[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

A Study of the Reactions between Citric and Acetylsalicylic Acids

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Introduction

The purpose of this research was to effect a chemical combination, which might be of therapeutic value, between citric acid and acetylsalicylic acid.

Previous Work.—F. Zernik[1] prepared a disalicylic acid ester of methylene citric acid which was marketed under the trade name of Novaspirin. Lehman[2] describes this product as a mild form of aspirin which can be easily administered and borne by the patient; its action, too, is claimed to be more rapid.

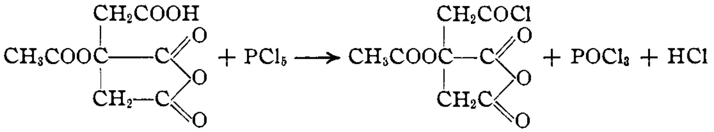
Berendes and Calleen[3] prepared succinyl-disalicyclic acid which is claimed to possess the same desirable therapeutic properties.

Salicylic monoglycol esters[4] and glyceryl esters[5] have been prepared

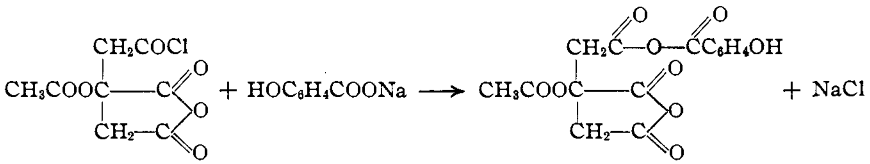
Discussion

Since it was desired to prepare a compound which would contain one mole of salicyclic acid or acetylsalicyclic acid and one mole of citric acid, it seemed best to change in some way three of the four functional groups of citric acid and at the same time block off the alcoholic group.

For this reason acetylcitric acid anhydride was prepared.[6] This was allowed to react with phosphorus pentachloride in order to prepare the acid chloride in the following way



The acid chloride was treated with sodium salicylate with the expectation that the reaction would go as follows



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(1) Zernik, *Apoth. Ztg.*, **22**, 508 (1907).

(2) Lehman, *Deut. med. Wochschr.*, **33**, 385–386 (1907).

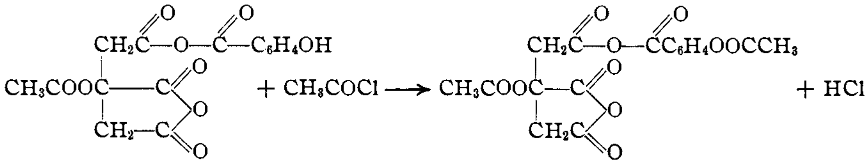
(3) Berendes and Calleen, German Patent 874,929, December 31, 1907.

(4) Badische Anilin und Soda Fabrik, German Patent 173,776, April 21, 1905.

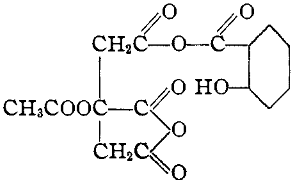
(5) Serger, German Patent 186,111, January 16, 1906.

(6) Klingemann, *Ber.*, **22**, 984 (1889).

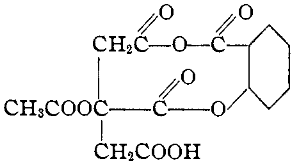
A reaction took place quite readily. After checking the compound by a quantitative saponification and a molecular weight determination, it was planned to acetylate it according to the following reaction



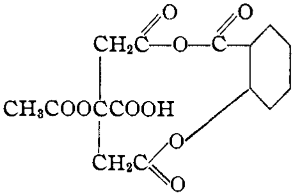
However, no acetylation took place and upon making a ferric chloride test for a phenol, negative results were obtained until the compound had stood for eight minutes in an aqueous solution at room temperature. This showed that there was no free phenol group in the compound and it could not have the structure represented by I. While (I) may have been first obtained, it rearranged into either (II) or (III) which have the same molecular weight.



I



II



III

The rate of hydrolysis of this compound was then determined in 0.0987 *N* hydrochloric acid at 38°. The products of this hydrolysis were acetic acid, citric acid, salicyclic acid and some aconitic acid. The results of the hydrolysis are shown in Table I.

It was found that after standing for five weeks in a well-stoppered bottle, the compound had a slight acetic acid odor and its melting point had decreased. A single recrystallization of the compound brought its melting point up to the original value. Thus it was evident that on standing some decomposition had taken place.

In attempting to form a combination between citric acid and acetylsalicylic acid many other reactions were tried. They will be briefly outlined and the products given as a matter of record.

1. Anhydrous citric acid was treated with an equivalent amount of acetylsalicylyl chloride in the presence of dimethylaniline. Salicylic acid.

acetylsalicylic acid and citric acid were obtained. They were formed by the addition of water at the end of the experiment.

2. Unsuccessful attempts were made to add acetylsalicylic acid to the double bond in aconitic acid both in the presence of zinc chloride and in the presence of a 2% sulfuric acid solution.

3. 2-Bromo-1,2,3-propanetricarboxylic acid was treated with sodium salicylate in ethereal solution. The products were sodium salicylate, sodium bromide, salicylic acid and aconitic acid.

4. Acetylsalicylyl chloride was treated with anhydrous citric acid. The reaction proceeded smoothly at 110° with the evolution of hydrogen chloride. An uncrystallizable gum was obtained. After standing for two months in a soda lime desiccator some crystals appeared. Analysis showed the presence of acetic, salicylic, citric and aconitic acids.

5. When alkaline citrates were used corresponding products resulted.

6. The sodium alcoholate of triethyl citrate was treated with acetylsalicylyl chloride in boiling ether. The quantitative amount of sodium chloride was obtained. Acetylsalicylic acid was recovered from the gum-like product. The residue reduced alkaline potassium permanganate and was probably triethyl aconitate.

7. In order to verify the results of the last experiment the triethyl ester of 2-chloro-1,2,3-propane-tricarboxylic acid was allowed to react with sodium salicylate in ethereal solution. A sirup was formed which was separated into salicylic acid and triethyl aconitate.

8. Direct esterification between acetylsalicylic and citric acids by means of esterification catalysts was attempted but the experiments were unsuccessful.

Experimental

Reaction of the Acid Chloride of Acetylcitric Acid Anhydride with Sodium Salicylate

Preparation of the Acid Chloride.—Forty grams (1 mole) of acetylcitric acid anhydride, 100 cc. of anhydrous petroleum ether and 38.4 g. (1 mole) of phosphorus pentachloride were mixed and warmed with stirring to about 25° on a water-bath until the evolution of hydrogen chloride had ceased. It was then filtered and the residue on the filter was washed with dry petroleum ether to remove the last trace of phosphorus oxychloride. The product was then recrystallized from chloroform and petroleum ether, m. p. 92–93°; yield 90%.

Anal. Calcd. for $C_8H_7O_6Cl$: Cl, 15.12. Found: Cl, 15.05.

Forty-one grams (1 mole) of the acid chloride of acetylcitric acid anhydride was dissolved in 200 cc. of chloroform and treated with 27 g. (1 mole) of sodium salicylate. The reaction was carried out at room temperature with rapid stirring until all the sodium salicylate was used.

The reaction mixture was then filtered and the residue taken up in 200 cc. of dry acetone. The acetone solution was filtered and the acetone removed from the filtrate under reduced pressure. The slightly brown residue was recrystallized from an acetone–chloroform mixture. A white crystalline compound was obtained, m. p. 162–163°; yield, 57.3%.

The molecular weight by elevation of the boiling point of pure acetone was 339 and 343 and as determined by a quantitative saponification was 335. The molecular weight calculated for $C_{15}H_{12}O_9$ was 336.

Attempted Acetylation of this Compound.—Eight grams of the above compound was boiled for three hours with 20 cc. of acetyl chloride but only a trace of hydrogen chloride was evolved. The acetyl chloride was distilled and the residue, after recrystallization, proved to be the original substance.

When 0.10 g. of this compound was suspended in 5 cc. of water, and a drop of 0.10% ferric chloride solution was added no color appeared until eight minutes had passed.

Determination of the Rate of Hydrolysis of this Compound.—Ten separate 0.2000-g. samples of the compound were placed in 150-cc. Erlenmeyer flasks and covered with 10 cc. of 0.0987 *N* hydrochloric acid. The flasks were stoppered and kept at 38°. At the indicated times the extent of the hydrolysis was determined by filtering a sample, washing the residue twice with water, and titrating the filtrate with 0.135 *N* sodium hydroxide, using phenolphthalein as the indicator.

The results of these titrations are shown in Table I.

TABLE I

Sample	Time	Cc. of 0.135 *N* NaOH used	% Hydrolysis
1	0 Min.	8.8	6.8
2	15 Min.	9.2	8.6
3	30 Min.	9.6	10.4
4	45 Min.	10.2	13.1
5	60 Min.	12.2	22.2
6	2 Hours	11.7	20.0
7	4 Hours	14.0	30.4
8	24 Hours	19.2	54.0
9	72 Hours	23.0	71.3

After the compound had stood for five weeks in a well-stoppered bottle, it had a slight odor of acetic acid and the melting point had fallen to 152°. The compound was recrystallized from an acetone–chloroform mixture and its melting point was again 162–163°.

Summary

1. General methods of esterification have been tried in an attempt to combine citric acid and acetylsalicylic acid. Esterification was not effected but several interesting mechanisms have been determined.

2. A chemical combination between acetyl citric acid and salicylic acid has been effected.

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