

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.

ALKOXY-CAFFEIN AND PROCESS OF MAKING SAME.

SPECIFICATION forming part of Letters Patent No. 757,330, dated April 12, 1904.

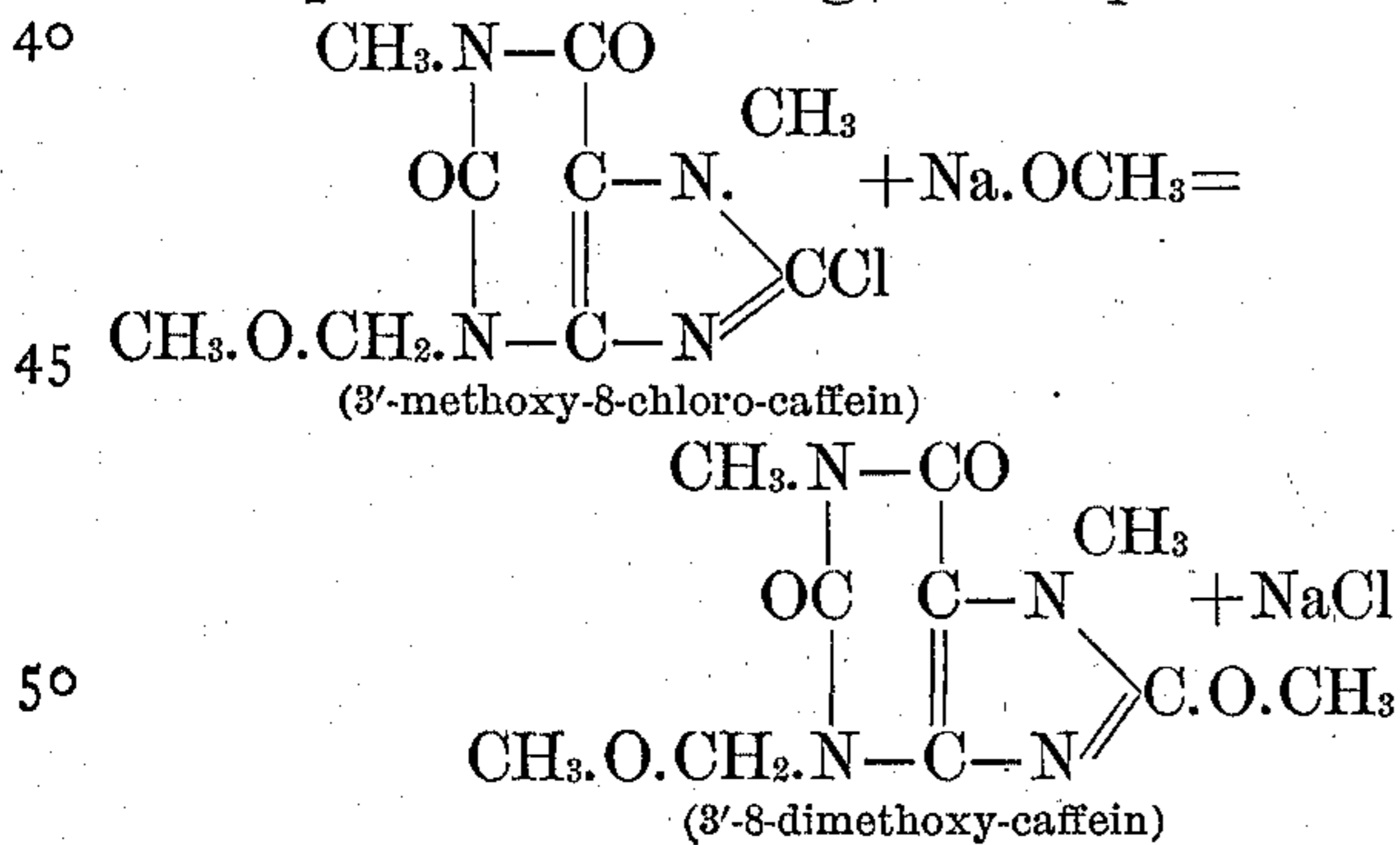
Original application filed April 16, 1898, Serial No. 677,857. Divided and this application filed February 10, 1903. Serial No. 142,777. (Specimens.)

To all whom it may concern:

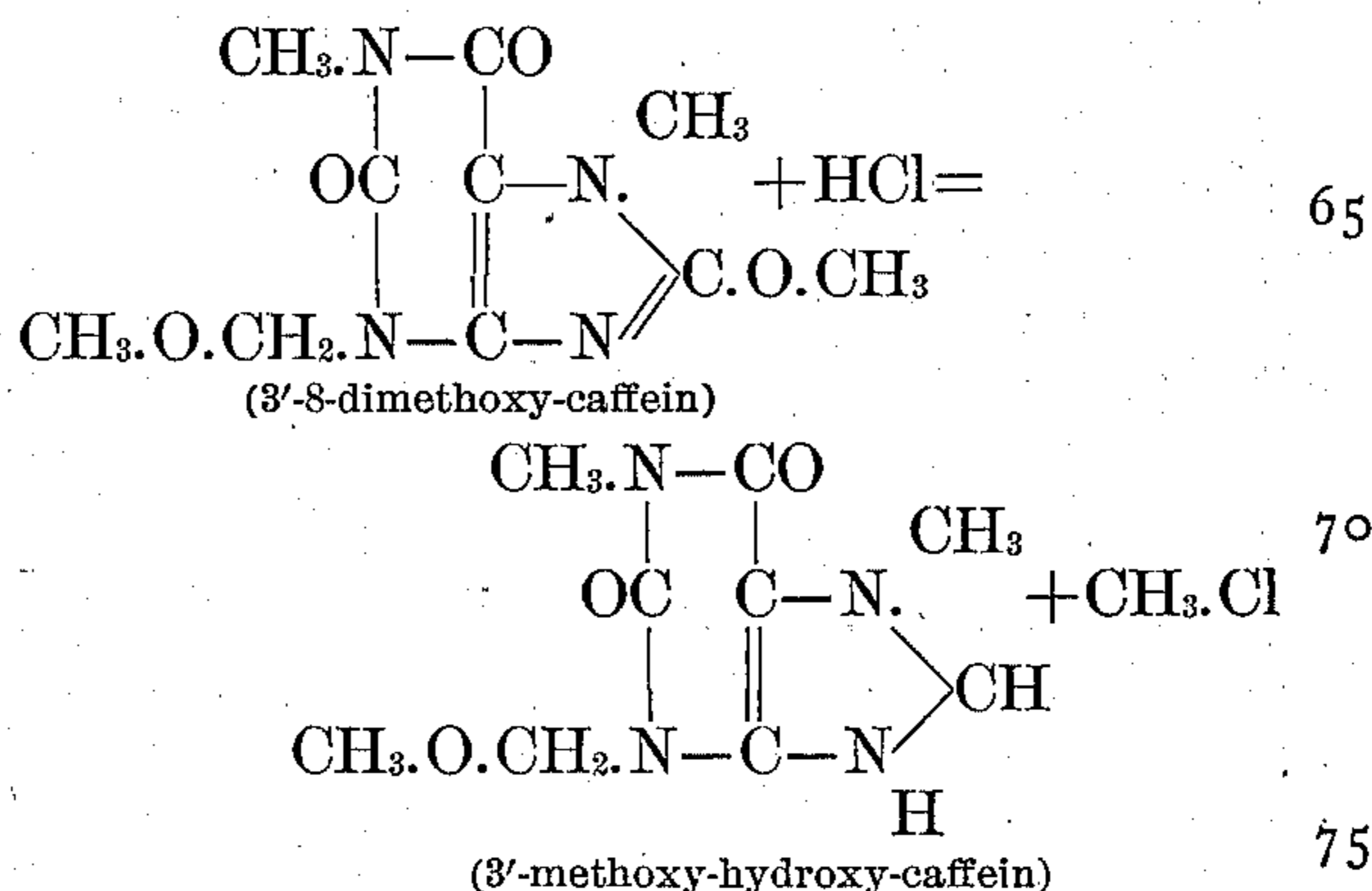
Be it known that FRITZ ACH, deceased, late a citizen of Germany, and a resident of Mannheim, Germany, did invent new and useful Improvements in Alkoxy-Caffeins and Method of Preparing Same; and I, MITFORD C. MASSIE, the duly-constituted administrator of the estate of said FRITZ ACH, deceased, do hereby 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 present invention relates to the art of preparing caffein derivatives, and in particular those new derivatives having the group $\text{C}_n\text{H}_{2n+1}\text{O.CH}_2$ bound to the nitrogen atom occupying the position 3 in the caffein or purin molecule, which compounds are to be designated by the generic term "alkoxy-caffeins."

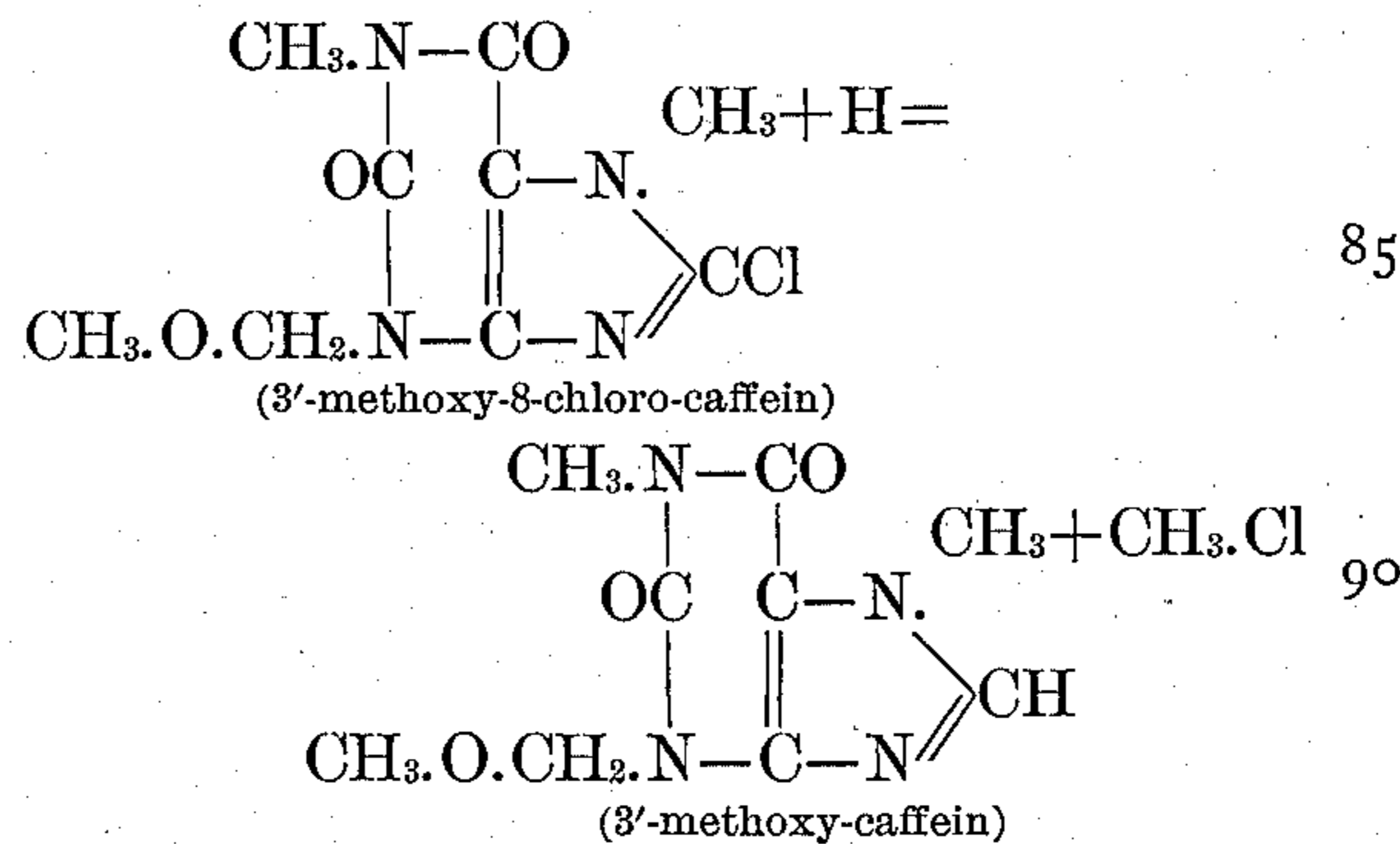
In this inventor's patent, No. 707,812, dated August 26, 1902, of which the present application is a division, there are described and claimed one class of the said compounds—viz., 3'-alkoxy-8-chloro-caffeine—and the method of preparing the same. As stated in said patent, the inventor discovered that in these substituted chloro-caffeins the chlorine atom attached to the carbon atom in the position 8 may, just as in chloro-caffeine proper, be replaced by hydrogen, methoxyl, ethyl, hydroxyl, or the amido group. We are thus enabled to obtain series of new uric-acid and xanthin derivatives. Thus, for example, if we cause an alkali-methylate, such as sodium-methylate, to act upon 3'-methoxy-8-chloro-caffeine, obtained by the action of methyl alcohol upon 3'-8-dichloro-caffeine, the new compound 3'-8-dimethoxy-caffeine is produced according to the equation:



By proceeding indirectly by way of this methoxy compound the chlorine atom (8) is in this case replaced by hydroxyl, just as in the case of chloro-caffeine itself. Thus if 3'-8-dimethoxy-caffeine is cautiously heated with dilute hydrochloric acid the methoxyl group bound to the carbon atom (8) is split off as methyl-chlorid, 3'-methoxy-hydroxy-caffeine being formed according to the equation:



If 3'-methoxy-8-chloro-caffeine is submitted to the action of reducing agents, the halogen atom is exchanged for hydrogen, 3'-methoxy-caffeine being obtained according to the equation:



The latter process of preparing the 3'-methoxy-caffeine and the product itself are not herein claimed, since they form the subject-matter covered in Patent No. 667,380, dated February 5, 1901. They are simply referred to by way of illustration.

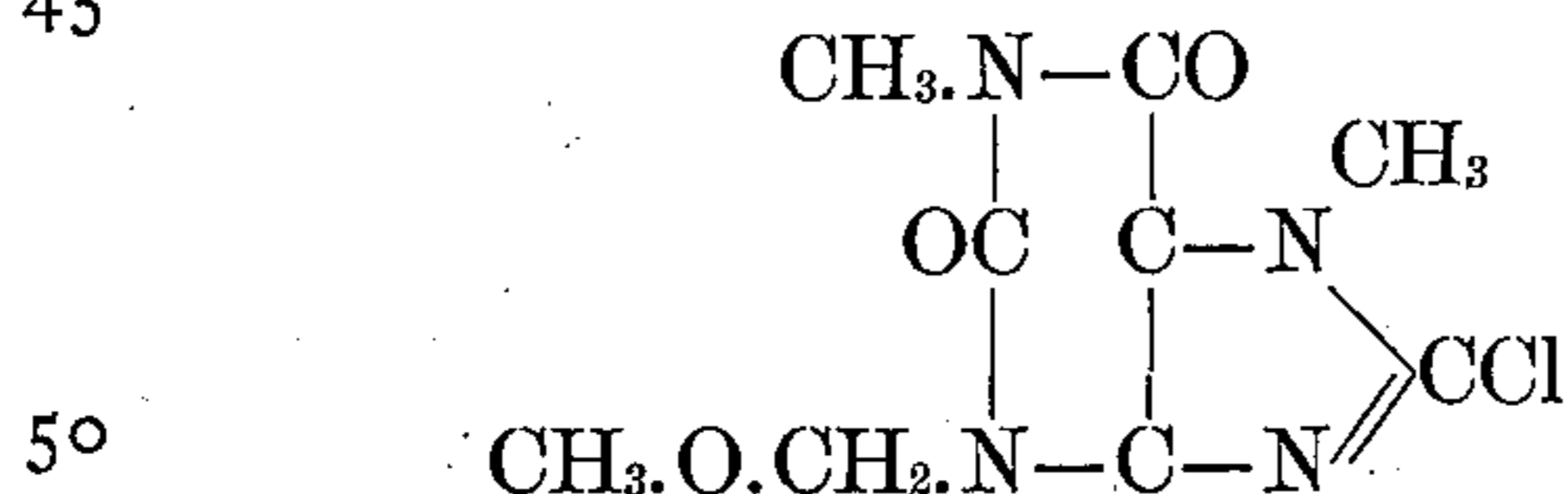
The present invention consists in the methods of treatment of the 3'-alkoxy-8-chloro-caffeine for the purpose of replacing the chlorine atom in the position 8 by hydrogen or its

radicals above mentioned and in such other features, steps, and combinations of steps as will hereinafter be set forth.

The invention will now be illustrated by the following detailed description of processes and the resultant compounds, which constitute what are considered the preferred embodiment of the said invention.

1. *Preparation of 3'-8-dimethoxy-caffein.*—

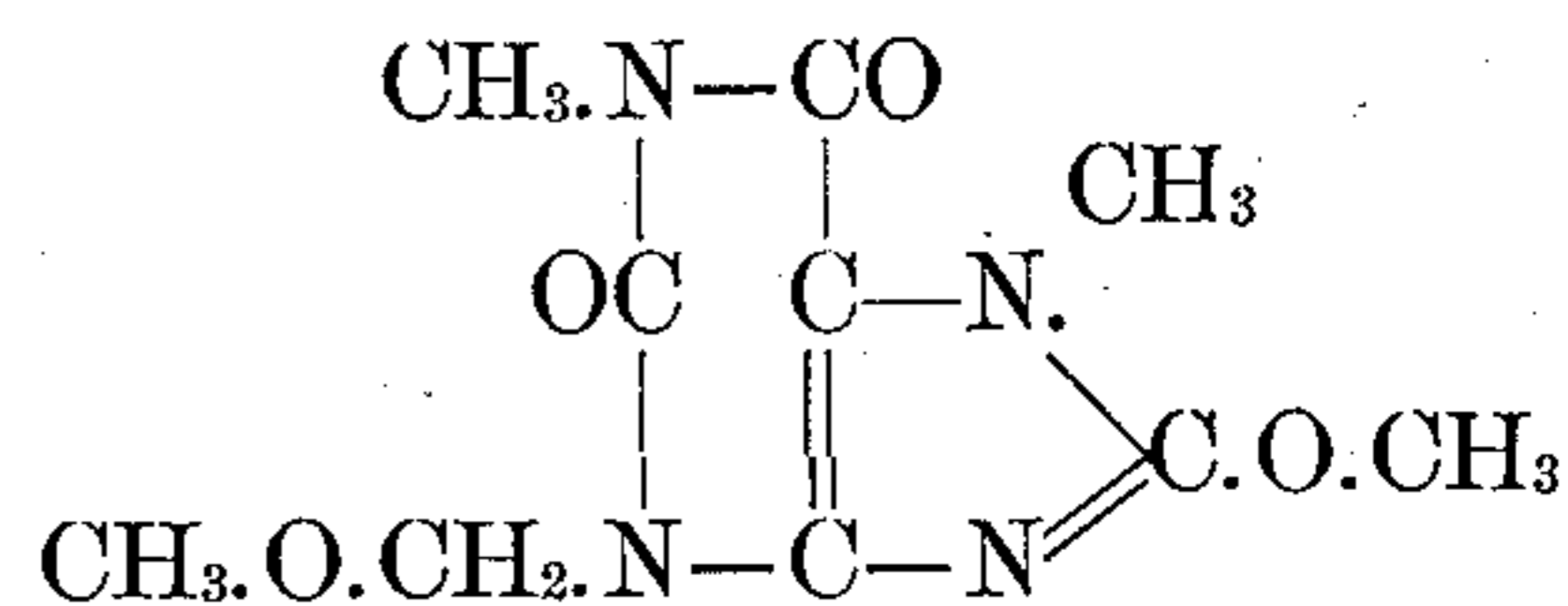
For the purpose of a full disclosure the starting material 3'-methoxy-8-chloro-caffein and the method of preparing the same will be first described. For this purpose 3'-methoxy-caffein, a compound which, together with its method of production, is described and claimed in Patent No. 667,380, dated February 5, 1901, granted to C. F. Boehringer & Soehne, as assignees of this inventor, will be used as the starting material. In preparing the 3'-methoxy-8-dichloro-caffein in its pure and crystalline condition it is not necessary to start with the 3'-8-dichloro-caffein; but one may employ directly the syrup or resinous substance which according to the above patent serves for the production of the crystalline product 3'-8-dichloro-caffein. Such syrup is boiled, together with about twenty times its weight of absolute methyl alcohol, for from five to six hours in a reflux cooler. The alcohol is then distilled off completely, and the residue is taken up with ether and washed with water to remove the hydrochloric acid. The ether is evaporated and a little (about two parts) methyl alcohol is poured over the residue, which after some time begins to solidify to a crystalline mass. This crystalline mass is then redissolved in methyl alcohol and recrystallized therefrom, whereby the new body 3'-methoxy-8-chloro-caffein is obtained in the form of fine shining needles felted together asbestos-like. An analysis of them gives figures corresponding to the formula $C_9H_{11}N_4O_3Cl$, the constitution of the new compound being represented in the structural formula



This new compound 3'-methoxy-8-chloro-caffein melts at 129° to 130° centigrade. With dilute nitric acid or with chlorin water it gives a strong murexid reaction. It is readily soluble in boiling water, hot alcohol, benzol, acetone, acetic ether, and chloroform. It is, moreover, readily soluble in fuming hydrochloric acid. If this solution is heated for some time on the water-bath, however, decomposition takes place, chloro-paraxanthin, which separates in the form of coarse colorless prisms, being formed, attended by a splitting off of formic-aldehyde and methyl-chlorid.

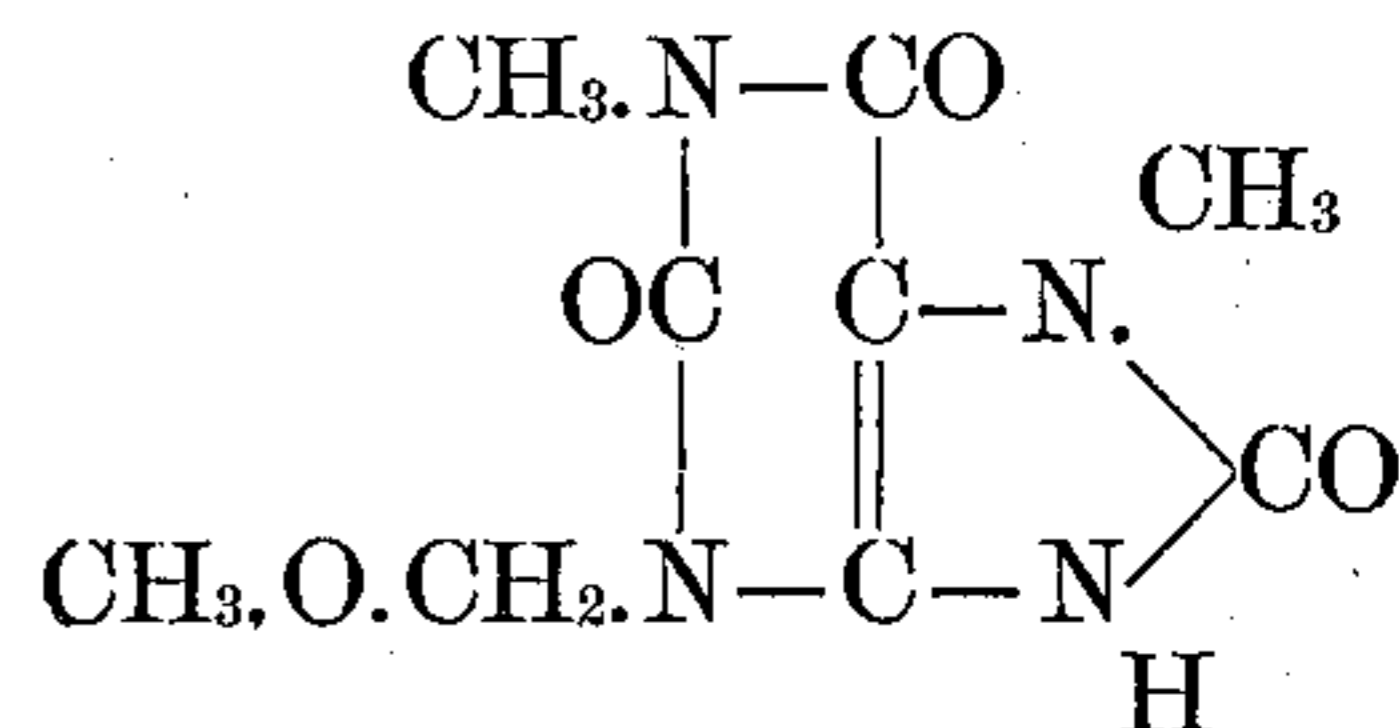
For the manufacture of the 3'-8-dimethoxy-

caffein one part, by weight, of 3'-methoxy-8-chloro-caffein is dissolved in ten parts, by weight, of methyl alcohol and heated to the boiling-point for about half an hour, together with somewhat more than the necessary quantity, according to computation of sodium-methylate. The mass is then evaporated to drive off the alcohol and the crystalline residue taken up with water. The resultant product after being recrystallized from dilute alcohol is then obtained in the form of fine needles aggregated concentrically, whose analysis shows them to have the formula $C_{10}H_{14}N_4O_4$. This new compound 3'-8-dimethoxy-caffein has the structural formula



It melts at 153° centigrade and gives a strong murexid reaction with dilute nitric acid or with chlorin water. It is readily soluble in hot water, methyl alcohol, and ethyl alcohol and benzol, and in cold acetone, chloroform, and acetic ether. In alkalies it is insoluble, but readily soluble in concentrated hydrochloric acid, by which, however, it is rapidly decomposed.

2. *Preparation of 3'-methoxy-8-hydroxy-caffein.*—In this process 3'-8-dimethoxy-caffein just described serves as a starting material, one part of the same, by weight, in a finely-powdered condition, being cautiously heated on the water-bath, together with about ten parts of hydrochloric acid of ten per cent. strength, the heating being continued until solution has taken place. During this treatment a copious evolution of methyl chlorid occurs. The solution being completed, the same is cooled with ice-water, whereby fine colorless acicular crystals are thrown out. After standing for several hours (four to five) the liquor is drained from the crystals by filtration, and they are washed with ice-water. The resultant product is recrystallized from methyl alcohol, whereby coarse colorless needles are obtained whose formula, according to analysis, is $C_9H_{11}N_4O_4$. This 3'-methoxy-hydroxy-caffein has the structural formula



When the same is heated rapidly, it softens at about 220° centigrade, and it melts at from 228° to 229° centigrade. It is readily soluble in water, hot methyl alcohol, and hot ethyl alcohol and also very soluble in alkalies, including ammonia. An ammoniacal solution of the same when nitrate of silver is added

thereto gives rise to a silver salt of the same, after boiling off the ammonia said silver salt crystallizing in the form of fine needles. 3'-methoxy-hydroxy-cafein gives a strong murexid reaction.

What is claimed, and desired to be secured by Letters Patent of the United States, is—

1. The process of preparing 3'-8-dialkoxy-cafein, which consists in treating 3'-alkoxy-8-chloro-cafein with alkali-alkylate.

2. The process of preparing 3'-8-dimethoxy-cafein, which consists in treating 3'-methoxy-8-chloro-cafein with sodium-methylate.

3. The process which consists in preparing 3'-8-dimethyl-cafein, which consists in dissolving 3'-methoxy-8-chloro-cafein in methyl alcohol and heating the solution to the boiling-point together with sodium-methylate, in the proportions, substantially as stated.

4. The process of preparing 3'-8-dimethyl-cafein which consists in dissolving 3'-methoxy-8-chloro-cafein in methyl alcohol and heating the solution to the boiling-point, together with sodium-methylate, in the proportions substantially as stated, then evaporating and taking up the residue with water.

5. The process of preparing 3'-alkoxy-8-hydroxy-cafein, which consists in treating dialkoxy-cafein with hydrochloric acid.

6. The process of preparing 3'-methoxy-8-hydroxy-cafein, which consists in heating 3'-8-dimethoxy-cafein with hydrochloric acid.

7. The process which consists in heating 3'-8-dimethoxy-cafein on the water-bath, together with dilute hydrochloric acid until solution takes place, all in the proportions, substantially as specified.

8. The process of preparing 3'-methoxy-8-hydroxy-cafein, which consists in heating 3'-8-dimethoxy-cafein on the water-bath, together with dilute hydrochloric acid until solution takes place, all in the proportions substantially as specified, then cooling, then allowing to stand, and then draining the resultant crystals.

9. The process of preparing 3'-methoxy-8-hydroxy-cafein, which consists in heating 3'-dimethoxy-cafein on the water-bath, together with dilute hydrochloric acid until solution takes place, all in the proportions substantially as specified, then cooling, then allowing to stand, then draining the resultant crystals, and, finally, after washing the crystals with ice-water, recrystallizing from methyl alcohol.

10. The process which consists in acting upon 3'-8-dichloro-cafein with an alcohol and treating the resultant 3'-alkoxy-8-chloro-cafein with an alkali-methylate.

11. The process which consists in acting upon 3'-8-dichloro-cafein with methyl-alcohol and then treating the resultant 3'-methoxy-8-chloro-cafein with sodium-methylate.

12. The process which consists in acting upon 3'-8-dichloro-cafein with an alcohol, then treating the resultant 3'-alkoxy-8-chloro-cafein with alkali-methylate and, finally, treating the resultant dialkoxy-cafein with HCl.

13. The process which consists in acting upon 3'-8-dichloro-cafein with methyl-alcohol, then treating the resultant 3'-methoxy-8-chloro-cafein with sodium-methylate, and, finally, acting upon the resultant 3'-8-dimethoxy-cafein with hydrochloric acid.

14. As a new chemical compound, 3'-methoxy-8-hydroxy-cafein having the structural formula hereinbefore given, which crystallizes in coarse colorless needles having a melting-point of about 228° to 229° centigrade, which is readily soluble in water, hot methyl alcohol and hot ethyl alcohol, and is also soluble in alkalies, including ammonia, and which gives a murexid reaction.

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

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

Witnesses:

ANTON GLOETZNER,
ALBANUS S. T. JOHNSON.