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The Synthesis of 3-Hydroxyphthalic Acid

By Ole Givold*

Oxidative studies carried out upon the pigment celastrol, a naturally occurring β -naphthoquinone, yielded a small quantity of material that melted at 244° C. and gave a positive phthalein test. Because the hydroxyl group that is present in this pigment was suspected of being adjacent to the carbonyl groups, 3-hydroxyphthalic acid was an anticipated oxidation fragment. A search of the literature revealed an apparent discrepancy in the melting point of 3-hydroxyphthalic acid. The "Handbook of Chemistry and Physics" gives the melting point of 3-hydroxyphthalic acid as 244° C., and solubilities which corresponded quite closely with those of the above-mentioned oxidation fragment. Heilbron's "Dictionary of Organic Compounds" reports the melting point of 3-hydroxyphthalic acid as 151° C. (with anhydride formation at 161–163° C.) and the melting point of the corresponding anhydride as 198–199° C., with solubilities which differed from those given in the "Handbook." In addition it reports a red color with ferric chloride. No red color with ferric chloride is given by the unknown.

It was therefore necessary to synthesize 3-hydroxyphthalic acid in order to make comparisons with the unknown. No attempt was made to develop good yields of any of the products obtained in this synthesis. 3-Aminophthalic acid was prepared in a pure state in order to report for the first time its melting point. It was not, however, used pure as an intermediate. The reduction of 3-nitrophthalic acid was accomplished

catalytically with either platinum or Raney nickel; whereas in the previous syntheses reported in the literature this was accomplished by tin or iron and hydrochloric acid, and no 3-aminophthalic acid was isolated as the intermediate. The 3-hydroxyphthalic anhydride prepared corresponded with that recorded in Heilbron's "Dictionary of Organic Compounds" with respect to solubilities and color reaction. The melting point was somewhat lower; however, no correction was made for stem emergence.

EXPERIMENTAL

3-Nitrophthalic Acid.—This compound was prepared according to the method given in "Organic Syntheses," Vol. I.

3-Aminophthalic Acid.—The 3-nitrophthalic acid was reduced in alcohol by means of platinum black or Raney nickel at 40 to 50 lbs. pressure and at room temperature. The reduction was accompanied by the formation of large quantities of an unidentified material that appeared to be a polymer. This side reaction was greatest with platinum. The catalyst was removed by filtration, the filtrate concentrated by spontaneous evaporation and the residue digested with water. The aqueous solution was separated from an oily water-insoluble residue. Concentration by spontaneous evaporation yielded crude 3-aminophthalic acid which after several crystallizations from water yielded orange rosettes that melted at 231–232° C. (uncorr.).

3-Hydroxyphthalic Anhydride.—3-Aminophthalic acid was diazotized by the usual method and the crude diazotized product was collected and washed several times with cold water. The diazonium product thus prepared was decomposed according to the directions given in "Organic Syntheses" for the preparation of *m*-nitrophenol. The reaction mixture was then extracted with ether in order to collect the crude 3-hydroxyphthalic acid. Attempts to purify the product by recrystallization from suitable solvents were unsuccessful. The crude material was

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then subjected to vacuum sublimation. The sublimate was crystallized from anhydrous ether until a constant melting point was obtained at 195° C. (uncorr.). The 3-hydroxyphthalic acid anhydride thus obtained was very pale yellow in color and gave a deep purple-red color with ferric chloride. It was soluble in water or alcohol.

3-Hydroxyphthalic Acid.—Hydrolysis of a sample of the 3-hydroxyphthalic acid anhydride yielded upon crystallization from anhydrous ether and petroleum ether very pale yellow crystals of 3-hydroxyphthalic acid that melted at 154° C. (uncorr.). This compound was soluble in water or alcohol and gave a deep purple-red color with ferric chloride.

The Influence of Carbohydrates and Salines upon the Separation of Chloral Alcoholate*

By Roland T. Lakey and Carl C. Pfeiffer

The first to record chloral alcoholate incompatibility was G. F. H. Markoe (1), who on June 4, 1885, read a paper entitled "On the Incompatibility of Chloral Hydrate in the Presence of Potassium Bromide and Alcohol" before the Massachusetts State Pharmaceutical Association. He stated that the following prescription was sent to him to determine whether the pharmacist had made a mistake in compounding, because it had subsequently separated into two layers:

℞	Potassium Bromide	
	Chloral Hydrate, $\bar{a}\bar{a}$	℥ijj
	Tr. Opii et Camp.	
	Syr. Zingiber, $\bar{a}\bar{a}$	℥iss

After experimenting with this prescription, he came to the conclusion that chloral alcoholate was formed and separated as a top layer. He also observed that potassium bromide, sodium bromide, sodium chloride and magnesium sulfate aided in causing the separation. From his studies he also claimed that calcium bromide, ammonium chloride, ammonium bromide and potassium nitrate did not produce any separation.

G. W. Hargreaves (2) published a study of this type of incompatibility in the June, 1932, issue of the JOURNAL of the AMERICAN PHARMACEUTICAL ASSOCIATION. By analysis, Hargreaves found the oily layer to consist of alcohol, chloral, chloral alcoholate and a small amount of saline. He also found that sucrose in the presence of potassium bromide would cause the separation of chloral alcoholate. These two pertinent

papers seem to be the only ones in the English literature on this subject.

This study was prompted by the renewed popularity of chloral hydrate in prescriptions and also by the fact that it has not always been easy to demonstrate this incompatibility to our classes. The purpose, then, of this investigation was to determine the "critical concentration" (a term used by Hargreaves) of each of the ingredients necessary to cause the separation of chloral alcoholate in a chosen basic formula containing chloral hydrate, alcohol, potassium bromide and sucrose.

EXPERIMENTAL

The basic formula chosen for this study is the same as the Elixir of Chloral and Potassium Bromide, Compound, N. F. VI (3):

℞	Chloral Hydrate	12.5 Gm.
	Potassium Bromide	12.5 Gm.
	Sucrose	10.5 Gm.
	Alcohol	...
	Water, <i>q. s. ad.</i>	50 cc.

One drop of a 1% solution of the fat-soluble dye Sudan III was added to each 50 cc. of the prescription. This serves to delineate any separated chloral alcoholate, since the red-colored dye concentrates in this layer. Kodachrome pictures were taken at the critical point in each experiment. The surface tensions of some of the separated and non-separated solutions were determined by the Du Noüy apparatus to ascertain whether marked changes in surface tension were involved in the separation of chloral alcoholate. All experiments were conducted at room temperature and no heat was used to effect solution of any of the solutes. All of the critical experiments were checked by repetition. The results of alterations made in the basic formula are given in tabular form.

From Table I it will be observed that separation into two layers occurred with 1% less alcohol when the chloral hydrate was first dissolved in alcohol. This

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