

CHANGES IN THE HYDROCYANIC ACID CONTENT OF CHLORODYNE ON STORAGE

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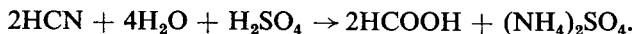
DURING an investigation into the possibility of the loss from Tinct. Chlorof. et Morph. B.P.C. (chlorodyne) of the volatile constituents after manufacture, a considerable decrease in the hydrogen cyanide content was observed in specially sealed control samples. This decrease was larger than could have occurred by volatilisation during the short periods for which samples were necessarily open during the experiments. 2 check samples drawn from stock manufactured at the beginning of this year and 3 samples of unknown age purchased from 3 other companies were found to have apparently lost between 80 per cent. and 93 per cent. of the theoretical hydrogen cyanide content. The more important reactions which could take place in chlorodyne resulting in a loss of free hydrogen cyanide have therefore been investigated.

THEORETICAL DISCUSSION

The 3 more important reactions which could lead to an apparent loss of hydrogen cyanide are (a) polymerisation, (b) hydrolysis and (c) addition to reducing sugars.

(a) Lewcock¹ showed that the apparent decomposition of aqueous solutions of hydrocyanic acid was due to the presence of traces of alkali cyanide or of alkali dissolved from the glass container and could be retarded by the addition of mineral acid; the addition of 1 per cent. of sulphuric acid (calculated on the hydrogen cyanide content) considerably retarded the decomposition and he suggested that "if as much as 10 per cent. of sulphuric acid (calculated on hydrogen cyanide content) could be added, such solutions for practical purposes would keep indefinitely." Walker and Eldred² have shown that the decomposition is due to polymerisation to a dark brown amorphous substance containing C, O, N and H in variable proportions. The polymerisation is initiated by alkaline impurities, and the polymer itself is a catalyst for the decomposition. Adams and Green³ have shown that even traces of ammonia and ammonium salts catalyse the polymerisation "with hydrogen cyanide concentrations ranging from very dilute. . . ." Dilute hydrocyanic acid usually contains added sulphuric acid to inhibit polymerisation, and of the other constituents of chlorodyne chloroform is known to have the same effect.⁴

(b) Hydrogen cyanide can be lost by acid hydrolysis to formic acid and ammonia.



Krieble and McNally⁵ and Krieble and Peiker⁶ studied the kinetics of this reaction and found it to be catalysed principally by the undissociated

mineral acid molecule but that sulphuric acid is a poor catalyst compared with other mineral acids. Loss of hydrogen cyanide is possible by this reaction since chlorodyne may contain approximately 0.003 per cent. of sulphuric acid; up to 0.06 per cent. of sulphuric acid may be added to dilute hydrocyanic acid as a stabiliser.

(c) Killiani^{7,8} showed that hydrogen cyanide reacts additively with dextrose to form a cyanhydrin, the reaction being accelerated by traces of ammonia. The function of the basic catalyst has been treated by Lapworth.⁹ Cyanhydrins are hydrolysed to 2-hydroxy acids with liberation of ammonia,⁷ and therefore hydrogen cyanide removed from solution by reaction with dextrose cannot be recovered by hydrolysis.

EXPERIMENTAL

The formula for chlorodyne requires 0.125 per cent. of hydrogen cyanide. Aqueous solutions of hydrogen cyanide of this concentration and freshly prepared chlorodyne solutions were treated as shown in Tables I and II and stored in flasks having ground-glass stoppers which were sealed with soft paraffin after each withdrawal of samples for periodic determination of hydrogen cyanide. The reducing sugar content of the treacle and liquorice used and the ammonia content of the liquorice and of a chlorodyne sample before and after storage were also determined.

According to Childs and Ball¹⁰ hydrogen cyanide is readily volatile in steam, and recovery by distillation is 99 per cent. quantitative. 30 ml. of mixtures of 50 ml. of chlorodyne diluted with 50 ml. of water were distilled into 20 ml. of water containing 5 ml. of dilute ammonia solution and 5 drops of potassium iodide solution and the distillate was titrated with 0.05N silver nitrate. Recovery experiments confirmed Childs and Ball's findings with a reproducibility of better than 1 per cent.

Appropriate dilutions of treacle and of liquorice were clarified with zinc acetate and potassium ferrocyanide,¹¹ the reducing sugar was determined by titrating Fehling's solution by Lane and Eynon's method¹² and calculated as dextrose.

Ammonia was determined by distillation from an alkaline solution of treacle and of liquorice into 0.1N sulphuric acid followed by back titration with 0.1N sodium hydroxide to screened methyl red indicator. The addition of a few drops of amyl alcohol to the contents of the distillation flask prevented excessive frothing.

DISCUSSION OF RESULTS

From Table I it is seen that there is no loss of hydrogen cyanide by volatilisation under the experimental conditions (1), neither acid hydrolysis nor ammonia catalysed polymerisation affecting the hydrogen cyanide content, at least in the early stages (2) (3). The rate of the addition reaction with reducing sugar is small in the presence of mineral acid or ammonium salt (4), (5), but the presence of ammonia increases the rate of reaction probably by its catalytic effect on the mutarotation of glucose and on the addition reaction (6).

Table II shows that the loss of hydrogen cyanide in chlorodyne is

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TABLE I

THE EFFECT OF ADDED REAGENTS ON THE HYDROGEN CYANIDE CONTENT OF 0.125 PER CENT. AQUEOUS SOLUTIONS

Added reagent	Time in days	Loss per cent.
1. Sulphuric acid, 0.0006 per cent. ..	15	Nil
2. Sulphuric acid, 0.06 per cent. ..	15	Nil
3. Ammonia, 0.02 per cent. ..	15	Nil
4. Dextrose, 1 per cent. ..	7	1
5. Dextrose, 1 per cent. ammonium chloride, 0.1 per cent. ..	7	1
6. Dextrose, 1 per cent.	0.1	38
ammonia, 0.1 per cent. ..	2	95

TABLE II

THE LOSS OF HYDROGEN CYANIDE FROM CHLORODYNE ON STORAGE AND THE EFFECT OF CONTAINER, CONSTITUENTS AND ADDED REAGENTS

.	Time in days	Loss per cent.
1. Glass container	6	14
	14	39
	37	63
2. Glass container	5	16
	13	39
	21	51
	4	13
3. Polythene container	4	12
4. Ammonium chloride, 0.1 per cent. added	4	17
	17	40
	0.05	30
	0.10	60
5. Ammonia, 0.1 per cent. added	0.15	80
	1	90
	3	95
	6	10
6. Chlorodyne solution prepared without treacle	14	26
	23	33
	28	42

progressive and the rate gradually declines with decreasing concentration (1), (2). Storage in an inert (polythene) container has no retarding effect (3). The addition of ammonium salt does not accelerate the reaction (4) but the effect of free ammonia is striking (5). The catalytic agent is present in the liquorice (6) which itself contains sufficient reducing sugar to react with the hydrogen cyanide.

The ammonia recovered by distillation from alkaline solutions of a sample of chlorodyne increased from 0.024 per cent. when freshly prepared to 0.076 per cent. after storage for 1 month, an increase of 0.052 per cent. The hydrogen cyanide content of the sample fell from 0.125 per cent. to 0.034 per cent., a decrease of 0.091 per cent. Had this quantity of hydrogen cyanide reacted with reducing sugar, alkaline hydrolysis of the cyanhydrin formed would have liberated an additional 0.057 per cent. of ammonia. The agreement between the calculated and the experimental figures is consistent with the postulated addition reaction.

The reducing sugar contents, calculated as dextrose, of the samples of treacle and liquorice used were 21 per cent. and 8 per cent. respectively. The ammonia content of the liquorice was 0.14 per cent. There is therefore a sufficiently large excess of each component to permit an ammonia catalysed addition reaction with the hydrogen cyanide.

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Consideration has been given to the stabilisation of chlorodyne and a method of maintaining the theoretical hydrogen cyanide content has been examined; the results of this work will be published later.

SUMMARY

1. Samples of chlorodyne from various manufacturers have been found to have lost as much as 90 per cent. of the theoretical hydrogen cyanide content.

2. The possible reasons for this have been examined. The experimental evidence suggests that hydrogen cyanide is removed by reaction with the carbonyl group of dextrose catalysed by ammonia derived from the liquorice extract.

I am indebted to Dr. Hersant and Mr. Ballard for their interest in this work, to Miss J. Charlton and Miss S. Spice for technical assistance and to the Directors of Messrs. May and Baker for permission to publish.

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DISCUSSION

The paper was presented by MR. H. A. GLASTONBURY.

DR. W. MITCHELL (London) said that he had confirmed the loss of hydrocyanic acid from chlorodyne and enquired whether the bases in liquid extract of liquorice had been determined by distillation with alkali, or by straight distillation without alkali, and whether ammonia had been identified in the distillate. In his own experiments with liquorice extract to which no ammonia had been added he had found 0.01 per cent. of bases calculated as ammonia by straight distillation and 0.14 per cent. by distilling with strong alkali. He could understand that free ammonia might catalyse the reaction, but doubted whether the bases naturally present in the liquid extract would do so. Chlorodyne made with this liquorice extract lost 5 per cent. of hydrocyanic acid in 24 hours. When chlorodyne was made with liquid extract of liquorice previously adjusted to pH 5.3 with either ammonia or caustic soda, a loss of 30 per cent. of hydrocyanic acid resulted in 24 hours, suggesting that the loss of stability was a pH effect.

DR. D. C. GARRATT (Nottingham) stated that if liquid extract of

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liquorice were distilled in the presence of mild alkali, e.g., magnesium oxide, no ammonia was evolved. Ammonia was only obtained if a strong alkali were used. His associates had observed over many years that chlorodyne made with extract of liquorice to which no ammonia had been added lost its hydrocyanic acid content almost immediately. Within 2 days the hydrocyanic acid present had dropped from 1.25 per cent. to 0.04 to 0.05 per cent. He questioned the conclusion of the author that the loss of hydrocyanic acid was due to a reaction catalysed by ammonia.

MR. N. L. ALLPORT (London) asked whether the authors had made any chlorodyne with liquid extract of liquorice made strictly in accordance with B.P. instructions, because according to the B.P. specification ammonia should not be present.

DR. F. HARTLEY (London) asked whether, in view of the analytical findings of the author, there was any justification for including hydrocyanic acid in chlorodyne.

MR. J. H. OAKLEY (London) said that hydrocyanic acid was a nuisance from the forensic angle and the loss due to volatilisation must not be forgotten. He was not convinced that it was worth adding. If the loss be made up, was there a danger that the hydrocyanic acid added in the first instance might have entered into some combination which still had toxic properties? The analytical specification should be in accordance with the keeping properties of the preparation.

MR. V. REID (London) asked whether, in view of the fact that hydrocyanic acid showed such loss on storage it would be possible to use cyanate. Would this have the same therapeutic effect as well as preventing loss?

MR. A. F. CALDWELL (Singapore) emphasised that the keeping properties of preparations was an all-important question in tropical countries, and said that he could see no value from the pharmacological point of view in the inclusion of hydrocyanic acid in chlorodyne.

DR. F. WOKES (King's Langley) stated that there was evidence that cyanides might be important biologically, and before specifying a given quantity of free or combined cyanide it was necessary to consider the biological effect. Cyanates were comparatively inert in the human body, but there was still a lot to be learnt of the metabolism of both cyanides and cyanates. He drew attention to a discrepancy between the method of expressing the experimental figure for the loss of hydrocyanic acid and the statement in the summary that as much as 90 per cent. had been lost.

MR. H. A. GLASTONBURY, in reply, said he was not concerned with the pharmacological question as to whether hydrocyanic acid should be present or not. Determinations had been carried out of the ammonia content of liquid extract of liquorice supplied by different manufacturers, and in all cases 0.2 per cent. of ammonia was found to be present, as determined by distillation in the presence of caustic soda. Attempts had been made to determine ammonia by straight distillation from an aqueous solution, and only approximately 0.05 per cent. had been found but

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because the liquorice caused excessive frothing, it had been necessary to discontinue the determination after half an hour. He had found that chlorodyne to which sulphuric acid had been added to bring the acidity to 0.1 N still showed similar loss of hydrocyanic acid and he did not consider the loss to be a pH effect. He still considered it probable that cyanide ions reacted with reducing sugars and that the reaction was catalysed by a basic substance, possibly ammonia.