

UNITED STATES PATENT OFFICE.

MITFORD C. MASSIE, OF WASHINGTON, DISTRICT OF COLUMBIA, ADMINISTRATOR OF FRITZ ACH, DECEASED, ASSIGNOR TO C. F. BOEHRINGER & SOEHNE, OF MANNHEIM-WALDHOF, GERMANY, A FIRM.

PROCESS OF MAKING THEOPHYLLIN.

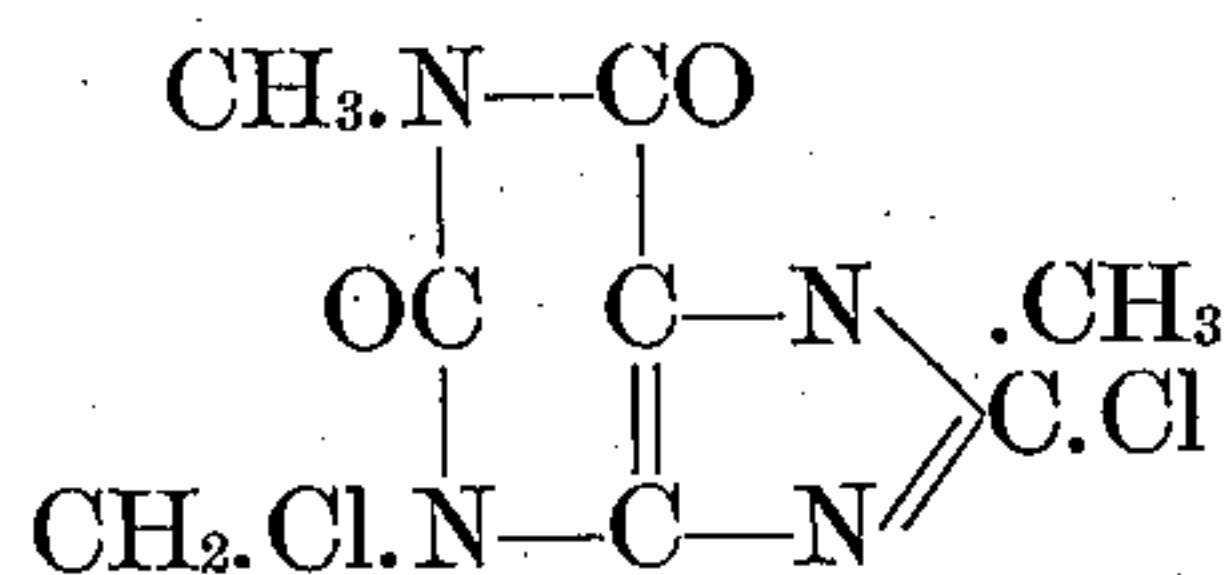
SPECIFICATION forming part of Letters Patent No. 768,533, dated August 23, 1904.

Original application filed February 7, 1903, Serial No. 142,591. Divided and this application filed January 25, 1904. Serial No. 190,566. (No specimens.)

To all whom it may concern:

Be it known that FRITZ ACH, deceased, late a citizen of Germany, and a resident of Mannheim, Germany, did invent new and useful Improvements in the Preparation of Theophyllin; and I, MITFORD C. MASSIE, residing at Washington, District of Columbia, the duly-constituted administrator of the estate of said FRITZ ACH, deceased, do hereby declare the following to be a full, clear, and exact description of the said invention of said decedent, such as will enable others skilled in the art to which it appertains to make and use the same, the said invention being described but not specifically claimed in application Serial No. 142,591, filed February 7, 1903, of which this is a divisional application.

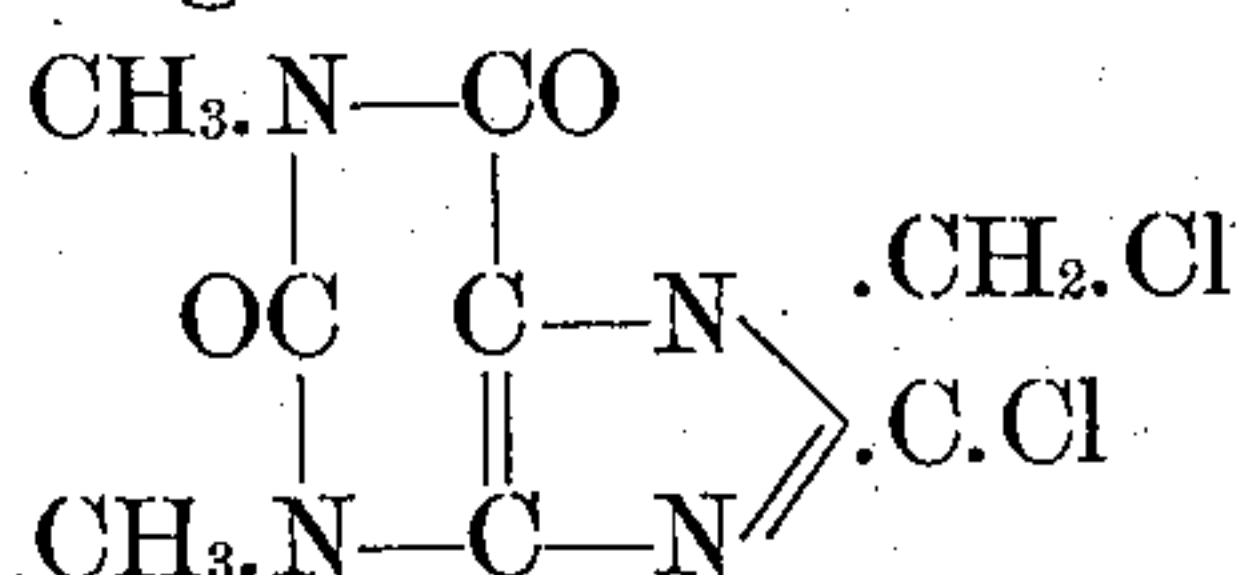
In United States Patent No. 660,744 a process for the preparation of paraxanthin or 1.7-dimethylxanthin has been described. That process starts with a 1.7-dimethyl-3-chloromethyl-8-chloroxanthin, having the structural formula



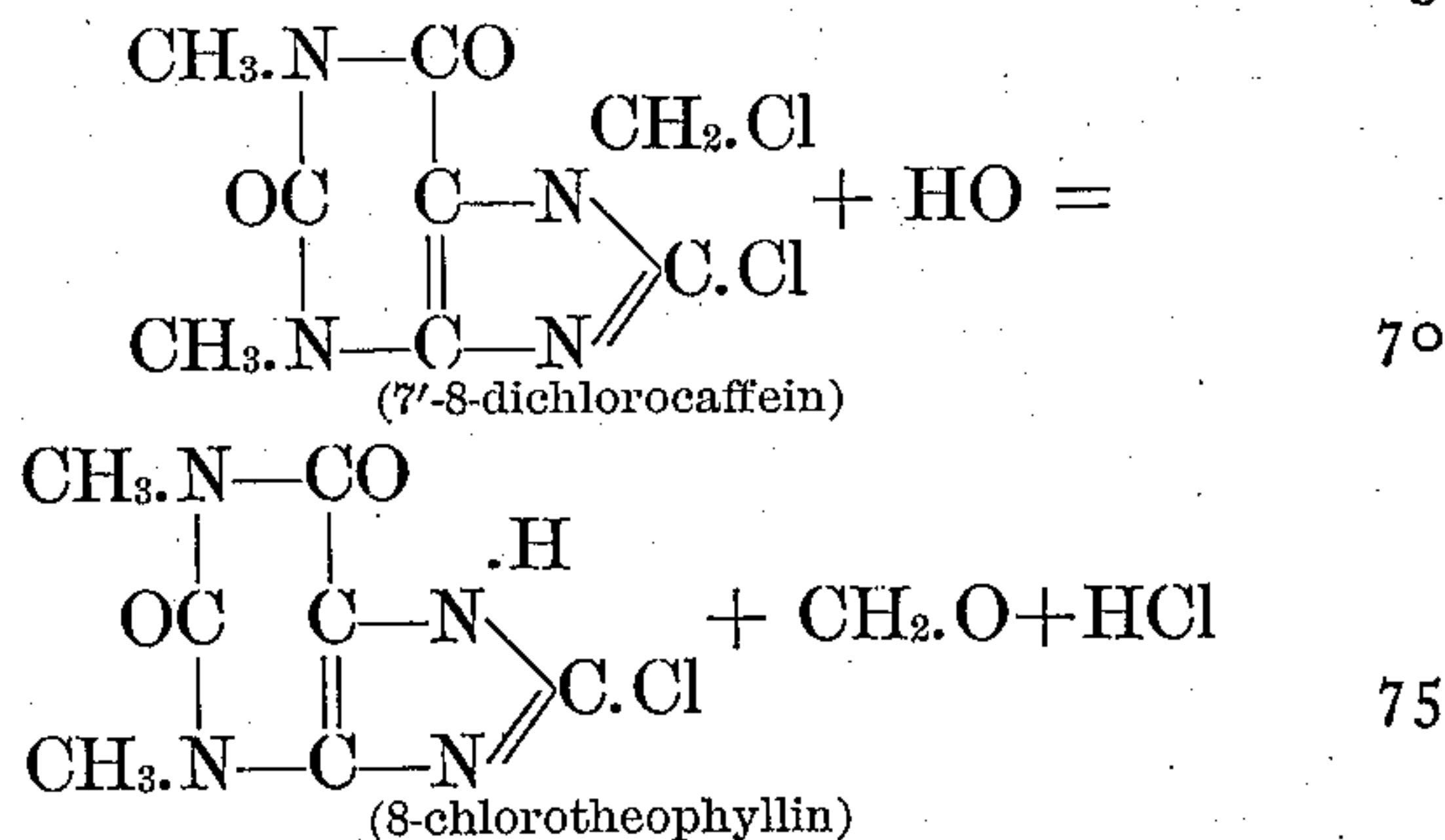
and which, as set forth in said patent, is prepared by subjecting 8-chlorocaffein to the chlorinizing action of a mixture of phosphorus pentachlorid and phosphorus oxychlorid at a temperature of about 150° centigrade.

It was found by this inventor that the chlorination of chlorocaffein may be made to proceed in other ways and take a different course if a solution of chlorin is caused to react upon the chlorocaffein while in a bath of nitrobenzol. Under these conditions no substitution of chlorin for a hydrogen atom of the methyl group bound to the nitrogen atom in the position 3 takes place, as in the substituted xanthin employed under the aforesaid patent; but the chlorin atom takes the place

of hydrogen atom in the methyl group in the position 7, so that in this case a 7'-8-dichlorocaffein, having the structural formula



is obtained. In this 7'-8-dichlorocaffein the chloromethyl group is readily split off similarly to the isomers described in the said United States Patent No. 660,744. If this body is heated with water, dilute acids, or alkalies, it is hydrolized concurrently with the formation of formic aldehyde and hydrochloric acid, 8-chlorotheophyllin or 1.3-dimethyl-8-chloroxanthin being formed according to the equation



The chlorotheophyllin thus obtained may readily be converted into the valuable therapeutic agent theophyllin by reduction methods, as set forth in United States Patent No. 569,489 to C. F. Boehringer & Soehne, assignees of Emil Fischer.

This application is a divisional application of this inventor's application, Serial No. 142,591, filed February 7, 1903.

A detailed description of the invention by reciting what is considered the best manner of carrying the same into effect will now be given.

Forty-five grams of 8-chlorocaffein are suspended in four hundred cubic centimeters of

- nitrobenzol, and into this suspension while maintained at a temperature of 50° centigrade and while constantly stirring or otherwise agitating the same chlorin is introduced in excess. It is preferable to add about 0.5 grams of iodine to the liquor. During the introduction of chlorin solution slowly takes place, and the major portion of the nitrobenzol is then distilled off in a vacuum, the balance of the nitrobenzol being then driven off by means of steam. The residue is then further treated with steam or water in a vaporous or in a gaseous state by passing currents of steam over into the same or otherwise until only a faint odor of formic aldehyde can be noticed. This causes the chlorotheophyllin and a small amount of chlorocaffein to go into solution, while the bulk of the chlorocaffein remains undissolved. The whole is then filtered, and the filtrate is thereupon evaporated to dryness. From the residue the 8-chlorotheophyllin is isolated by extracting with an aqueous solution of ammonia and then precipitating from the ammoniacal solution by acids.
- Having thus fully described the invention, what is claimed as new, and desired to be secured by Letters Patent, is—
1. The process which consists in submitting 8-chlorocaffein to the action of chlorin contained in nitrobenzol.
 2. The process which consists in submitting 8-chlorocaffein to the action of chlorin contained in nitrobenzol, and then driving off the nitrobenzol.
 3. The process which consists in heating 8-chlorocaffein with chlorin contained in nitrobenzol, and then distilling off the nitrobenzol.
 4. The process which consists in heating 8-

chlorocaffein with nitrobenzol containing chlorin in excess.

5. The process which consists in submitting 8-chlorocaffein to the action of chlorin contained in nitrobenzol, driving off the nitrobenzol, and causing steam to act on the residue.

6. The process which consists in heating 8-chlorocaffein with nitrobenzol containing chlorin in excess, driving off the nitrobenzol, and causing steam to act on the residue.

7. The process which consists in submitting 8-chlorocaffein to the action of chlorin contained in nitrobenzol, driving off the nitrobenzol, causing steam to act on the residue, filtering, and drying the filtrate.

8. The process which consists in heating 8-chlorocaffein with nitrobenzol containing chlorin in excess, filtering, and drying the filtrate.

9. The process which consists in submitting 8-chlorocaffein to the action of chlorin contained in nitrobenzol, driving off the nitrobenzol, causing steam to act on the residue, filtering, drying the filtrate, and isolating the resultant 8-chlorotheophyllin.

10. The process which consists in heating 8-chlorocaffein with nitrobenzol containing chlorin in excess, filtering, drying the filtrate, and isolating the resultant 8-chlorotheophyllin.

In testimony whereof I affix my signature in the presence of two witnesses.

MITFORD C. MASSIE,
Administrator of the estate of Fritz Ach,
deceased.

Witnesses:

E. O. HILDEBRAND,
F. H. SCHOTT.