

## DECOMPOSITION OF CITRIC ACID BY FERRIC IRON.\*

BY S. I. PELTZ AND E. V. LYNN.<sup>1</sup>

It is a well-known fact that many preparations of iron undergo decomposition when exposed to light. This is particularly true of those containing quinine and strychnine (I. Q. S.). Although some of the used solutions of iron are stable, the problem of possible deterioration and of means to prevent it has long been a challenge to the pharmacist.

The best known method for avoiding such changes is to exclude the light, a simple procedure but one not always completely practicable. With only partial protection, the rate of changes is roughly proportional to the intensity of light, but eventually the preparation alters in color, evolves gas or deposits muddy or crystalline precipitates; possibly all three of these take place simultaneously in the same solution.

All of the solutions which decompose in this way contain ferric iron and some salt of an organic acid. Indeed, these two factors seem to be the exclusive ones, although secondary changes may occur subsequently.

Many of the numerous papers which have appeared on this subject are entirely empirical. In order to prepare stable solutions of iron, some have added various reagents, others have furnished an excess of acid or have nearly neutralized, while still others have altered the methods of preparation or have suggested many other schemes, all without substantiated reasons for so doing. Practically all of these proposals have been tried unsuccessfully. This literature is well summarized by Burt (9). Scientific investigations of the subject are very few and much of the present evidence is insufficient and even contradictory.

It is known that oxidation of citric acid will give rise to carbon dioxide, acetone and other volatile products. This may take place under the influence of heat and manganese dioxide (1), of sunlight and uranic oxide (2, 3), or of sunlight or ultraviolet and ferric compounds (4, 6, 7, 8, 9), or of oxygen and light (5). The nature of the products in each case has never been adequately investigated and much of the past or present surmises are conflicting.

The more specific changes which follow reaction of ferric salts and citric acid are largely matters of conjecture. Using an ultraviolet (mercury arc) lamp, Benrath (7) found that acetone and formaldehyde are formed, together with hydrocyanic acid and nitrous oxide from the ferric nitrate used. Mueller (8) found that ferric iron is reduced to ferrous in the sunlight and that carbon dioxide is produced. Burt (9) confirmed these results and obtained the iodoform test for acetone after distilling an exposed solution. He also decided that three molecules of carbon dioxide are produced for each molecule of acetone and formulated the reaction as



We were able to confirm the formation of carbon dioxide and to establish that it is the only gaseous product. Flasks containing 2.5 Gm. of citric acid in 50 cc. of water and 0.25 Gm. of ferric hydroxide were connected to potash absorption bulbs and exposed to sunlight. When all evidence of reaction had ceased, the bulbs

\* Presented before the Scientific Section, A. Ph. A., Minneapolis meeting, 1938

<sup>1</sup> Professor, Massachusetts College of Pharmacy.

were found to have increased in weight by  $0.075 \pm 0.0005$  Gm. Separately collected samples of the gas were completely absorbed by potash in a Hempel pipette.

Besides evolution of gas, the only distinct change is disappearance of the brown ferric hydroxide. Where there is sufficient of the latter to start with, it is only reduced in amount. Careful examination also shows that the originally colorless solution is now very slightly greenish yellow and contains ferrous but not ferric ions, as shown by tests with ferricyanide and thiocyanate. After standing away from sunlight for a short time but exposed to the air, the almost colorless solution gradually acquires a darker greenish tinge. This is probably brought about by direct oxidation in the air, as is experienced with many ferrous solutions. Exposure to sunlight always results in removing the color and tests for ferric iron.

Neither acetone nor formaldehyde could be identified in the final solution. The experiments of Burt could be duplicated, but his assumption that acetone is formed seems to be erroneous. The residual solution gave no iodoform and no color with alkaline sodium nitroprusside (Rothera or Legal). Distillation gave a neutral liquid which responded to the iodoform reaction, as Burt had shown, but no nitroprusside test. Furthermore no oxime could be obtained from the first distillate. Tests for formaldehyde in either liquid were negative.

The exact combination of iron in the decomposed solution was not discovered. After removal of the iron by hydrogen sulfide, which was easily accomplished contrary to Burt's experience, and evaporation of excess sulfide, ether failed to extract significant amounts from the acidified solution, although it will remove appreciable quantities of citric acid from its aqueous solution. On the other hand, a calcium salt was readily formed by precipitation and this was found to contain 31.05 per cent of CaO as compared with 33.73 per cent from normal calcium citrate. Also, portions of the original ferrous liquid, after evaporation and ignition, gave 29.15 per cent of ferric oxide, as compared with 30.76 per cent from normal ferrous citrate. Acetates and oxalates could not be identified.

Finally it was determined that neutral citrates will not decompose with ferric hydroxide in strong sunlight. The iron goes into solution as might be expected, but none of it was found in the ferrous state. In galenicals which contain citrates and do deteriorate, we may assume primary formation of free acid by hydrolysis or otherwise.

#### SUMMARY.

1. Citric acid is at least partially decomposed by ferric hydroxide in the sunlight to give carbon dioxide and a soluble ferrous salt, probably a citrate. Alkali citrates do not decompose under the same conditions.

2. No acetone and no formaldehyde can be detected in the final solution. A substance is found in a distillate which gives the iodoform reaction but no nitroprusside test.

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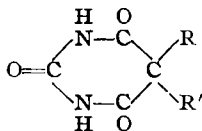
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### CROTYL SUBSTITUTED BARBITURIC ACID DERIVATIVES.\*

BY EDWARD E. SWANSON<sup>1</sup> AND WILLIAM E. FRY.<sup>1</sup>

In a previous communication (1), it was observed that there is obvious relationship between the pharmacological action and the chemical structure of certain barbituric acid derivatives. In the primary or secondary alkyl substituted compounds, with an increase in the number of C-atoms in the alkyl group, both the minimal anesthetic dose (M. A. D.) and the minimal lethal dose (M. L. D.) grow relatively smaller, but when the alkyl radical is longer than 5 C-atoms, the amount required to produce anesthesia or death in rats again increases. As the alkyl chain lengthens, the therapeutic index, or ratio between M. L. D. and M. A. D., appears to be gradually greater. The duration of action becomes shorter. More recently, it has been reported that the substitution of a methyl or an ethyl group on the nitrogen (nitrogen alkyl substituted barbituric acid derivatives) (2), or the substitution of an allyl or methallyl (2-methyl-allyl) (3) on one of the 5-5 positions, or a sulfur atom (4) in place of the 2 C-atom obviously reduces the duration of action. This shorter duration of action is independent of the quantity of drug administered.

The present investigation deals with the study of a number of new crotyl (3-methyl-allyl) substituted barbituric acid derivatives synthesized by Doran and Shonle (5), with the general formula:



wherein R-alkyl radical may be a primary or secondary alkyl radical with 2 to 5 C-atoms; and R', a crotyl (3-methyl-allyl) radical.

Albino rats weighing 80 to 125 Gm. (average 99 Gm.) were used in this study. Solutions of the sodium salts of the compounds were injected intraperitoneally. The M. A. D., the duration of action, and the M. L. D. were determined by using 5 animals for each dose level.

As shown in Table I, these barbituric acid derivatives have a much shorter duration of action. Thus, the substitution of a crotyl (3-methyl-allyl), similar to the nitrogen alkyl barbituric acids and methallyl (2-methyl-allyl) compounds, produces a change (shorter) in the duration of action. Compound number 6, Crotyl-*n*-butyl-thio barbituric acid, shows convulsions with little or no hypnotic or anesthetic properties.

\* Presented before the Scientific Section, A. Ph. A., Minneapolis meeting, 1938.

<sup>1</sup> From the Lilly Research Laboratories, Indianapolis, Indiana.