AN INVESTIGATION INTO THE ACTION OF BASES ON CHLOROFORM*

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The reaction of a number of bases with chloroform has been studied by titration of the liberated halide ion. The results are interpreted in the light of strength of the base, and steric factors. The examination of solutions of strong bases such as piperidine and pyrrolidine in chloroform B.P. indicates that the base reacts with an impurity present. This paper provides additional confirmation, to that obtained by Caws and Foster, of the presence of reactive halogeno-hydrocarbons in this solvent. Methods are also described for assessing the quality of a sample of chloroform B.P., and for preparing chloroform free from these reactive impurities.

THERE are many references in the literature to impurities in chloroform and to methods for removing them[1–5]. Water, alcohols, carbonyl chloride, chlorine and hydrochloric acid are well-known impurities in chloroform. Recently Caws and Foster[6,7] showed that other impurities were present which cause a small error in the B.P. assay process for strychnine salts.

As early as 1862 interest was reported[8,9] in the decomposition of chloroform by alcoholic potash. An extensive investigation has been made[10] of the rates of reaction of all the chloro-, bromo-, and iododerivatives of methane (except CI_4), several halogeno derivatives of ethane and the chloro-derivatives of toluene with bases such as potassium hydroxide, tetra-alkyl ammonium hydroxides, ammonia and piperidine. Hine[11] investigated the kinetics of the basic hydrolysis of chloroform in aqueous dioxan and found that strongly basic reagents were more reactive to chloroform.

Observations on the reactions of a variety of organic bases with chloroform and other organic halides have also been recorded[12–18]. For example, phenylhydrazine, benzylamine, and trimethylamine react with chloroform to give the respective hydrochlorides, whilst piperidine reacts with alkyl bromides to give the hydrobromide.

$$R{\cdot}Br + 2C_5H_{10}NH = C_5H_{10}N{\cdot}R + C_5H_{10}NH{\cdot}HBr$$

Much of interest has arisen from the use of chloroform as a solvent for alkaloids. Watkins and Palkin[19] discussed chloroform as a suitable solvent for alkaloidal assays indicating that it caused appreciable errors when used. They suggested that these errors were due to a "partial neutralisation" of the alkaloid during its extraction and that these could be eliminated by prolonged refluxing of the solvent with the alkaloid, preferably brucine before extracting the base. The reaction between ephedrine and chloroform[20,21] yielding the hydrochloride is a well-known

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test for ephedrine. Klemperer and Warren[22] investigated the composition of water-soluble crystals which separated when strychnine or brucine was refluxed with chloroform. They claimed that these were dichloromethochlorides of each alkaloid having one ionisable chlorine atom per molecule. Caws and Foster[6,7] have shown that reaction between strychnine and chloroform B.P. occurs due to the presence of reactive impurities like chlorobromomethane in the solvent. They isolated strychnine chloromethobromide and showed that the chloroform recovered at this stage produced very little, if any, reaction with further quantities of strychnine. Gas chromatography indicated various samples of chloroform B.P. to contain as much as 0·5 per cent v/v chlorobromomethane and up to 0·1 per cent v/v methylene dichloride. These impurities were found to be much reduced in chloroform recovered from reaction with strychnine.

Now, in a reaction of the type:

$$B + A - X \rightarrow BA + X$$

where B is an organic base and A — X a reactive halogeno-compound, the relative reactivity of various bases B may correspond roughly to their strengths[11]. But, several types of reactions are known where steric factors, depending on the structure of both the base and the organic halide are more important considerations. In reactions such as:

$$RR'R''N: + A - X \rightarrow RR'R''\overset{+}{N}: A + X^-$$

involving quaternisation it is known that when groups R become increasingly more bulky the reaction is retarded. Brown[23] interprets this in terms of a Frontal (F) strain, which is the strain involved in the compression of groups in A by those in the base molecule B required for the formation of the cation $(B:A)^+$. The effect and extent of this hindrance in the reactions of various bases with halogen compounds has been extensively studied[24–32]. Thus in considering reactions involving bases reference to their dissociation constants as a guide to their reactivity must be treated with reserve. The use of acids of larger steric requirements than the proton, such as trimethyl boron[28–30] has resulted in a shift of emphasis from the consideration of polar to steric effects.

Experimental

When chloroform reacts with a base, ionised halogen is liberated. The reaction was studied therefore by measuring the amount of halide ion liberated after definite time intervals. For this purpose the Volhard method was found to give more reliable and reproducible results than the Mohr and adsorption indicator methods. The quantities of ferric alum, nitric acid and nitrobenzene used were kept constant.

Materials

Chloroform B.P. was used throughout the work except where otherwise stated.

Bases. Each of the following bases were distilled into a flask protected by anhydrous calcium chloride and soda lime, the first four being fractionated using a 12-inch rod and disc column. Piperidine 105–106°;

pyrrolidine 87–88°; *N*-ethylpiperidine 129°; 2-methylpiperidine 118°; *cyclo*hexylamine 135°; benzylamine 184°; 2-phenylethylamine 92–93°/19 mm.; *n*-butylamine 77–78°; di-*iso*propylamine 84°; triethylamine 88–89°. Storage, if necessary, was in dark glass bottles in separate desiccators over anhydrous calcium chloride and soda lime.

Methylene dichloride, redistilled, was obtained and its boiling point checked.

Chlorobromomethane was redistilled at 68–69°.

A proportion of base to chloroform of 0·01 to 0·03 moles was found to yield measurable quantities of halide ion. The base was weighed into a glass ampoule, followed by 2·50 ml. chloroform (weight per ml. 1·48 g.) and the ampoule sealed. Two ampoules were prepared for each base reacting with chloroform for each time interval. The reactions were studied at 20° ± 0·02° and 60° ± 0·02°. At 60° titrations were at two hourly intervals but for weak bases at 20°, intervals of twenty-four hours were necessary. The contents of an ampoule were collected, excess base neutralised with 6N nitric acid and 1·0 ml. of 6N acid was added in excess. A suitable volume of 0·02N silver nitrate solution and 0·5 ml. of saturated ferric alum solution was then added and the excess silver nitrate titrated with 0·02N ammonium thiocyanate in the presence of 1·0 ml. of nitrobenzene. Control experiments were made on all samples of chloroform. At no time did they require more than 0·02 ml. of the silver nitrate solution.

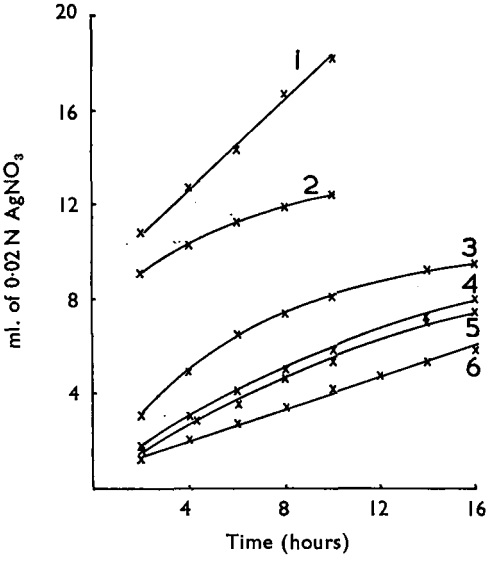


FIG. 1. Reaction between base and chloroform B.P. temperature 60°.

1. Pyrrolidine (11·12).
2. Piperidine (11·13).
3. 2-Methyl piperidine (10·99).
4. *n*-Butylamine (10·61).
5. 2-Phenylethylamine (9·83).
6. Benzylamine (9·34).

RESULTS

Reaction of Bases with Chloroform B.P.

These will be discussed in the light of the dissociation constants of the bases (Table I), and steric factors. The reactions between chloroform and the bases: benzylamine, 2-phenylethylamine, *n*-butylamine, 2-methylpiperidine, piperidine, pyrrolidine at 20° are recorded in Table II and at 60° in Figure 1. Table III summarises the results obtained for the bases: *N*-ethylpiperidine, *cyclo*hexylamine, di-*iso*propylamine and triethylamine.

The reactivity of benzylamine, 2-phenylethylamine, *n*-butylamine and 2-methylpiperidine increases with increasing pKa values. But di-*iso*-propylamine and triethylamine are considerably less reactive than is expected from their pKa values. A comparison of the rates of reaction of pyrrolidine, piperidine and 2-methylpiperidine indicates distinct differences, whilst their pKa values agree closely. *N*-Ethylpiperidine is also considerably less reactive than would be expected from its pKa value.

TABLE I

pKa VALUES OF BASES USED

Base	pKa
Piperidine	11·13
Pyrrolidine	11·12
Di-*iso*propylamine	11·05
2-Methylpiperidine	10·99
Triethylamine	10·80
*cyclo*Hexylamine	10·64
n-Butylamine	10·61
N-Ethylpiperidine	10·40
2-Phenylethylamine	9·83
Benzylamine	9·34
Strychnine	7·37

TABLE II

REACTION BETWEEN BASES AND CHLOROFORM B.P. TEMPERATURE 20°

Time	ml. 0·02N $AgNO_3$ required				Time	ml. 0·02N	$AgNO_3$ reqd.
Days	Benzyl amine	2-Phenyl-ethylamine	*n*-Butyl-amine	2-Methyl-piperidine	Hours	Piperidine	Pyrrolidine
1	1·17	0·88	1·27	1·96	2	1·46	3·06
2	1·67	1·48	1·93	3·35	4	2·66	5·05
3	2·19	2·08	2·80	4·46	6	3·85	6·43
4	2·77	2·58	3·31	5·50	8	4·77	7·28
5	3·27	—	3·84	6·26	10	—	7·90
6	3·67	3·59	4·50	6·93	12	6·46	—
7	—	3·94	5·18	7·38	14	7·00	8·52
8	—	—	5·40	7·72	16	7·32	8·75

TABLE III

REACTIONS BETWEEN BASES AND CHLOROFORM B.P. AFTER INTERVAL OF 24 HOURS AT 20°

Base	ml. 0·02N $AgNO_3$ required
N-Ethylpiperidine	0·02
*cyclo*Hexylamine	0·10
Di-*iso*propylamine	0·02
Triethylamine	0·20

Clearly another factor other than the strength of the base is involved. Steric effects explain these irregularities. Thus triethylamine and di-*iso*-propylamine have large steric requirements in their interaction with chloroform. Those of benzylamine, 2-phenylethylamine and *n*-butyl-amine are small since the nitrogen atom is not hindered by bulky groups. The low reactivity of *cyclo*hexylamine may be associated with the buckling

of the ring. The decrease in the rate of reaction of 2-methylpiperidine compared with piperidine is due to the position of the methyl group. Thus an increased F strain in the molecule of the adduct has to be overcome. The marked decrease in rate of reaction noted with *N*-ethylpiperidine is due to the ethyl group. The increased reactivity of pyrrolidine over piperidine results from the decreased F strain characterising the five-membered ring adduct compared with that present in the six-membered ring adduct formed with chloroform. Thus the two α-methylene groups of pyrrolidine are held back to a greater extent from the portion of the halogenohydrocarbon molecule co-ordinating with the nitrogen atom than similar groups in piperidine and therefore give less steric hindrance to the reaction involving pyrrolidine.

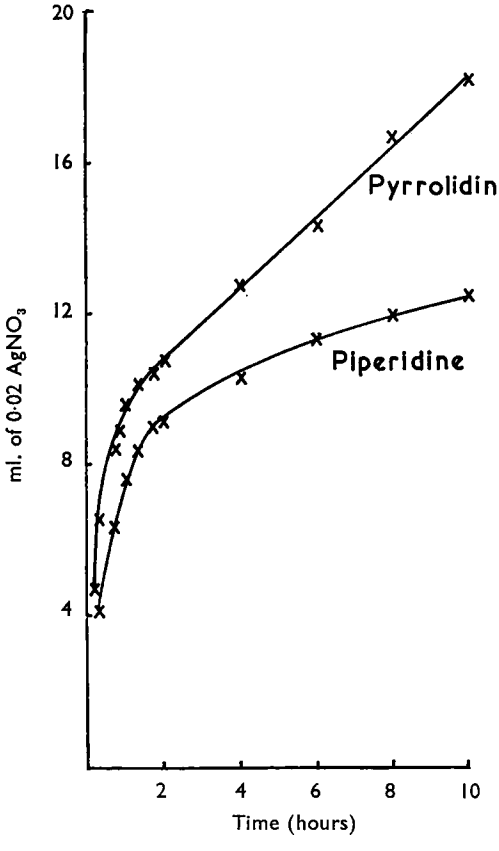


FIG. 2. Reaction between base and chloroform B.P. Temperature 60°.

The curves for piperidine and pyrrolidine (Fig. 1) indicate that, at 60°, both have a high initial rate of reaction with chloroform. Hence each reaction was investigated closely for the first two hours and the results, shown in Figure 2, seem to indicate the presence of a reactive impurity[7] in chloroform B.P. This is supported by the observation that the marked increase in the rates of reaction of piperidine and pyrrolidine with chloroform at 20° (Table II) compared with other bases is not so pronounced at 60° (Fig. 1). The explanation might well be that at the lower temperature all the chlorobromomethane in chloroform had not reacted completely with any one of the bases, whilst at the higher temperature both piperidine and pyrrolidine decompose all the chlorobromomethane during the first two hour period, resulting in further reaction being comparatively slow. Complete removal of chlorobromomethane probably results in a liberation of halide ion equivalent to approximately 9·0 ml. 0·02N silver nitrate solution.

Effect of Addition of Chlorobromomethane to Chloroform B.P.

To test the above assumptions it was decided to add successive quantities of 0·25 (K) 0·50 (L) per cent v/v chlorobromomethane to chloroform and re-examine the reactions with piperidine. A comparison of curves K and L with that for chloroform B.P. (Fig. 4) suggests that chloroform contains about 0·25 per cent v/v chlorobromomethane, since the abrupt change in slopes of each of the curves occurs at approximately 9·0 (E); 17·0–18·0 (K); 26·0–28·0 (L) ml. of 0·02N silver nitrate solution.

Purification of Chloroform B.P.

At this stage it became apparent, that in addition to strychnine[7], both piperidine and pyrrolidine could be used to remove chlorobromomethane and possibly methylene dichloride from chloroform (Fig. 2). The method of Caws and Foster[7] was first attempted. Chloroform samples recovered from boiling under reflux with strychnine for various intervals of time were examined by reaction with piperidine, using the usual proportions of reactants at 60° (Fig. 3). It is clear that refluxing for 7 days at these concentrations is required to remove the impurity (or reduce its concentration to a minimum).

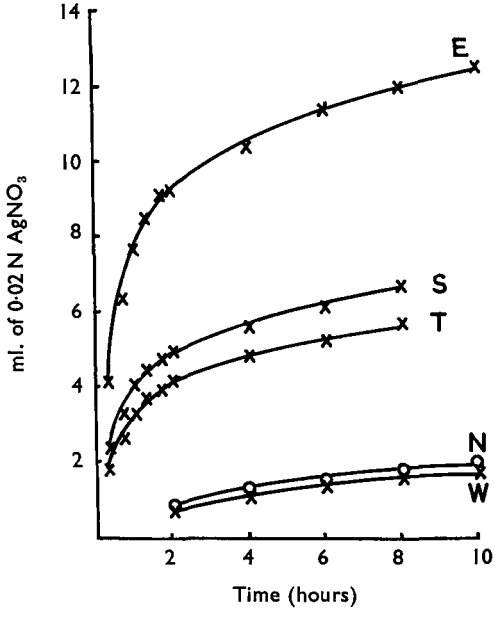


FIG. 3. Purification of Chloroform B.P. Temperature 60°.
Reaction between piperidine and recovered chloroform samples obtained by (i). refluxing 500 ml. chloroform B.P. with 10 g. of strychnine for (S) 10 hours (T) 22 hours, (W) 7 days, or (ii) refluxing 250 ml. chloroform B.P. with 7·1 g. of pyrrolidine for 72 hours. (Sample N.)
E = Reaction between piperidine and chloroform B.P.

Next, an attempt was made at employing pyrrolidine for this purpose. 7·1 g. of pyrrolidine (molar fraction) was boiled with 250 ml. chloroform under reflux for 72 hours. The separated chloroform was repeatedly acid washed followed by repeated water washing before standing over anhydrous calcium chloride for 24 hours and redistilling, 60·5 to 61·0°. The application of the piperidine reaction to the recovered chloroform (Fig. 3, curve N) indicates complete or almost complete removal of reactive halogeno-compounds.

An attempt was also made at removing the reactive impurities in chloroform by boiling under reflux with an ethanolic solution of potassium hydroxide. The piperidine reaction was applied to the chloroform before

treatment (this sample of chloroform B.P. was different from that used in the rest of the investigations) and also to the chloroform recovered (Table IV). It is clear that this method does not remove the impurities. Examination of the white solid separating during boiling showed it to be potassium chloride. No trace of bromide could be detected[33].

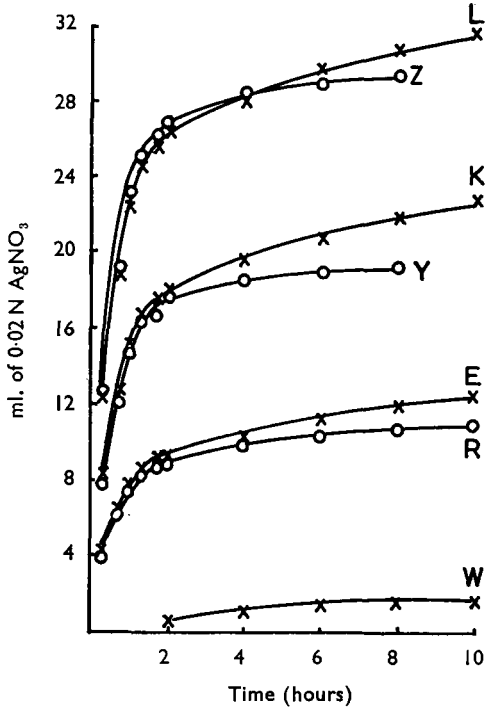


FIG. 4. Reaction between piperidine and chloroform. Temperature 60°.

×	W = purified chloroform			
O	R = " "	+ 0·25 per cent	CH_2ClBr
O	Y = " "	+ 0·50 per cent	"
O	Z = " "	+ 0·75 per cent	"
×	E = chloroform B.P.			
×	K = " "	+ 0·25 per cent	"
×	L = " "	+ 0·50 per cent	"

Effect of Addition of Halogeno-methanes to Purified Chloroform

Having now prepared chloroform free from reactive impurities it seemed of interest to examine the action of piperidine on samples prepared from purified chloroform so as to contain 0·25 (R); 0·5 (Y); 0·75 (Z) per cent v/v chlorobromomethane, respectively. It can be seen (Fig. 4) that the abrupt change of slope in the curves occur at approximately the same corresponding volumes of 0·02N silver nitrate solution as with chloroform B.P. (E) and samples of chloroform B.P. containing 0·25 (K); 0·50 (L) per cent v/v chlorobromomethane.

Further examination shows, however, that after the first two-hour interval the following pairs of curves (E,R), (K,Y) and (L,Z) deviate from one another. The explanation for this may well be that curves R, Y and Z represent the action of piperidine on pure chloroform after

TABLE IV

ATTEMPTED PURIFICATION OF CHLOROFORM B.P.*

REACTION BETWEEN PIPERIDINE AND (*a*) CHLOROFORM B.P. (*b*) CHLOROFORM RECOVERED

Time		ml 0·02 N $AgNO_3$ required	
Hours	Min.	Chloroform B.P.	Chloroform recovered
	20	3·61	3·29
	40	5·35	5·31
1	00	6·21	6·15
1	20	6·90	6·82
1	40	7·27	6·77
2	00	7·72	7·41
4		8·66	8·40
6		9·54	9·14
8		10·55	9·78
10		11·42	—

* 7 g. potassium hydroxide, 100 ml. 95 per cent ethanol, 200 ml. chloroform B.P. refluxed for 44 hours Temperature 60°.

first reacting with the chlorobromomethane whilst curves E, K and L represent the action of piperidine on firstly, chlorobromomethane and then on chloroform plus another less reactive impurity, possibly methylene dichloride. Consequently, a sample was prepared from purified chloroform to contain 0·50 per cent v/v methylene dichloride. The piperidine

TABLE V

REACTIONS OF BASES WITH DIFFERENT SAMPLES* OF PURIFIED CHLOROFORM

	ml. 0·02N $AgNO_3$ soln. required					
	1		2		3	
Base	2 hours	16 hours	2 hours	16 hours	2 hours	16 hours
2-Methylpiperidine	0·63	—	0·29	—	0·41	1·10
n-Butylamine	0·63	—	0·24	0·84	0·34	0·93
Benzylamine	0·83	—	0·39	0·88	0·45	1·45

*The samples were prepared from chloroform B.P. after refluxing respectively with (1) pyrrolidine for 72 hours, (2) pyrrolidine for 24 hours, recovered and refluxed with additional base for further 4 days, (3) strychnine for 9 days.

reaction on this sample showed methylene dichloride to be considerably less reactive than chlorobromomethane.

The "Preparation" of Chloroform B.P. from Purified Chloroform

This was attained by adding to purified chloroform (*a*) 0·25 per cent v/v chlorobromomethane and (*b*) 0·10 per cent v/v methylene dichloride. Subjection to the piperidine reaction (Fig. 5) indicates that the addition of 0·10 per cent methylene dichloride virtually superimposes curve R (purified chloroform + 0·25 per cent v/v CH_2ClBr) onto curve E (Chloroform B.P.). This result appears to confirm that strychnine and pyrrolidine

remove chlorobromomethane and methylene dichloride from chloroform B.P. In fact, it was also shown that refluxing with pyrrolidine, at the concentrations previously indicated, for only 24 hours removed the reactive impurities almost entirely, as indicated by the piperidine reaction.

Since chloroform B.P. contains ethanol, the effect of adding controlled amounts of this to chloroform B.P. (already containing 1 to 2 per cent)

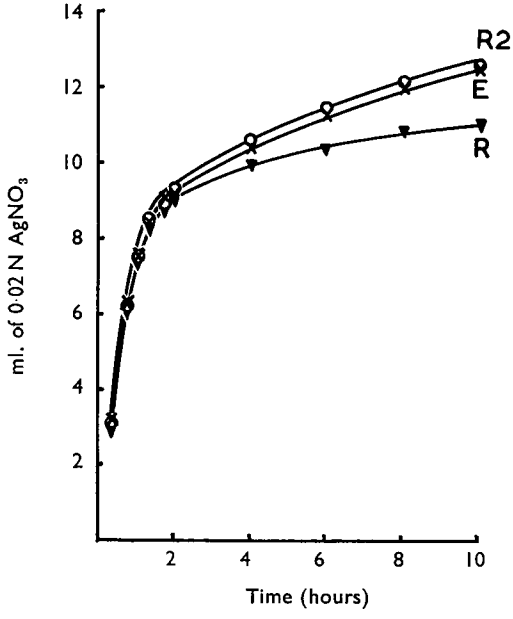


FIG. 5. Reaction between piperidine and purified chloroform containing added volumes of chlorobromomethane and methylene dichloride. Temperature 60°.

E = chloroform B.P.
R = purified chloroform + 0·25 per cent v/v CH_2ClBr
R2 = purified chloroform + 0·25 per cent v/v CH_2ClBr + 0·10 per cent v/v CH_2Cl_2

and to purified chloroform was investigated. No significant differences in extent of reaction with piperidine were noticed, when small amounts of ethanol were present.

Reaction of Bases with Purified Chloroform

At this stage, the action of organic bases, e.g. *n*-butylamine, benzylamine and 2-methylpiperidine on purified chloroform was examined (Table V). The reaction of piperidine with chloroform purified by both the strychnine and pyrrolidine methods are shown in Figure 3 (curves W and N). The reaction of pyrrolidine with chloroform purified by strychnine is shown in Figure 6 where it is compared with that of piperidine. Thus the decomposition affected by each of these bases is considerably less than that recorded in their reactions with chloroform B.P. It is difficult to decide whether or not the bases are attacking pure chloroform

(Table V) as the reactions may be due to small quantities of reactive impurities which have escaped removal. It does seem, however, that pyrrolidine and possibly piperidine react with pure chloroform.

Discussion

Though this paper does not offer any direct evidence on the mechanism of reaction of the bases studied with chlorobromomethane, dichloromethane and possibly chloroform itself, it may well be that quaternisation is involved. It is interesting to note that in the reaction of piperidine with purified chloroform containing 0·25 per cent v/v chlorobromomethane (Fig. 4, curve R) the change of slope in the curve, taken to signify the completion of reaction with chlorobromomethane, occurs between corresponding readings of approximately 8·0 and 9·5 ml. 0·02N silver nitrate solution. It can be calculated that this volume would be required provided only that both the chlorine and bromine content of the added chlorobromomethane were completely ionized. To account for this a quaternary ion of the following type may be formed, requiring two molecules of base per molecule of chlorobromomethane:

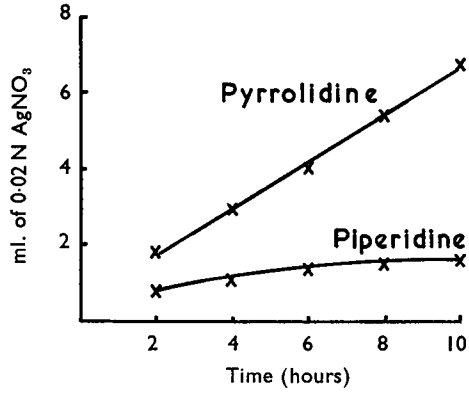
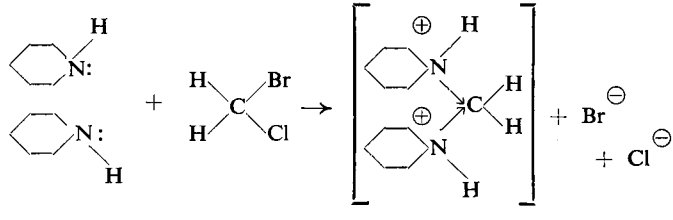


Fig. 6. Reaction between base and purified chloroform.
Temperature 60°.



The fact that strychnine, piperidine and pyrrolidine react preferentially with the chlorobromomethane in chloroform B.P. whilst a strong base such as potassium hydroxide does not, suggests that a particular structural feature embracing the basic nitrogen atom may be a necessary requirement. This structural feature is believed to be closely associated with the "tying back" of other groups attached to the nitrogen atom. This is effectively obtained in such molecules as those of strychnine, piperidine and pyrrolidine.

It has been suggested[7] that the origin of the chlorobromomethane impurity in chloroform B.P. is the commercial chlorine used in its manufacture. A survey of the technical literature by the present author confirms this view. It is reasonable to suppose that methylene dichloride is also present especially as some chloroform may be manufactured by the chlorination of methane.

The particular sample of chloroform B.P. used throughout this investigation appears to contain approximately 0·25 per cent v/v chlorobromomethane and 0·10 per cent v/v methylene dichloride. It has, however, been stressed[7] that chloroform B.P. can be expected to be a variable product.

This paper also indicates a method for assessing the quality of a sample of chloroform B.P., by treating it under the conditions prescribed with piperidine, following the rate of reaction and observing the position where the change of slope of the curve takes place.

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