

UNITED STATES PATENT OFFICE.

FRITZ ACH, OF MANNHEIM, GERMANY, ASSIGNOR TO C. F. BOEHRINGER & SOEHNE, OF WALDHOF, GERMANY.

PROCESS OF MAKING URIC-ACID DERIVATIVES.

SPECIFICATION forming part of Letters Patent No. 632,828, dated September 12, 1899.

Application filed November 13, 1897. Serial No. 658,453. (Specimens.)

To all whom it may concern:

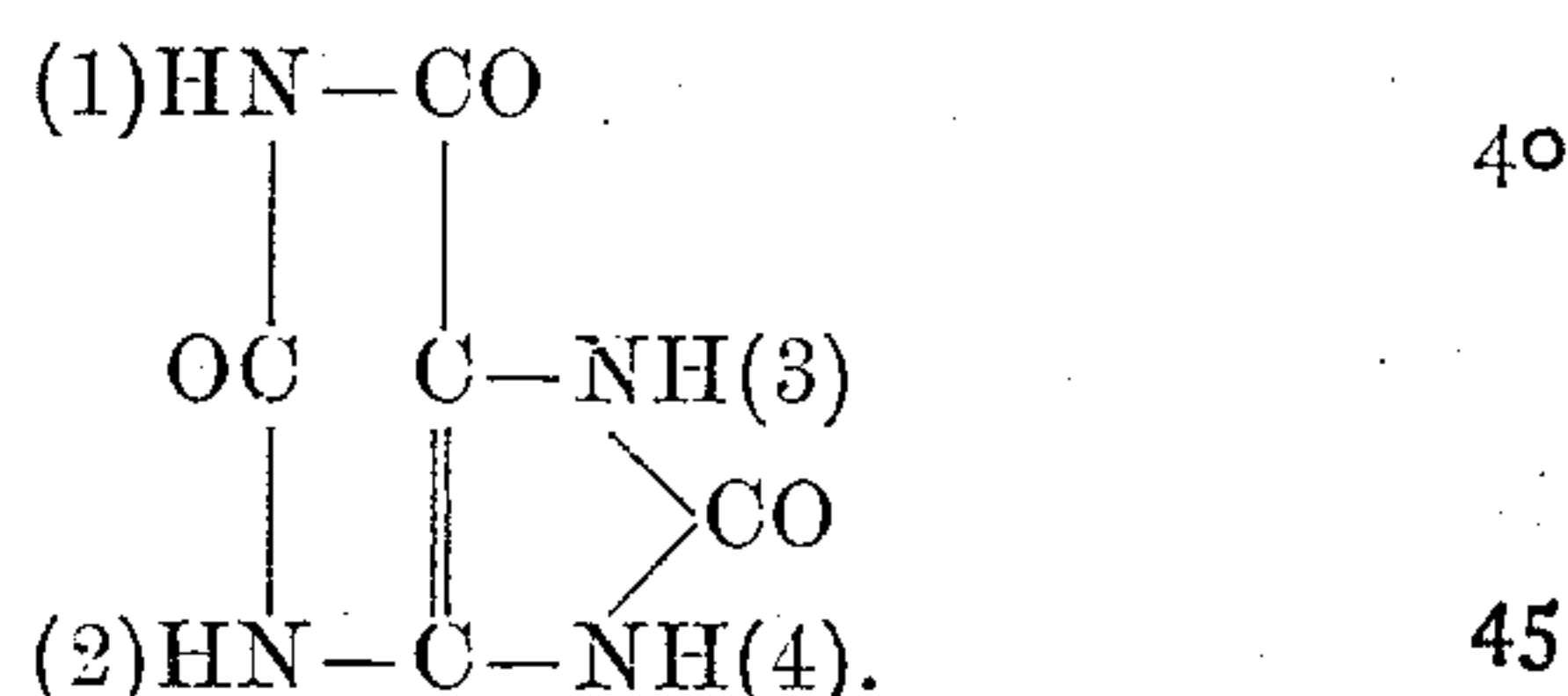
Be it known that I, FRITZ ACH, a citizen of the Empire of Germany, residing at Mannheim, in the Empire of Germany, have invented certain new and useful Improvements in the Art of Obtaining the Derivatives of Uric Acid; and I do hereby declare the following to be a full, clear, and exact description of 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 art of obtaining the derivatives of uric acid, and in particular the alkyl derivatives—that is to say, those derivatives in which the hydrogen atoms of the imido groups of the uric acid are replaced, one, several, or all, by alkyl radicals, thus forming mono, di, tri, or tetra alkyl-uric acids.

In order to clearly elucidate the position occupied by this invention with respect to the prior state of the art, I deem it best to briefly review the same, so far as necessary, for purposes of comparison.

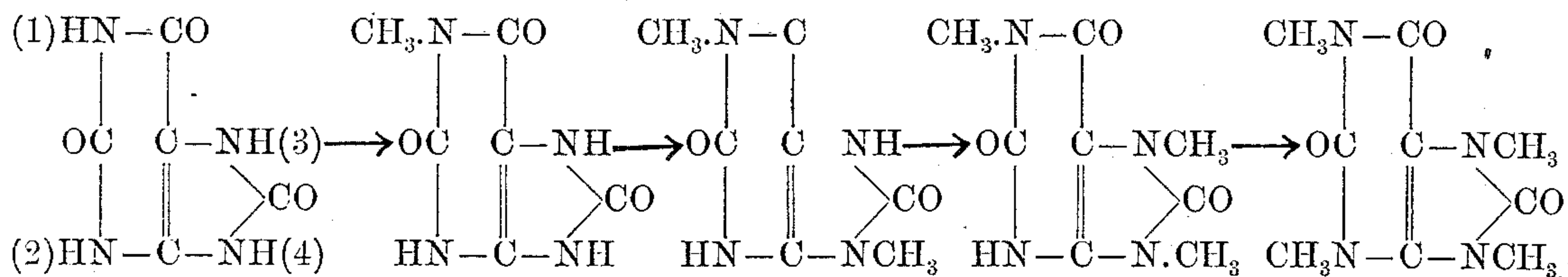
Alkylized uric acids have formerly been prepared by the action of haloid ethers upon alkaline solutions of uric acid or of its alkyl derivatives. These processes are set forth in Letters Patent of the United States to Emil Fischer, granted December 27, 1898, No. 616,700, for "Alkyl derivatives of uric acid

and process of making the same." The course of this alkylation is best represented with the aid of the structural formula of uric acids, the four imido groups or hydrogen atoms being each designated with a numeral, according to the suggestion of Emil Fischer, (*Berichte der Deutschen Chemischen Gesellschaft*, 17, p. 1786,) thus:



The introduction of the alkyl radicals into the uric-acid molecule under the former method takes place successively and in the order 1-4-3-2, these numerals here and throughout this specification representing the particular hydrogen atoms designated by these numerals in the above formula.

In the examples given in the former methods 1-monomethyl-uric acid is first formed, then by continuing the reaction (1-4) dimethyl-uric acid, then (1-4-3) trimethyl-uric acids, and finally (1-4-3-2) tetramethyl-uric acid. This course of alkylation is represented in the following series:

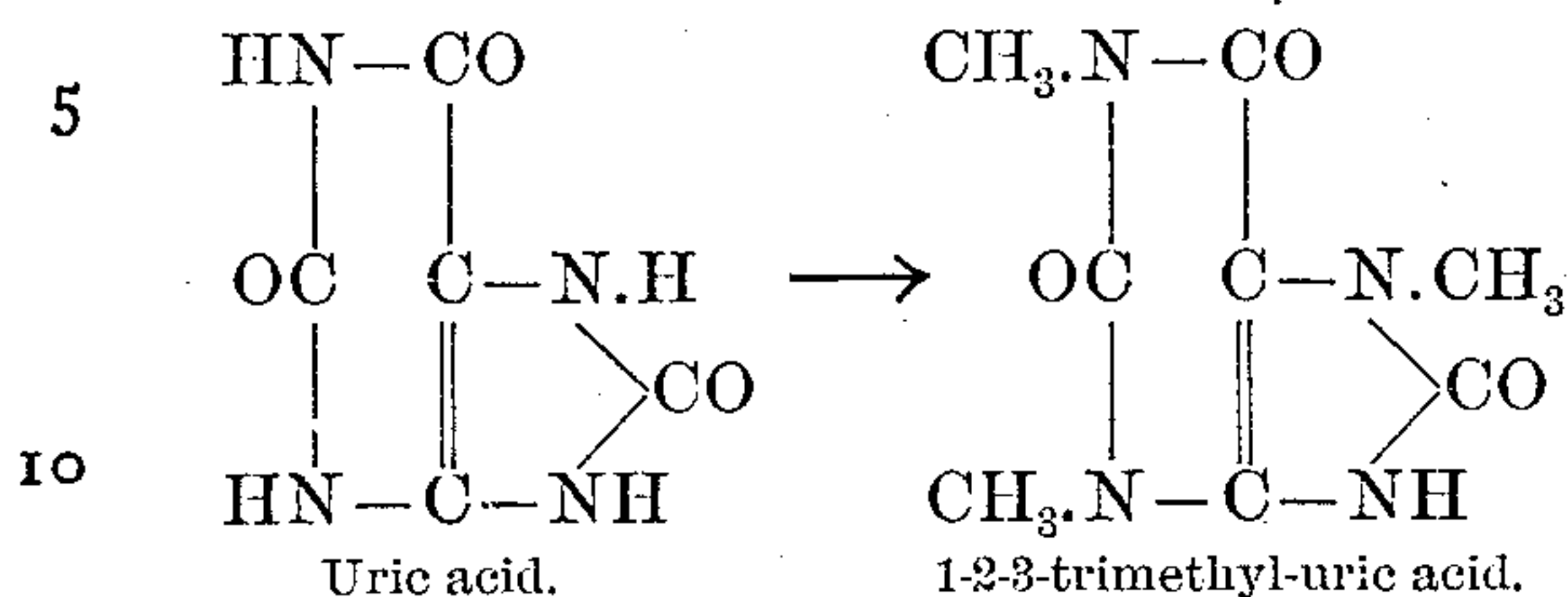


I have found as the result of my experiments and investigations in this field that the course of alkylation may be changed and caused to take place in another direction than that set forth in the patent above referred to. I have thus discovered a manner of carrying out the generic invention set forth in said application in a manner which is specifically new.

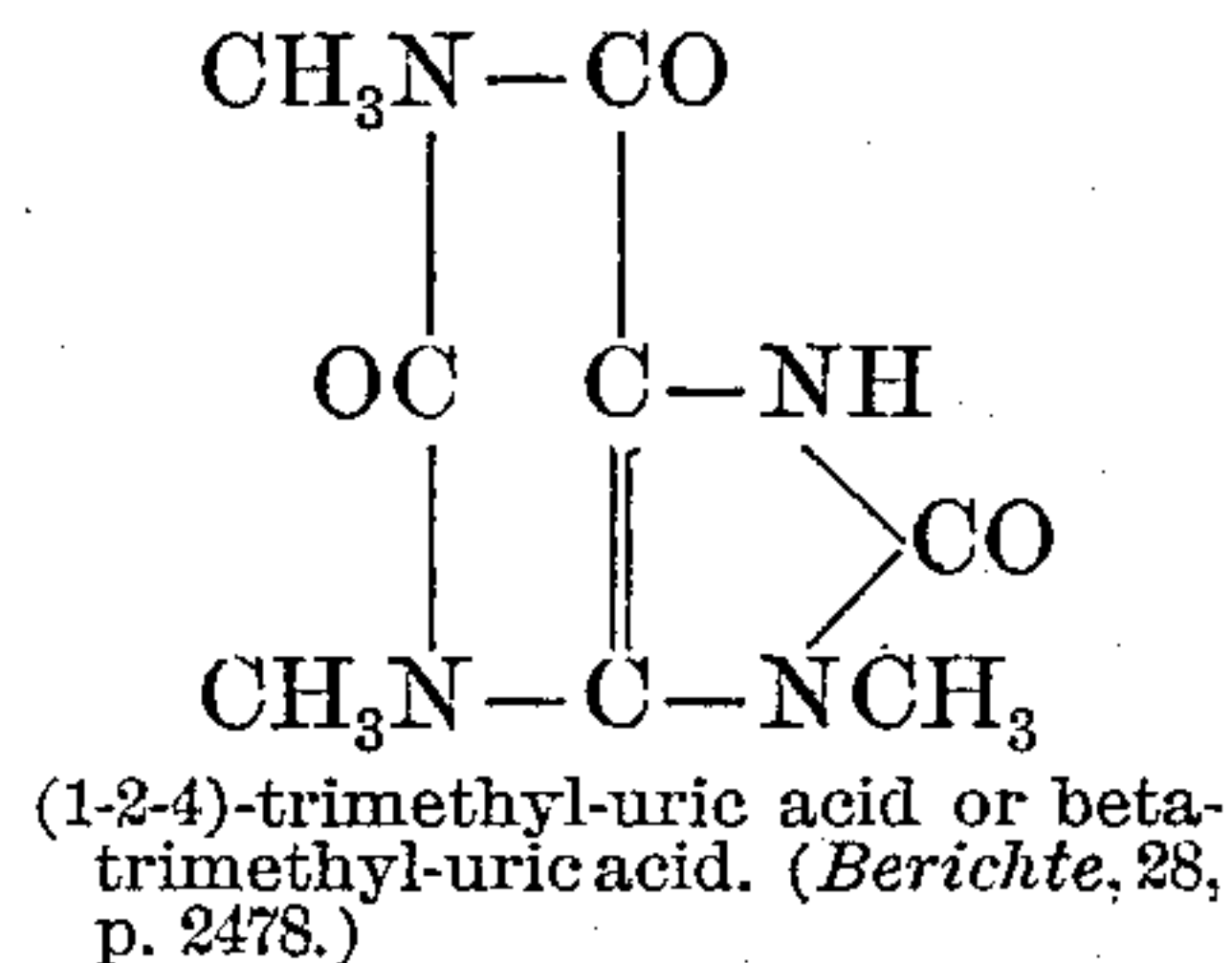
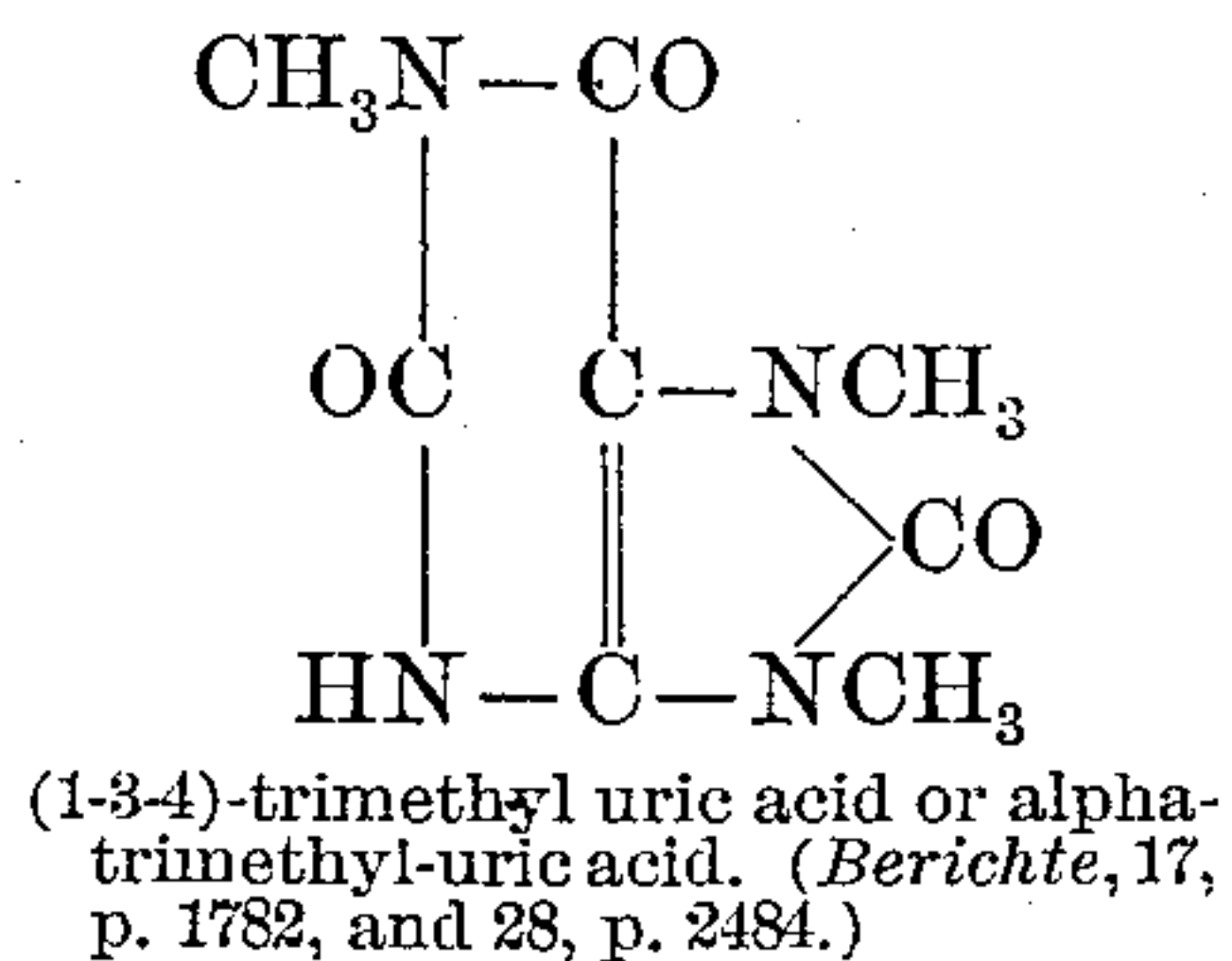
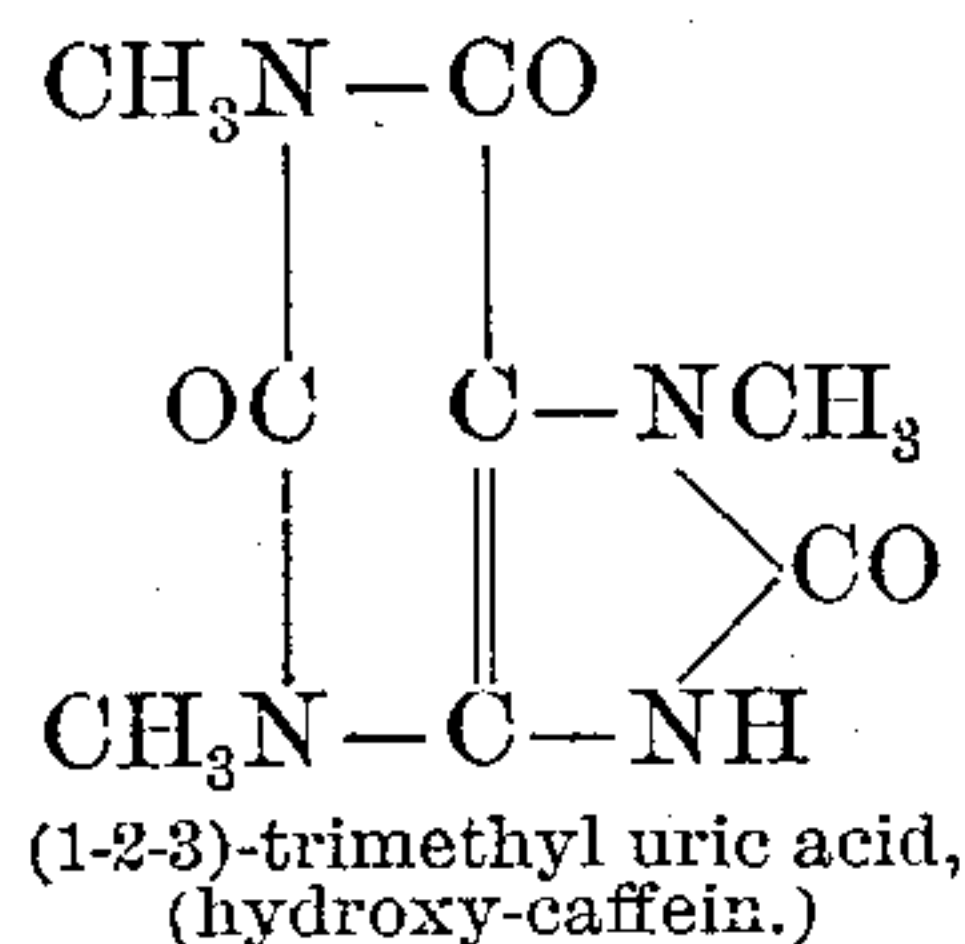
Under my new process the alkyl radicals

are introduced into the uric-acid molecule, so as to replace the hydrogen atoms 1, 2, and 3, or, in other words, to be bonded to the nitrogen atoms of the imido groups 1, 2, and 3 instead of to those of the imido groups 1, 3, and 4, as in the aforesaid application. When the alkylation consists, specifically, in methylating or introducing methyl radicals into the uric acid under this novel method, there is

produced the hitherto-unknown 1-2-3 trimethyl-uric acid. The conversion which takes place may be represented thus:

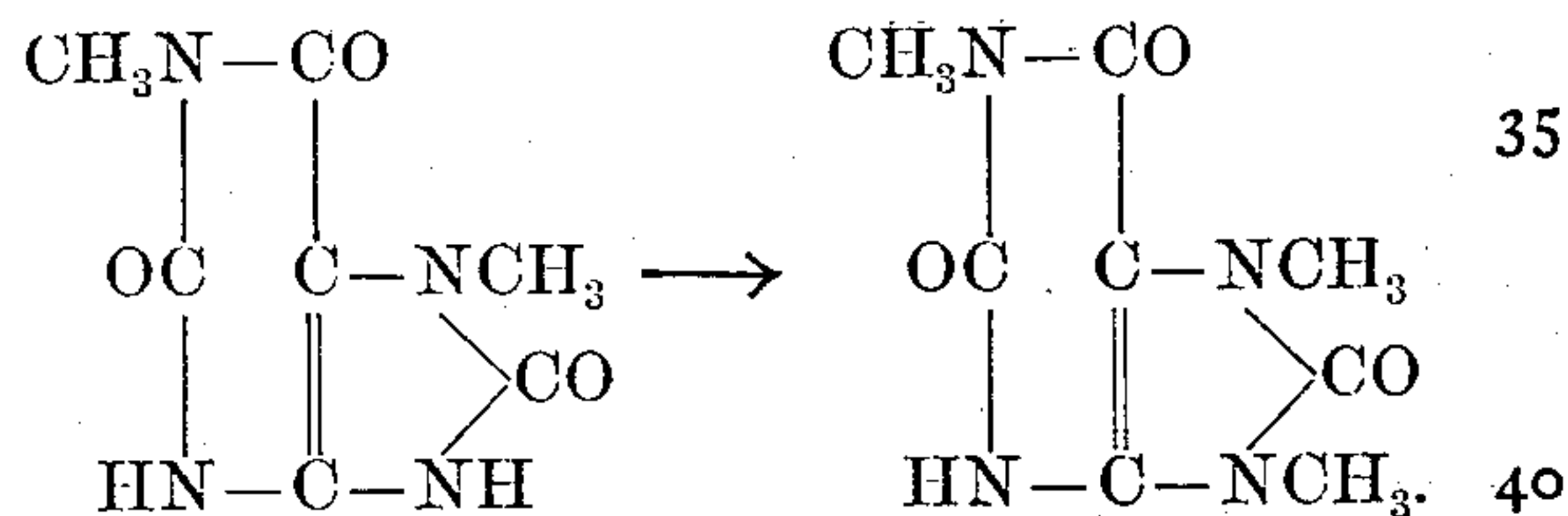


The effect of my new method is not confined to alkylizing uric acid proper, but follows also when the same is applied to alkylizing partially-alkylized uric acids, the latter when treated according to the said new method yielding final products which differ from those obtained when applying the former methods. Thus, *e. g.*, if delta-dimethyl-uric acid, which according to the researches of Emil Fischer (*Berichte*, 28, p. 2482) has the formula of a (1-3) dimethyl-uric acid, undergoes further methylation under the old methods, either by the action of methyl-iodid upon the corresponding lead salt (*Berichte*, 28, p. 2484) or (under the above-named application to Fischer) by acting upon an alkaline solution or mixture of the dimethyl-uric acid with a haloid ether and heating, we obtain alpha-trimethyl-uric acid or (1-3-4)-trimethyl-uric acid, a compound already known. This change is exhibited thus:

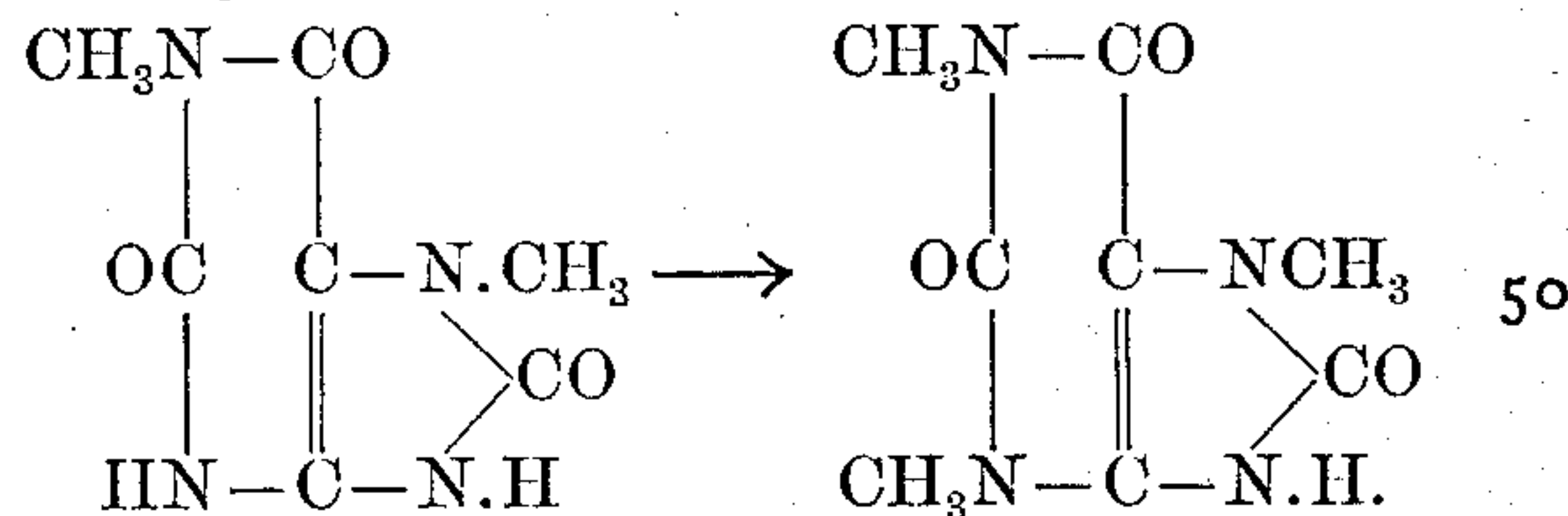


Since hydroxy-cafein is readily converted into caffein, (see Emil Fischer in *Liebig's Annalen*, 215, 271, and 263,) it is manifest that the practical importance of my new method of alkylizing uric acid is greatly enhanced.

The results thus outlined are obtained by alkylizing uric acid proper or its alkyl derivatives (all of which compounds are for the purposes of this application designated in the claims and elsewhere by the generic term "uric acid," the particular uric acid in which none of the hydrogen atoms have been replaced by alkyl radicals being herein designated as "uric acid proper") in an alkaline bath or solution at a low temperature, preferably the freezing-point. The new method is, moreover, particularly characterized by the fact that in dissolving the free or partially-alkylized uric acid enough alkali is added at the beginning of the operation that all of the imido groups are maintained completely saturated throughout the entire operation.



When, however, my new method is applied in methylating (1-3)-dimethyl-uric acid, the resulting product, though a trimethyl-uric acid, is not the one obtained above, but (1-3-2)-trimethyl-uric acid:



This trimethyl-uric acid, which, as seen above, may be obtained by methylation of uric acid proper and (1-3)-dimethyl-uric acid, according to my new method, is isomeric with the two trimethyl-uric acids already known—viz., (1-3-4) or alpha-trimethyl-uric acid and (1-2-4) or beta-trimethyl-uric acid and can be shown to be identical with hydroxy-cafein prepared by Emil Fischer from caffein or chloro-cafein. (See *Liebig's Annalen*, 215, 268.) It is believed to be desirable to place the structural formulæ of these three trimethyl-uric acids in juxtaposition for purposes of comparison:

Under the former methods of alkylizing with the aid of alkali the process was carried out at a raised temperature and the amount of alkali employed was no more than that required by the haloid ether employed. From the above it will be seen that my invention, broadly considered, consists in changing the course of alkylation by causing the same to proceed at a low temperature and also in adding so much alkali that all of the imido groups of the uric acid acted on are continually kept saturated. Finally the invention consists in such further features, steps, and methods, all as will be hereinafter set forth, and pointed out in the claims.

The following examples will serve to illustrate what I consider the best manner of carrying out my invention, the proportions given being all expressed in weight.

1. *Preparation of 1-2-3-trimethyl-uric acid or hydroxy-cafein from uric acid proper.*— Ten parts of uric acid are brought into solution in two hundred parts of water by means

of twenty parts (corresponding to five molecules) of caustic potash of eighty-per-cent. strength. The solution is well cooled with ice-water, and thirty parts, corresponding to three and one-half molecules, of methyl-iodid are added, and the whole is then shaken until the methyl-iodid disappears. Of the three and one-half molecules of methyl-iodid only three molecules are necessary to furnish the necessary amount of methyl. The remaining one-half molecule of the iodid is added only for practical reasons and to assist the operation of the process. The quantity of the caustic potash added must be in the proportion of at least four molecules of the caustic potash to one molecule of the acid, the amount of five molecules of caustic potash to one of the acid given above being deemed preferable. It is desirable to then cool for the first twelve hours with ice-water. After the reaction is completed the clear alkaline solution is acidulated slightly and evaporated down or concentrated to one-half its volume. Any dimethyl-uric acid that may remain over will be separated out on standing for several hours while the solution is being cooled and is removed by filtration. The filtrate is thereupon evaporated or concentrated to one-half its volume until crystallization takes place. Upon cooling a large proportion of the resultant hydroxy-cafein crystallizes out in the form of fine needles. The remainder of the hydroxy-cafein is obtained by first evaporating the filtrate to dryness and then extracting the hydroxy-cafein therefrom with a suitable solvent—such as, for example, chloroform. After the solvent has evaporated off the hydroxy-cafein remains as a slightly-colored crystalline mass, which is obtained in a perfectly pure condition by once dissolving the same in water.

The 1-2-3-trimethyl-uric acid possesses all of the characteristic properties which have been ascertained by Emil Fischer (see *Liebigs Annalen*, 215, p. 268) for hydroxy-cafein prepared from caffein.

2. *Preparation of 1-2-3-trimethyl-uric acid or hydroxy-cafein from 1-3-dimethyl-uric acid.*—5.8 parts of 1-3-dimethyl-uric acid are dissolved in fifty parts of water by 4.5 parts, corresponding to two molecules of caustic potash of eighty-per-cent. strength. The solution is cooled with ice-water and after adding 5.5 parts, corresponding to one and one-third molecules, of methyl-iodid the whole is shaken until the methyl-iodid disappears. The clear liquid is slightly acidulated and evaporated down to one-half its bulk. On cooling the hydroxy-cafein crystallizes out in colorless needles, which on redissolving in water and recrystallizing may be obtained in a pure condition. This product is identical with the compound which has formerly been prepared from caffein.

In carrying out my invention, of which the above examples are an illustration, the methyl-

iodid may be replaced by other haloid ethers, such as methyl-chlorid or methyl-bromid. The esters of other acids besides the halogen acids may be employed for alkylizing under my invention. Thus, for example, the alkyl-esters of sulfuric acid, nitric acid, benzene-sulfo-acid, &c., may be substituted for the methyl-iodid in the above two examples of carrying out my invention. Where other alkyl groups are introduced into uric acid, the corresponding halogen-alkyls or haloid ethers, such as ethyl-chlorid or iodid, are manifestly to be employed. Other alkalies may be used instead of the caustic potash, and instead of the aqueous alkaline solution alcoholic aqueous alkaline solution of the uric acid may be employed.

In general my process may be modified in many particulars without departing from my invention, which relates to the preparation of any alkyl-uric acids, as already stated, and consists, broadly, in changing the course of replacing the hydrogen atoms in uric acids by any alkyl radicals and in causing the alkylation to proceed at a low temperature and also in adding enough alkali to keep all of the imido groups of the uric acid saturated.

As already stated, the term "uric acid" as employed in the claims generically comprises both uric acid proper—that is, the uric acid in which none of the imido groups have been alkylized—and mono-alkyl-uric acids, dialkyl-uric acids, &c.—i. e., those uric acids in which one or more of the imido groups have been alkylized.

What I claim, and desire to secure by Letters Patent of the United States, is—

1. The process which consists in treating an alkaline solution of a uric acid with an alkyl-ester at a low temperature.

2. The process which consists in dissolving a uric acid in water by an alkali, the alkali being added in a proportion to keep all of the imido groups of the uric acid saturated, then lowering the temperature and adding an alkyl-ester.

3. The process which consists in treating an alkaline solution of a uric acid with a haloid ether at a low temperature.

4. The process which consists in dissolving a uric acid in water by the aid of alkali, the alkali being added in a proportion sufficient to keep the imido groups of the uric acid saturated, then lowering the temperature and adding a haloid ether.

5. The process which consists in dissolving uric acid proper in water together with caustic potash in the proportion of at least four molecules of the caustic potash to one molecule of the acid, then cooling the solution and then adding methyl-iodid in the proportion of three molecules to one molecule of the acid, and shaking the mixture.

6. The process which consists in dissolving the uric acid proper in water together with caustic potash in the proportion of at least

four molecules of the caustic potash to one molecule of the acid, then cooling the solution, and then adding methyl-iodid in the proportion of at least three molecules to one molecule of the acid, shaking the mixture and cooling for a long period.

7. The process which consists in dissolving uric acid proper in water together with caustic potash in the proportion of at least four molecules of the caustic potash to one molecule of the acid, then cooling the solution and adding methyl-iodid in the proportion of at least three molecules to one molecule of the acid, shaking and cooling the mixture for a long period until the methyl-iodid disappears, and then acidulating and concentrating or evaporating the liquid, then filtering and concentrating or evaporating the filtrate and allowing a portion of the hydroxy-cafein to separate out of the solution by crystallization.

8. The process which consists in dissolving uric acid proper in water, together with caustic

potash, in the proportion of at least four molecules of the caustic potash to one molecule of the acid, then cooling the solution, then adding methyl-iodid in the proportion of three and one-half molecules to one molecule of the acid, while continuously shaking the mixture cooling a second time for a long period, then acidulating and reducing the volume by evaporation or otherwise, then filtering and concentrating or evaporating the filtrate and allowing a portion of the hydroxy-cafein to separate out of the solution by crystallization, again filtering and evaporating the filtrate to dryness and then extracting the remainder of the hydroxy-cafein from the residue with a solvent of the same.

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

FRITZ ACH.

Witnesses:

BERNHARD C. HESSE,
JACOB ADRIAN.