Spirit of Chloroform due to the loss of chloroform because of its volatility. All samples were withdrawn at a temperature of 25° C. In measuring chloroform liniment care should be taken that none of the liniment touches the sides of the flask but instead the tip of the pipette must be kept submerged in the alcohol. Also in measuring the samples a measuring pipette should be used rather than a transfer pipette. In refluxing, the condensers must be well cooled and all rubber stoppers must be wrapped in tin foil.

SUMMARY AND CONCLUSIONS.

Method I is preferred for the assay of Spirit of Chloroform. With a well-cooled condenser of proper length (the Allihn type with the condensing tube consisting of a series of bulbs is preferred) and an approximately 5 normal alcoholic solution of potassium hydroxide, there is very little danger of loss of chloroform during hydrolysis. Equally good results are obtained by performing the hydrolysis under pressure, but the special apparatus required and the attendant dangers resulting from operations under pressure make these methods of less convenience. A recovery of 98.32% is obtained by this method, which is well within the allowable limits for the chloroform content of Spirit of Chloroform.

By diluting chloroform liniment to ten times its volume with alcohol, and mixing 10 cc. of this dilution with 20 cc. of water and 5 cc. of sulphuric acid before distilling, the chloroform is completely removed in the first 10 cc. of distillate and is completely retained by 50 cc. of the alcoholic alkali. The same conditions govern completeness of hydrolysis and loss of chloroform as in the assay of the spirit. An average recovery of 98.12% is obtained, as compared with an average recovery of 97.64% by direct hydrolysis of the diluted liniment. The presence of fatty acid during direct hydrolysis causes a loss in recovery of approximately 0.6%.

It is believed that direct hydrolysis of Spirit of Chloroform with alkali under a reflux condenser, and distillation of diluted chloroform liniment followed by alkaline hydrolysis under a reflux condenser are of sufficient convenience and accuracy to warrant their adoption as Pharmacopœial methods of assay.

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