

UNITED STATES PATENT OFFICE.

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TRIMETHYL-PSEUDO-URIC ACID AND PROCESS OF PREPARING SAME.

SPECIFICATION forming part of Letters Patent No. 667,388, dated February 5, 1901.

Application filed December 28, 1897. Serial No. 664,083. (No specimens.)

To all whom it may concern:

Be it known that I, EMIL FISCHER, a citizen of the Empire of Germany, residing at Berlin, in the Empire of Germany, have invented certain new and useful Improvements in Preparing Uric Acids and Their Derivatives; and I do hereby declare the following to be a full, clear, and exact description of the invention, such as will enable others skilled in the art to which it appertains to make and use the same.

This invention relates to the preparation of uric acid and its derivatives, and in particular the manufacture of the same from the corresponding pseudo-uric acids.

Hitherto pseudo-uric acid could only be converted into uric acid by fusing or melting it together with oxalic acid. In operating with dimethyl-pseudo-uric acid in which the two methyl groups are bound to the two nitrogen atoms of the alloxan nucleus the same result was also obtained by boiling with the anhydrid of acetic acid and zinc chlorid, as set forth in the article by E. Fischer and L. Ach in *Berichte der Deutschen-Chemischen Gesellschaft*, Vol. 28, page 2473. Both processes are impracticable for industrial purposes and are only scientifically valuable. I have found that these conversions may be effected in a practically available manner if the pseudo-uric acids are acted on in the wet way, preferably in the presence of mineral acids, although in some cases the mere heating of an aqueous solution is sufficient.

In order to make my invention, which consists in the methods, steps, and features pointed out in the claims hereunto annexed, fully and clearly understood by those skilled in the art, I will now describe a number of examples embodying the same. The proportions are all given by weight.

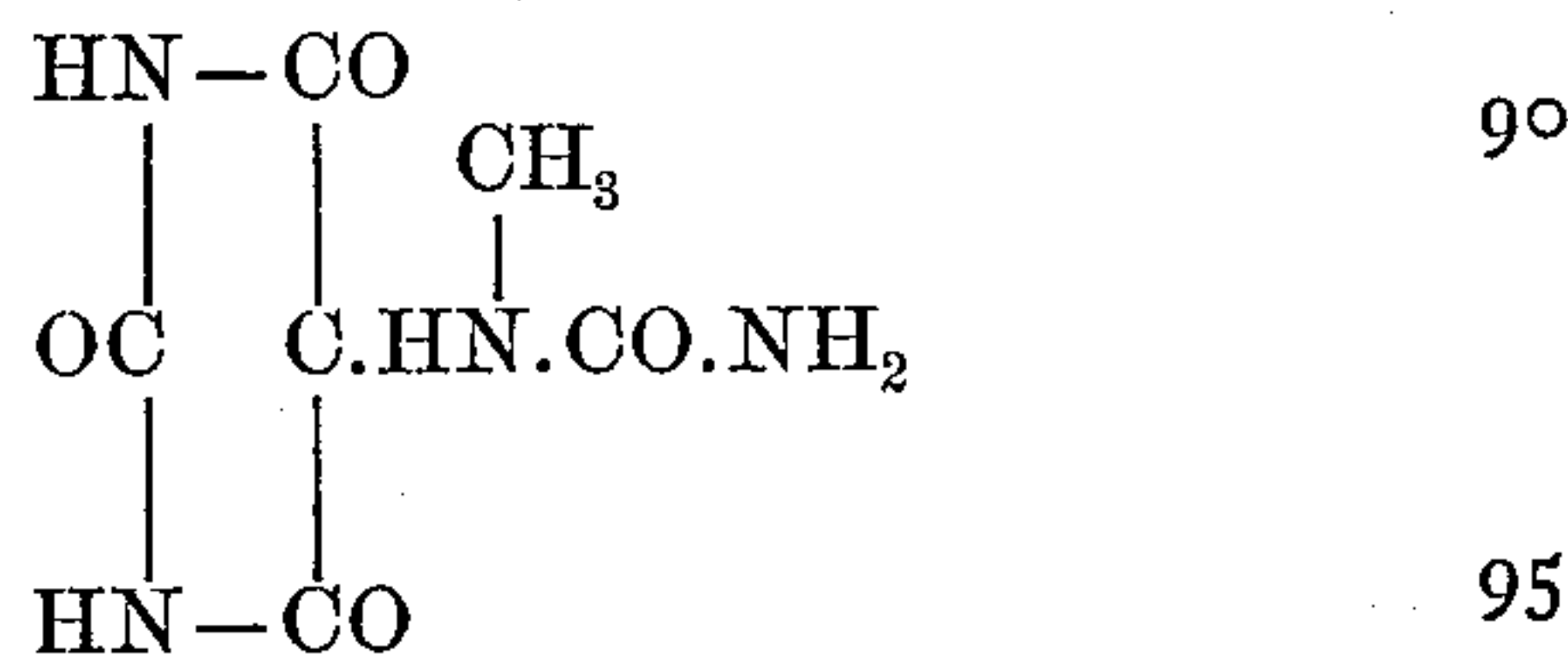
1. *Conversion of pseudo-uric acid into uric acid.*—To one part of finely-powdered pseudo-uric acid I add five hundred parts of hydrochloric acid of twenty-per-cent. strength and boil the mixture until complete solution takes place, which occurs after some time. The liquid is then evaporated over an open fire until it is reduced to about the one-fifteenth part of its original volume. As a result of this treatment the largest portion of the uric acid which has been formed is separated out

or precipitated in crystalline form. This separation takes place already while the liquid is still warm. The liquid is then allowed to cool and diluted with water (about ten parts) and then filtered. If pure starting material is employed in this process, the uric acid obtained is completely colorless and the yield represents over eighty per cent. of the pseudo-uric acid employed.

2. *Preparation of gamma-dimethyl-uric acid.*—I take one part of the dimethyl-pseudo-uric acid, which has been described by Tschow in *Berichte der Deutschen-Chemischen Gesellschaft*, Vol. 27, page 3088, and add to it seven parts of hydrochloric acid of twenty-per-cent. strength and heat on the water-bath. A clear solution forms in the beginning of the action, and after about fifteen minutes the resultant gamma-dimethyl-uric acid crystallizes out of the solution. After thus heating for an hour the mass is allowed to cool and the crystals are separated by filtration. In this process the yield also represents about eighty per cent. of the pseudo-compound employed.

Instead of a twenty-per-cent. hydrochloric acid a one-per-cent. acid may be employed; but in this case it is necessary to boil for from eight to ten hours.

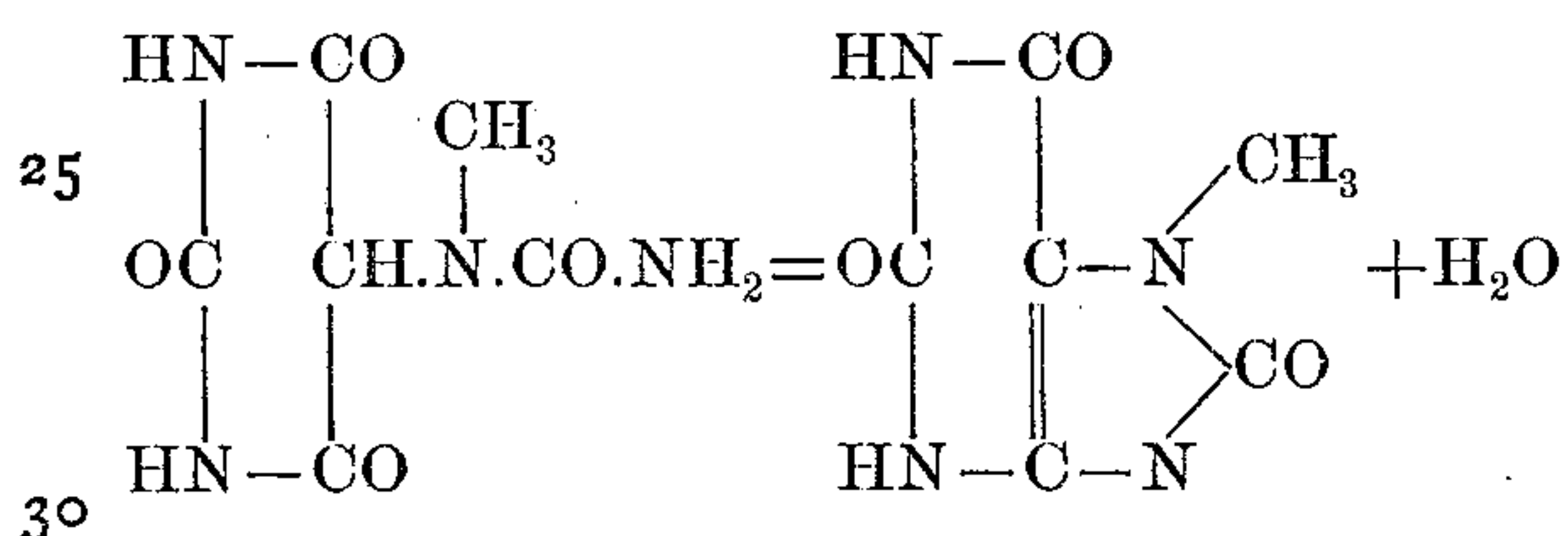
3. *Preparation of gamma-monomethyl-uric acid.*—By a reaction the same as that employed for the production of pseudo-uric acid (see Liebig and Wöhler in *Annalen*, Vol. 26, page 266, and Baeyer, *Ibid*, Vol. 127, page 3) I may obtain monomethyl-pseudo-uric acid having the formula



if in the place of the sulfite of ammonium there employed a solution of sulfite of methylamin is taken. The resultant gamma-methyl-pseudo-uric acid dissolves in about twenty-three parts of boiling water, and on cooling the solution it is thrown out in the form of very small colorless crystals containing one molecule of water of crystallization. The con-

version into the corresponding uric acid takes place more rapidly than in the two above-described examples. If this monomethylpseudo-uric acid is heated to boiling with 5 twenty times its quantity of hydrochloric acid of twelve-per-cent. strength a clear solution is first formed, and the crystallization of the resultant gamma-monomethyl-uric acid begins already after the lapse of a few minutes and 10 while the liquid is warm. After having heated the mass for about half an hour the reaction is closed. The same is then allowed to cool, when the balance of the methyl-uric acid is thrown out to the largest extent in the form 15 of crystals. In this case also the reaction proceeds almost quantitatively, and the resultant product is in every respect identical with the gamma-monomethyl-uric acid which has first been obtained by me from theobromin. 20 (See *Berichte*, Vol. 28, page 2492.)

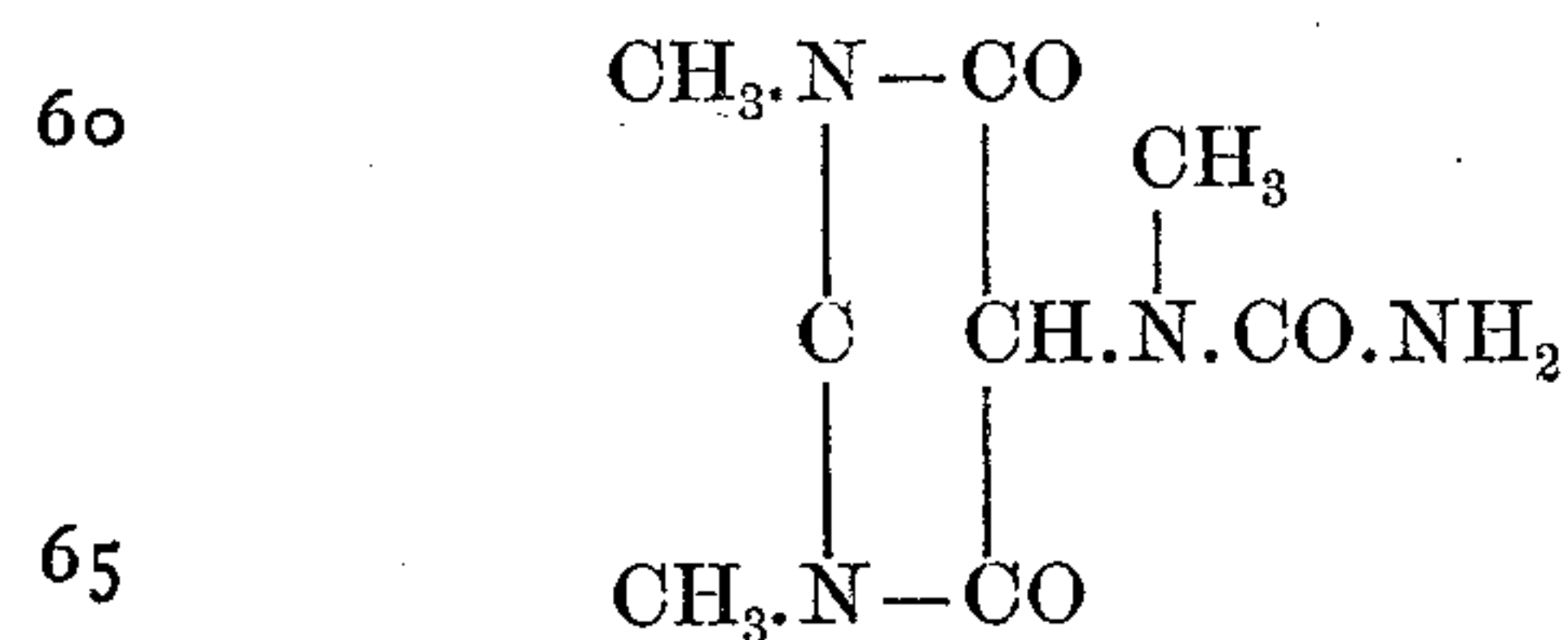
The reaction takes place according to the equation



If instead of the twelve-per-cent. hydrochloric acid a one-per-cent. acid is employed, the reaction takes place in the same way, but requires a correspondingly longer heating. The crystallization of the gamma-monomethyl-uric acid then begins after the lapse of about a half-hour, and after one and one-half hours the amount of the resultant uric acid will have already reached two-thirds of the pseudo-uric acid employed. In this example the coöperation of the mineral acid is not even necessary, since the same reaction takes place when heating a mere aqueous solution of the methyl-pseudo-uric acid to 100° centigrade. Only under these conditions it is much slower.

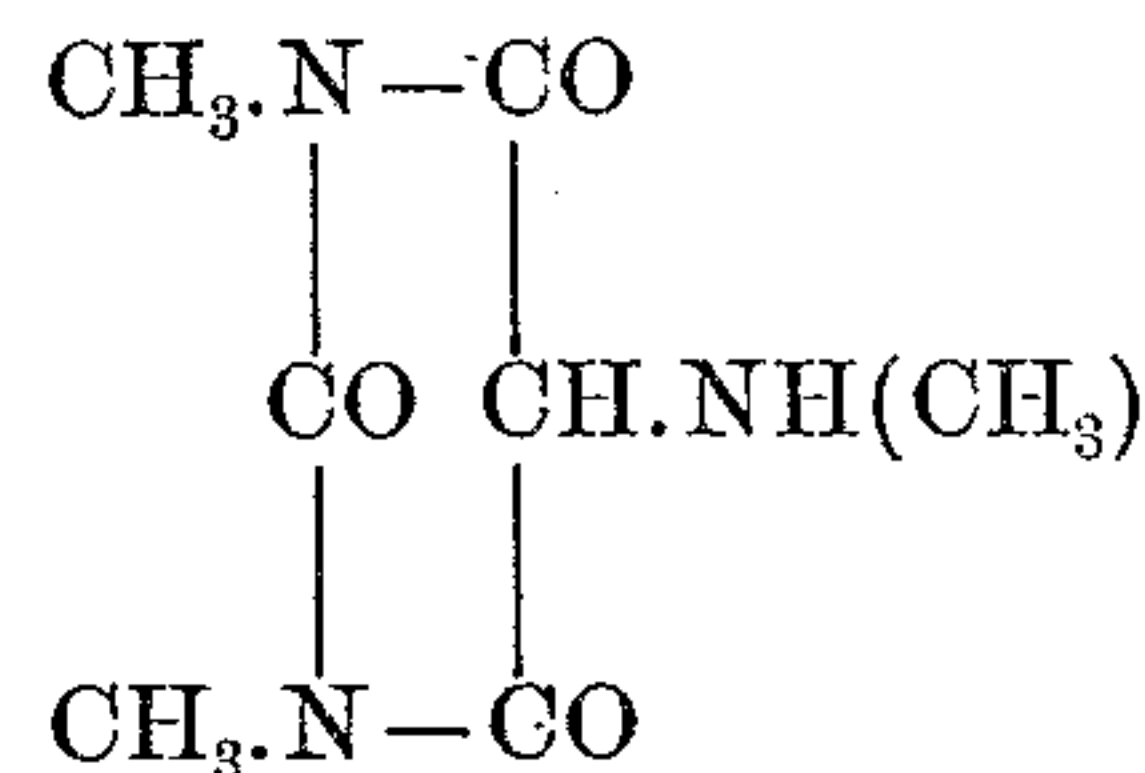
If, *e. g.*, an approximately-saturated aqueous solution of monomethyl-pseudo-uric acid is heated on the water-bath, the separation of the gamma-monomethyl-uric acid commences
50 after the lapse of three-quarters of an hour; but even at the end of three hours the conversion will have taken place only to the extent of one-third. Hence for the practical utilization of the reaction the addition of mineral
55 acid is to be preferred.

4. *Conversion of 1-3-7-trimethyl-pseudo-uric acid into hydroxycaffein.*—1-3-7-trimethyl-pseudo-uric acid, having the formula:



and which is a new compound, first discovered

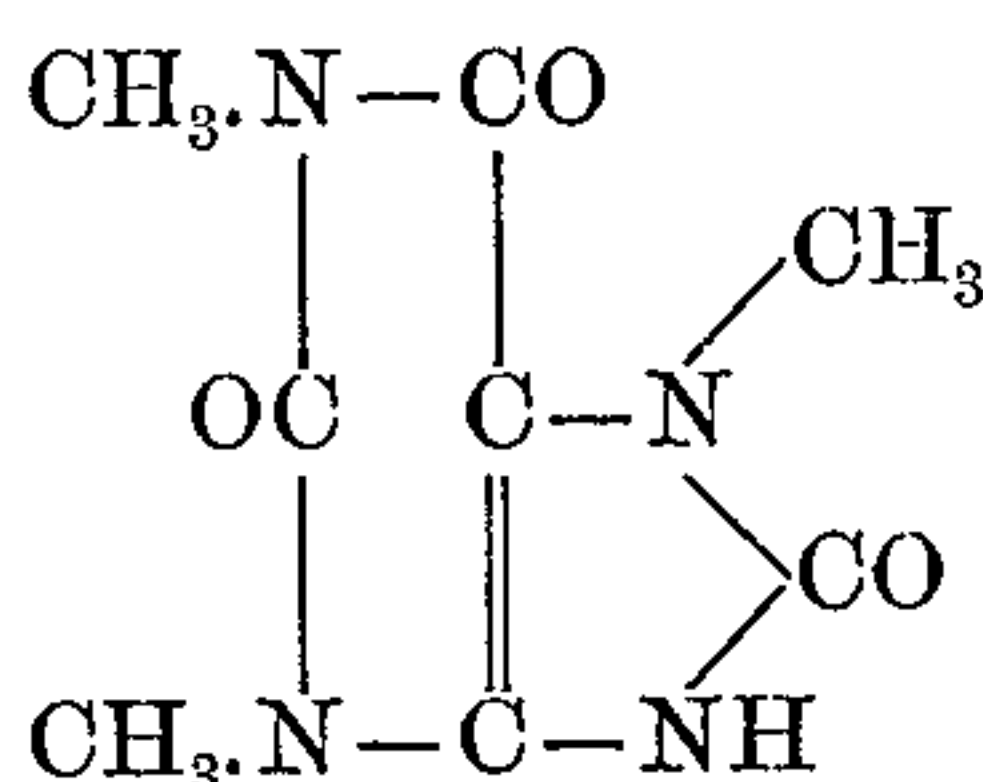
by me, may be obtained from dimethyl-alloxan according to known reactions by employing sulfite of methylamin instead of the sulfite of ammonium. (See E. Fischer, *Berichte der Deutschen-Chemischen Gesellschaft*, Vol. 30, page 564.) This method of preparation in detail is as follows: When acting on dimethyl-alloxan with neutral sulfite of methylamin, there is formed first a product of addition corresponding to the compounds of the ketones with bisulfites. The same is constant in the cold and may be obtained in a crystalline form in the following manner: Five grams of commercial solution of methylamin containing about thirty-three per cent. of the base are saturated with sulfur dioxide, and then about five grams more of methylamin are added until the odor of the base becomes perceptible. Thereupon the same is neutralized with carbonic-acid gas, whereupon a solution of five grams dimethyl-alloxan in five grams water is added. If the liquid remains at the ordinary temperature, colorless needles are soon separated out in copious quantity, which are then recrystallized from a small quantity of warm water. If, however, the above mixture of dimethyl-alloxan and methylamin sulfite, together with the separated crystals, is allowed to stand at ordinary temperature, the crystals will go into solution after the lapse of about twenty-four hours, and the solution now evidently contains the salt of a thio acid, since on heating with dilute hydrochloric acid abundant quantities of sulfuric acid are formed. On heating the solution to from 60° to 70° centigrade and maintaining this temperature for one hour this thio salt is rapidly formed, this reaction being attended by a further reaction which leads to the formation of 1-3-7-trimethyluramil, which on cooling the solution is separated from the same in crystalline form. This trimethyluramil, which has the structural formula:



and which forms the intermediate product in my method of preparing the above trimethylpseudo-uric acid, is a very stable body when dry and remains unchanged even in contact with air for a considerable time at ordinary temperatures. When in a moist condition or in aqueous solution, the access of air soon colors it purple-red. When heated to over 100° centigrade in the capillary tube, it also turns red, and when rapidly heated to 200° centigrade it is entirely decomposed without any sharply-defined melting action. In hot water it is soluble with comparative facility, crystallizing out of the same in the form of colorless needles. It is still more soluble in dilute

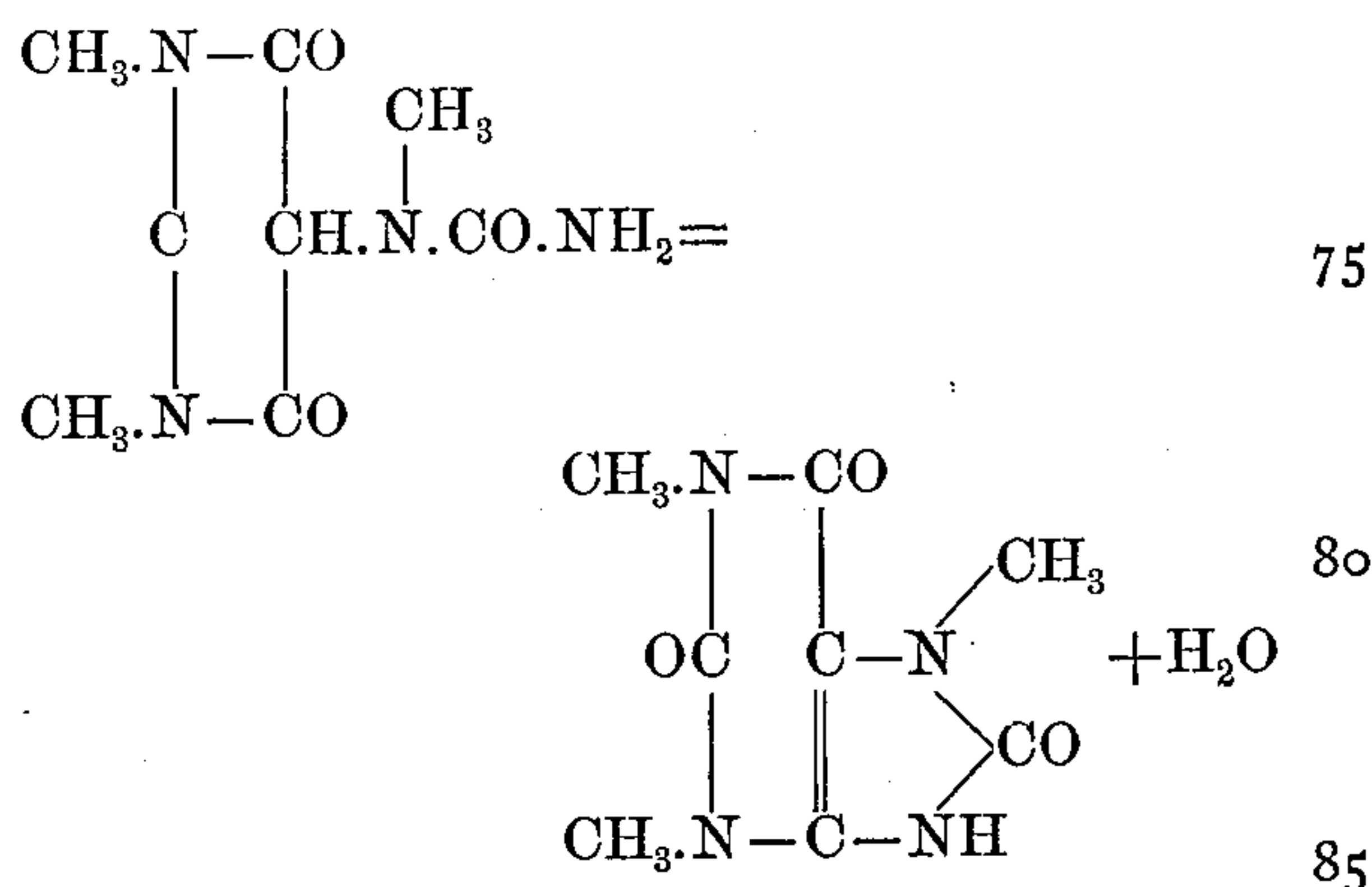
hydrochloric acid. It is also soluble in alkalis, but may be separated therefrom by immediately neutralizing with acetic acid. It is destroyed on boiling with alkalis.

5 The 1-3-7-trimethyl-uric acid is very readily prepared from the trimethyluramil by heating the latter with a solution of cyanate of potassium. The crude product may be directly employed for this purpose if the same
10 has been freed from ammonium salts by careful washing with cold water. For example, three grams of the 1-3-7-trimethyluramil are heated on the water-bath with two grams pure potassium dissolved in five cubic centimeters
15 of water. A clear solution soon forms and after heating for half an hour the conversion will have been completed. If after cooling the resulting colorless liquid is treated carefully with hydrochloric acid, the 1-3-7-trimethyl-uric acid will be precipitated in the
20 form of a crystalline powder. The trimethylpseudo-uric acid so obtained is soluble in about four parts hot water and on cooling crystallizes therefrom in the form of colorless obliquely-truncated prisms of considerable
25 size which contain one molecule of water of crystallization. This acid has no constant melting-point. On heating the same rapidly it will melt with attendant decomposition in the neighborhood of 195° centigrade.
30 When slowly heated, a partial melting takes place between 180° and 190° centigrade, a product of decomposition being then formed which does not melt at 300° centigrade. In alcohol it is only soluble with difficulty even
35 when heated. In forming hydrochloric acid (specific gravity 1.19) it is readily soluble at ordinary temperature. This trimethylpseudo-uric acid is, as I have found, readily converted into the corresponding trimethyl-uric acid or hydroxycaffein. For this purpose
40 one part of the trimethylpseudo-uric acid is heated, together with ten parts of hydrochloric acid of one-per-cent. strength, on the water-bath. A clear solution first forms, and after the lapse of about a half-hour the trimethyl-uric acid begins to separate out. At the end of one and one-half hours the mass
45 is allowed to cool, and the crystalline precipitate which has formed is separated by filtration. The reaction proceeds almost quantitatively. The trimethyl-uric acid is identical with hydroxycaffein, which, according to my recent researches, does not possess the molecular
50 structure formerly attributed to it, but must have the formula:



65 since by methylating in the wet way it is readily converted into tetramethyl-uric acid.

This new manner of preparing hydroxycaffein is hence, generically, the same process as the conversion of pseudo-uric acid into uric acid proper, and it corresponds to the equation: 70



Just as in the previous example, the reaction will take place also in the absence of mineral acids; but in that case a much longer time is required for its completion. If, for example, a ten-per-cent. aqueous solution of the trimethylpseudo-uric acid is heated to 100° centigrade, the crystallization of hydroxycaffein does not begin until after the lapse of several hours, and even after five hours the conversion will be scarcely half completed. 95

In the hereinbefore-described processes the hydrochloric acid may be replaced by sulfuric acid and other mineral acids, and it is to be observed, therefore, that my invention, generically considered, is not confined to the particular mineral acid employed. 100

The term "pseudo-uric acid" as employed in the claims is to be understood as covering both the pseudo-uric acid proper as well as its alkyl derivations—the alkylpseudo-uric acids. 105

What I claim, and desire to secure by Letters Patent, is—

1. The process of preparing trimethylpseudo-uric acid which consists in treating 110 dimethyl-alloxan with sulfite of methylamin.

2. As a new chemical compound, trimethylpseudo-uric acid having the formula above given and which dissolves in about four parts of hot water, and crystallizes therefrom in 115 colorless, obliquely-truncated prisms which contain one molecule of water of crystallization.

3. The process of preparing a uric acid which consists in heating a pseudo-uric-acid 120 solution.

4. The process of preparing a uric acid which consists in heating a pseudo-uric acid in the presence of a mineral acid.

5. The process of preparing a uric acid 125 which consists in adding hydrochloric-acid solution to a pseudo-uric acid and heating the mixture.

6. The process of preparing trimethyl-uric acid or hydroxycaffein which consists in heating trimethylpseudo-uric acid in solution. 130

7. The process of preparing trimethyl-uric

acid which consists in heating trimethyl-pseudo-uric acid in the presence of a mineral acid.

8. The process of preparing trimethyl-uric
5 acid which consists in adding hydrochloric acid to trimethyl-pseudo-uric acid and heating the mixture.

9. The process of preparing trimethyl-uric acid which consists in adding one part of tri-

methyl-pseudo-uric acid to ten parts of one- 10
per-cent. hydrochloric acid and heating the mixture on the water-bath, and then cooling.

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

EMIL FISCHER.

Witnesses:

CHAS. H. DAY,
HENRY HASPER.