

A STUDY OF THE INCOMPATIBILITY OF CHLORAL HYDRATE AND ALCOHOL IN THE PRESENCE OF SOLUBLE SALTS.

BY GEORGE W. HARGREAVES.

The incompatibility of chloral hydrate and alcohol has long been recognized; however, the literature on this subject is quite meager. It is stated in the United States Dispensatory (1) that hydro-alcoholic solutions of chloral hydrate in the presence of bromides or other saline ingredients frequently show a separation into two layers, the upper of which contains part of the alcohol and all of the chloral. This statement is only partly correct, because it was found in this study that all of the chloral hydrate is not separated out in one layer, in all cases. Furthermore, whether the layer containing chloral is the upper or lower one is determined by the particular concentration of the solution under consideration. The only study of any importance was carried out, in 1885, by Markoe (2) who concluded that the separation in the following prescription was due to the formation of chloral alcoholate:

Potassium Bromide	of each 3 drachms
Chloral Hydrate	
Camphorated Tincture of Opium	of each 1½ fluidounces
Syrup of Ginger	

He also found that beside potassium bromide, the addition of sodium bromide, sodium chloride and magnesium sulphate to strong solutions of chloral hydrate together with alcohol determined the separation of the liquid into two layers. In his article no specific examples are given of the above cases and the same is true of his additional observations that ammonium bromide, calcium bromide, ammonium chloride and potassium nitrate fail to disturb the same chloral hydrate solutions.

Ruddiman (3) gives the following prescription as an example of this type of incompatibility:

Chloral Hydrate	4 drachms
Potassium Bromide	3 drachms
Elixir	sufficient quantity to make 2 ounces

The combination of bromides with chloral hydrate is recommended by various authorities on pharmacology and therapeutics such as Sollman (4) and Solis-Cohen (5).

A proprietary preparation is said to contain the following:

Alcohol	10%	}	To each fluidounce
Chloral Hydrate	91 grs.		
Potassium Bromide	91 grs.		
Cannabis, soluble extract	1 gr.		
Hyoseyamus, soluble extract	1 gr.		

This corresponds in composition and strength to the N. F. preparation Compound Mixture of Chloral and Potassium Bromide; the latter, however, being non-alcoholic.

This investigation was undertaken in an endeavor to determine the nature of the reaction and some of the conditions affecting it.

While this study was being made, the writer had occasion to compound the following prescription in the college dispensary.

Chloral Hydrate	2 drachms
Sodium Bromide	4 drachms
Elixir Lactated Pepsin	sufficient to make 2 ounces

The elixir contains 15 per cent of alcohol. Shortly after mixing the above ingredients, an oily layer separated on the surface. This was colored a very deep red and had evidently taken up some of the coloring matter from the elixir. The physician, upon being consulted, ordered it dispensed with a "shake well" label and stated that he had been using this mixture for several years with much success.

EXPERIMENTAL.

Preliminary.—The prescription given by Ruddiman was used as the basis of some preliminary tests, 20 per cent of alcohol by volume being substituted for the elixir. It gave a clear solution at first which after standing a few minutes became turbid and, finally, an oily layer, having a volume of about 10 cc. separated at the bottom. The lower layer was separated off and found to be quite soluble in both alcohol and water. The aqueous layer on being shaken with an additional quantity of potassium bromide, gave an additional quantity of oil which separated on the surface.

Upon compounding again and substituting distilled water for the 20% alcohol a clear solution was obtained which did not separate even upon standing several days.

Another trial was made without the bromide and a stable clear solution resulted.

Substitution of sodium chloride likewise caused separation. This indicated that the rôle of the saline ingredient is to cause the "salting out" of the oily substance.

Composition of the Oily Layer.—For determination of the composition of the oily layer the mixture was made up in a double quantity, the oily layer separated and taken up in ether. After drying over anhydrous sodium sulphate, the ether was distilled off and the residue fractionated. First a small fraction of alcohol came over, then a fraction of chloral and finally chloral alcoholate which was identified by its boiling point (115°), melting point (46°) and its action with nitric acid. A small amount of crystalline solid remained in the distilling flask and this was identified as potassium bromide.

Another sample was prepared and the oily layer collected and dried as above. Instead of distillation, however, it was allowed to stand in an evaporating dish over night. There resulted a crystalline mass of chloral alcoholate together with an oily liquid which was identified as chloral.

It is expected to study this reaction later from a quantitative standpoint.

Conditions of Separation.—In order to study the effect of concentration on the reaction, a series of samples of various alcoholic strengths and concentrations of both chloral hydrate and potassium bromide were compounded. The results are given in the following tables.

TABLE I.

No.	Chloral Hydrate.	KBr.	Alcohol % q. s. ℥ii.	Result.
1	2 drachms	4 drachms	10	No separation
2	2 drachms	4 drachms	20	Separation
3	2 drachms	4 drachms	30	Separation
4	2 drachms	4 drachms	40	Separation
5	2 drachms	4 drachms	50	No separation

Table II.—Nos. 1-5; Chloral hydrate, 3 drachms; Potassium bromide, 4 drachms; Alcohol, consecutively by tens in percentage (Alcohol % q. s. ℥ii—this applies to all alcohol employed)—10, 20, 30, 40, 50 as first table; separation occurred in all solutions, except first—10 per cent.

Table III.—Nos. 1-5; Chloral hydrate, 4 drachms; Potassium bromide, 4 drachms; separation occurred in all except first.

Table IV.—Nos. 1-5; Chloral hydrate, 4 drachms; Potassium bromide, 3 drachms; Alcohol, by tens in percentage as first table; same results as Table I.

Table V.—Nos. 1-5; Chloral hydrate, 3 drachms; Potassium bromide, 3 drachms; Alcohol by tens in percentage as first table; separation occurred in none of the solutions.

EFFECT OF SUGAR ON THE "SALTING OUT" PROCESS.

The results in Table V would indicate that there should be no separation in the prescription given by Markoe. It was found that upon compounding the following mixture:

Chloral Hydrate		Chloral Hydrate	℥iii
Potassium Bromide	aa ℥i	Potassium Bromide	℥ii
Diluted alcohol		Syrup	
Syrup	aa q.s. ℥i	Alcohol 40%	aa q. s. ℥ii

an oily layer separated. Evidently the sugar also affects the salting out process. In another trial separation was quite rapid in the following:

All the above results were duplicated using sodium bromide. Ammonium bromide and calcium bromide were tested according to Table IV and gave analogous results.

DISCUSSION OF RESULTS.

In Table V, numbers 2, 3 and 4, what might be termed a "critical concentration" is reached. The addition of a small quantity of either chloral hydrate or potassium bromide to these samples will cause separation. With a low concentration of alcohol either the reaction does not take place or not enough chloral and chloral alcoholate are formed to be thrown out of solution. With 40% and 50% alcohol and a concentration of two drachms of potassium bromide to the fluidounce, part of the bromide is insoluble.

SUMMARY.

1. Separation in hydro-alcoholic solutions of chloral hydrate with soluble salts is affected by the concentration of chloral hydrate, alcohol and salt.
2. The conditions of separation are given for the concentrations which might be met with in dispensing.
3. Sugar affects the salting out process, making a smaller amount of salt necessary to cause separation.
4. The oily layer was found to consist of alcohol, chloral, chloral alcoholate and a small quantity of dissolved salt.

REFERENCES.

- (1) "United States Dispensatory," Wood and LaWall, 21st Edition, 1926, Lippincott.
- (2) G. F. H. Markoe, *Am. J. Pharm.*, 57 (1885), 370.
- (3) Ruddiman, "Incompatibilities in Prescriptions," 5th Edition, 1925, J. Wiley & Sons, page 127.
- (4) Sollman, "Manual of Pharmacology," 3rd Edition, 1928, Saunders, page 173.
- (5) Solomon Solis-Cohen, "Pharmaco-therapeutics," 1928, D. Appleton, page 1629.

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CHEMICAL STUDIES OF THE FRESH JUICE OF THE MAGUEY PLANT.—(MANSO FINO, KARW).

(Continued from page 356, April number, *Jour. A. Ph. A.*)

A PRELIMINARY REPORT.

BY HERMAN D. JONES.*

PAPER NO. 2.

METHOD OF OBTAINING THE OILS AND CRYSTALS.

There has been found in the aguamiel an oil which doubtless gives to the maguey its characteristic odor, since on being extracted, the oil has the same odor as the maguey or the fresh juice, except that it is more pronounced. It is present in large quantities in the leaves and in small quantities in the finished syrup.

The dry maguey leaves were powdered and passed through a 40-mesh sieve to remove fibre and to assure good exposure to the solvent or extract the oil. Four kilos of this powder were extracted with sulphuric ether for 24 hours. As the ether became saturated with the oils, they were precipitated in the flask. When extraction was complete, the ether and extract were placed in an 8-liter flask and sufficient ether added to bring all the oils into solution. This was then filtered and this ether solution treated with twice its volume of petroleum ether. A small quantity of a cream-colored compound was precipitated, removed by filtering and set aside for further study. The petroleum ether was next removed by distillation on water-bath under vacuum. The volume was reduced to approximately the same as the original solution, when it was treated with twice its volume of methyl alcohol. Of the three distinct layers which appeared, the thin dark, oily ones at the bottom and top were separated and set aside for further study. The remaining bulky, light layer was placed in a still and the ether and alcohol removed under vacuum until the volume of heavy, oily solution was quite small. This residue was allowed to stand in an evaporating dish without heat for several weeks until no alcohol odor was perceptible. Then on inspection there appeared many white, glistening crystals whose physical properties appear below.

PHYSICAL PROPERTIES.

Color—white. Odor and taste—none.

Structure—crystalline, very thin parallelogram.

Ignition test—burns with smoky flame without residue.

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