

UNITED STATES PATENT OFFICE.

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

XANTHIN HOMOLOGUE AND PROCESS OF MAKING SAME.

SPECIFICATION forming part of Letters Patent No. 667,381, dated February 5, 1901.

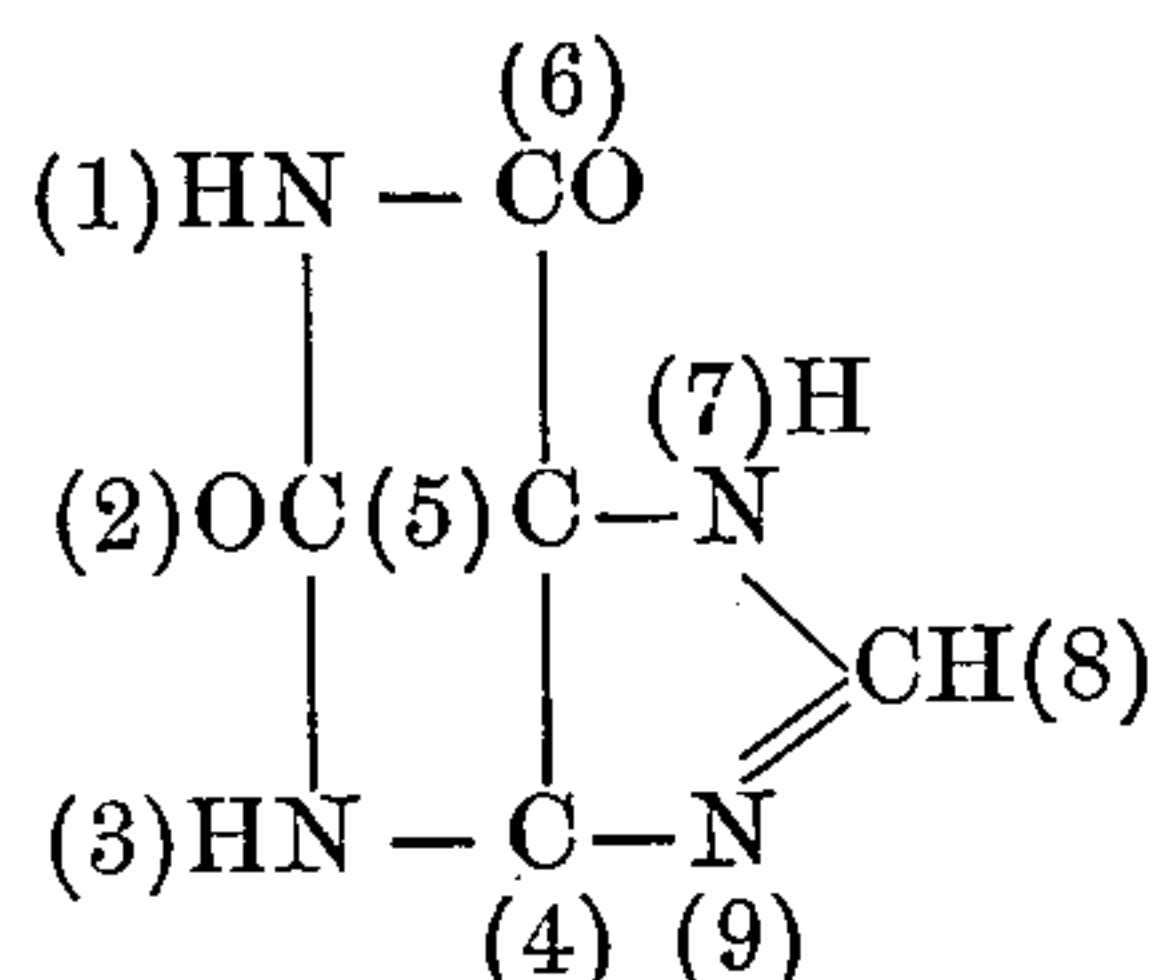
Application filed July 18, 1900. Serial No. 24,031. (No specimens.)

To all whom it may concern:

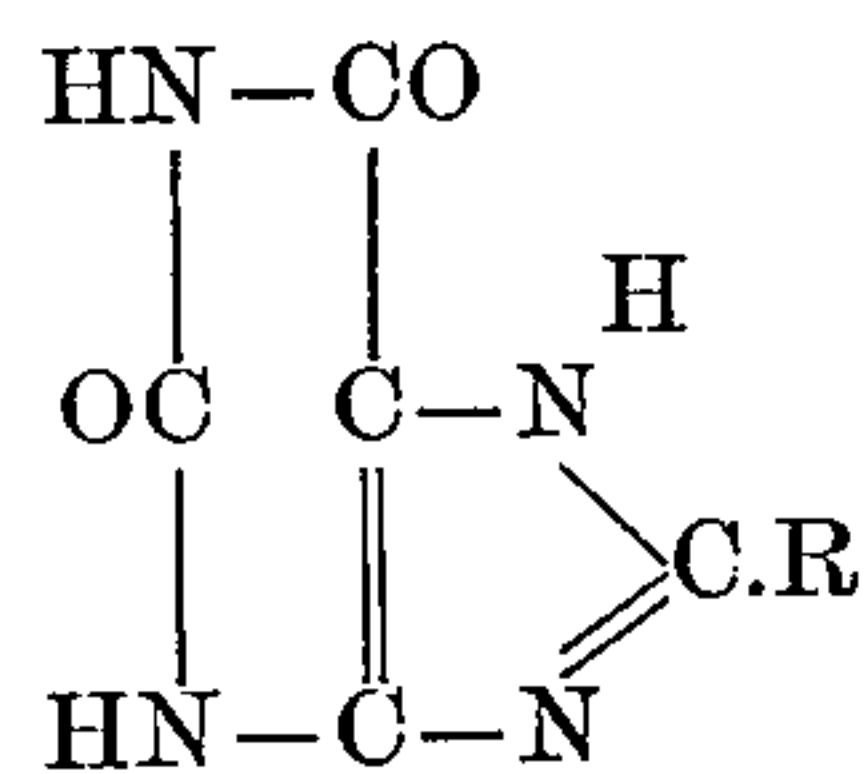
Be it known that I, FRITZ ACH, a citizen of the Empire of Germany, residing at Mannheim, in the Empire of Germany, have invented certain new and useful Improvements in the Art of Preparing Homologues of Xanthin; and I do hereby declare the following to be a full, clear, and exact description of the invention, such as will enable others skilled in the art to which it appertains to make and use the same.

The present invention relates to the art of preparing derivatives of xanthin with special reference to the homologues of this purin, its object being the preparation of homologues in which the hydrogen atom bound to the carbon atom in the position 8 is replaced by an alkyl radical.

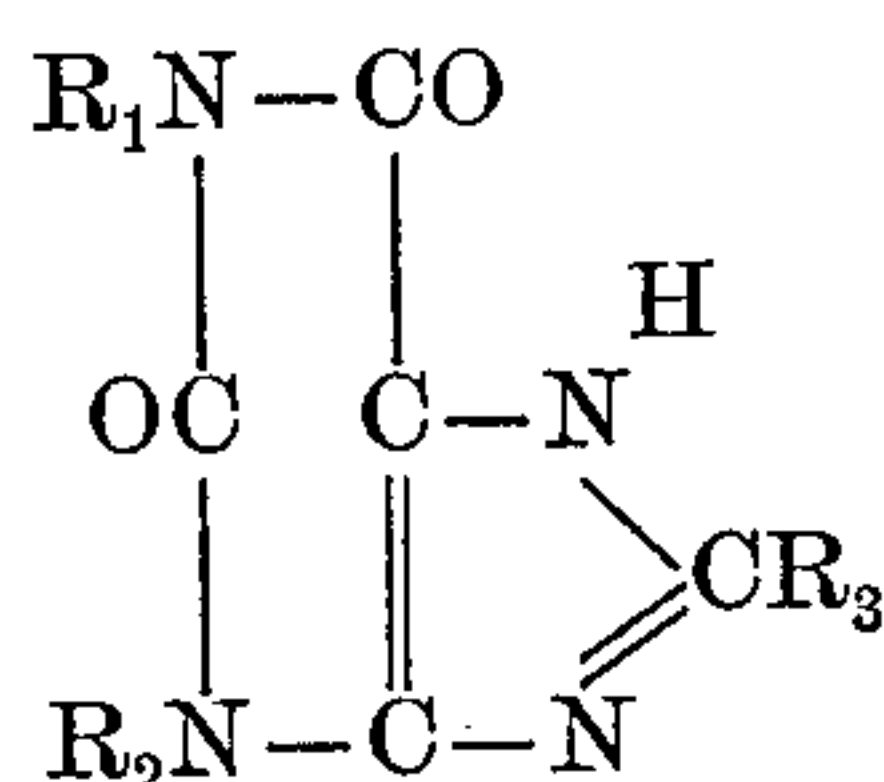
The structural formula of xanthin is:



(See, e. g., *Berichte der Deutschen Chemischen Gesellschaft*, Vol. 30, page 549, and Letters Patent of the United States No. 631,706.) The general formula of these homologues would be:



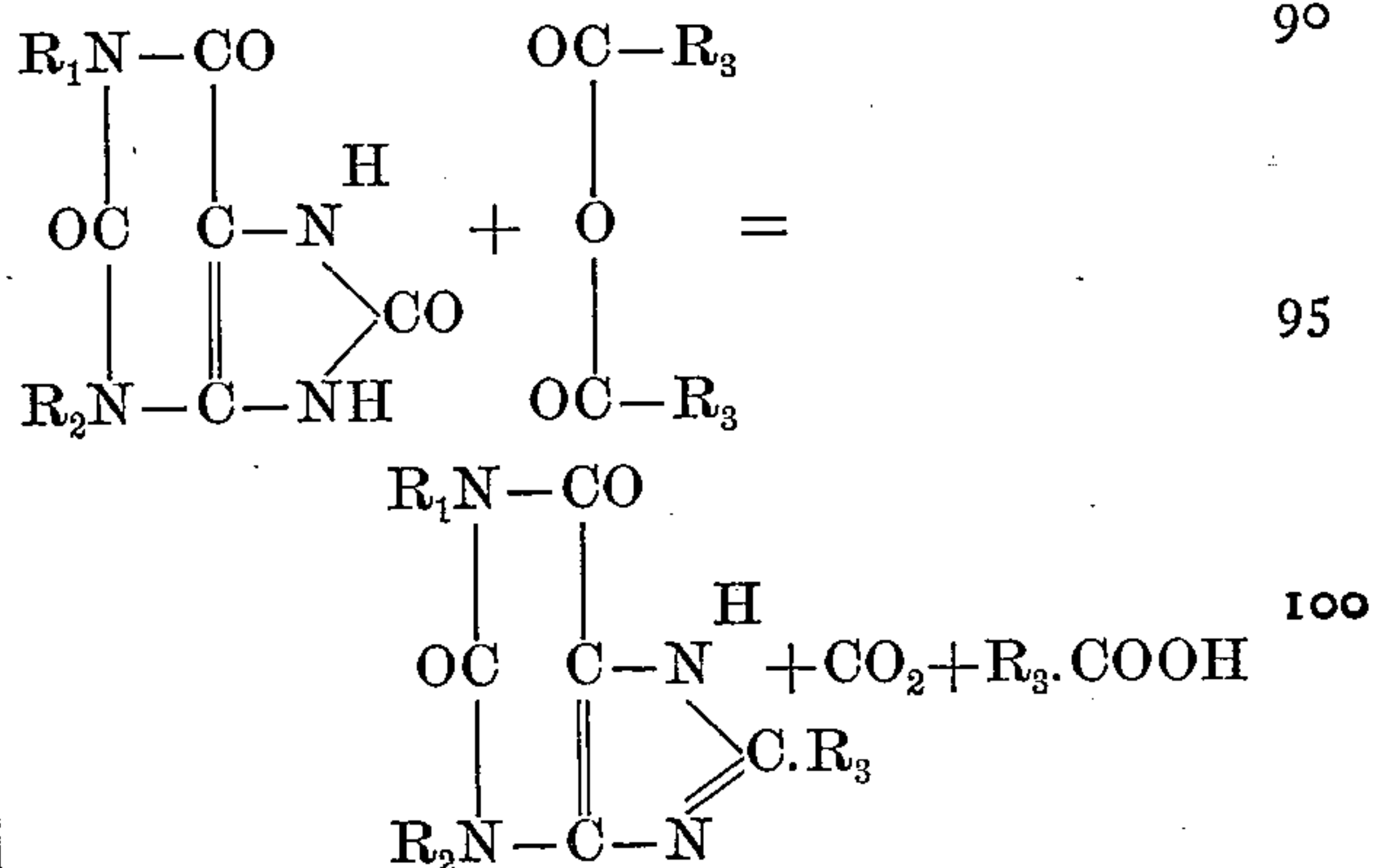
or



or the like, where R, R₁, R₂, and R₃ represent alkyl radicals. These xanthin deriva-

tives have not hitherto been known or produced. I have found in the course of my experiments and researches that such alkyl-xanthins may be readily prepared by causing an organic acid anhydride to act upon uric acid, such as uric acid proper or its alkyl derivatives. The reaction takes place with the evolution of carbon-dioxid on heating the reagents together under pressure, as well as by boiling in an open vessel combined with a reflux apparatus. This conversion of the uric acid into the corresponding 8-alkyl-xanthin takes place in most cases apparently without the formation of a solution, and it is completed when a sample of the separated product of the reaction will no longer reduce an ammoniacal silver solution after thoroughly boiling the two together. This new process renders it possible for the first time to proceed directly and in one operation from the uric-acid series to the xanthin series.

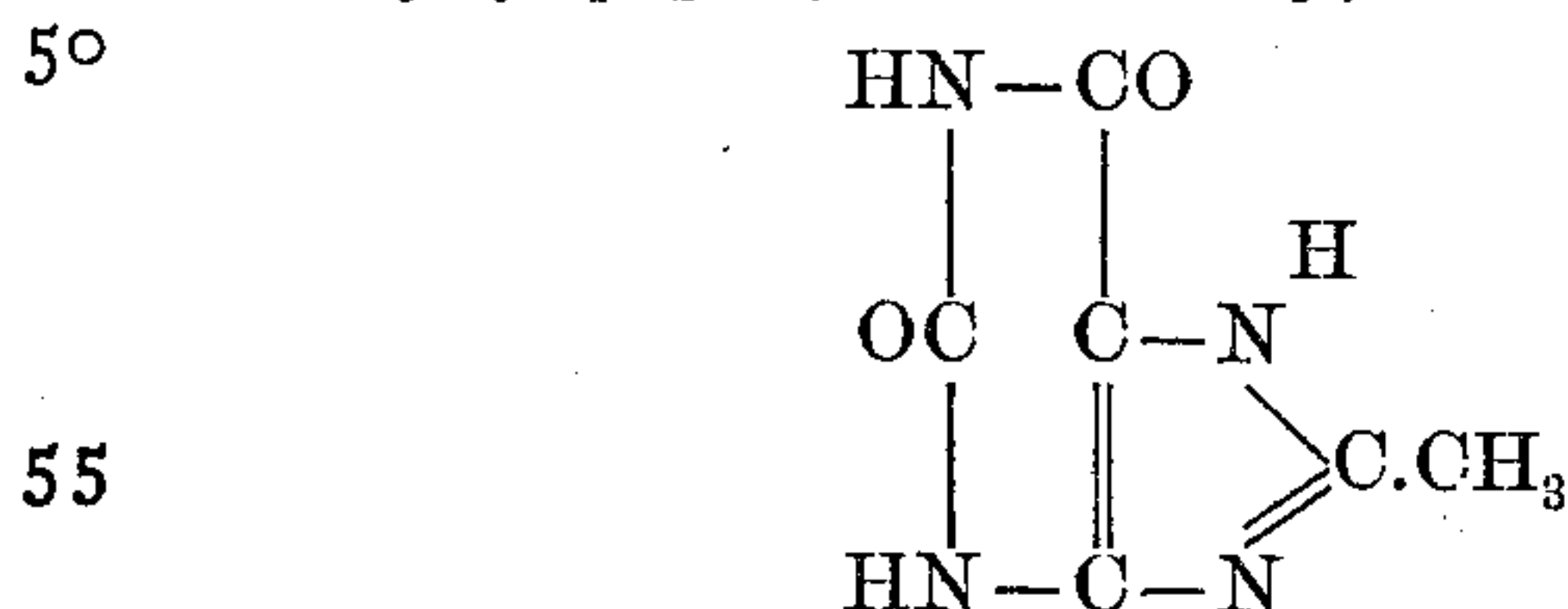
According to experiments and observations hitherto made the uric acids which are susceptible to the above reaction are uric acid proper and the derivatives of the same, in which the alkyl radical or radicals are bound to the alloxan nucleus—such, for example, as 3-methyl-uric acid or 1-3-dimethyl-uric acid—while those uric acids in which the alkyl radical or radicals are bound to the nitrogen atoms occupying the positions 7 or 9—such as 7-methyl-uric acid, 3-9-dimethyluric acid, or 1-3-7-trimethyl-uric acid—are not changed on treating them with acid anhydrides. My present invention may therefore be generically expressed by the following general equation:



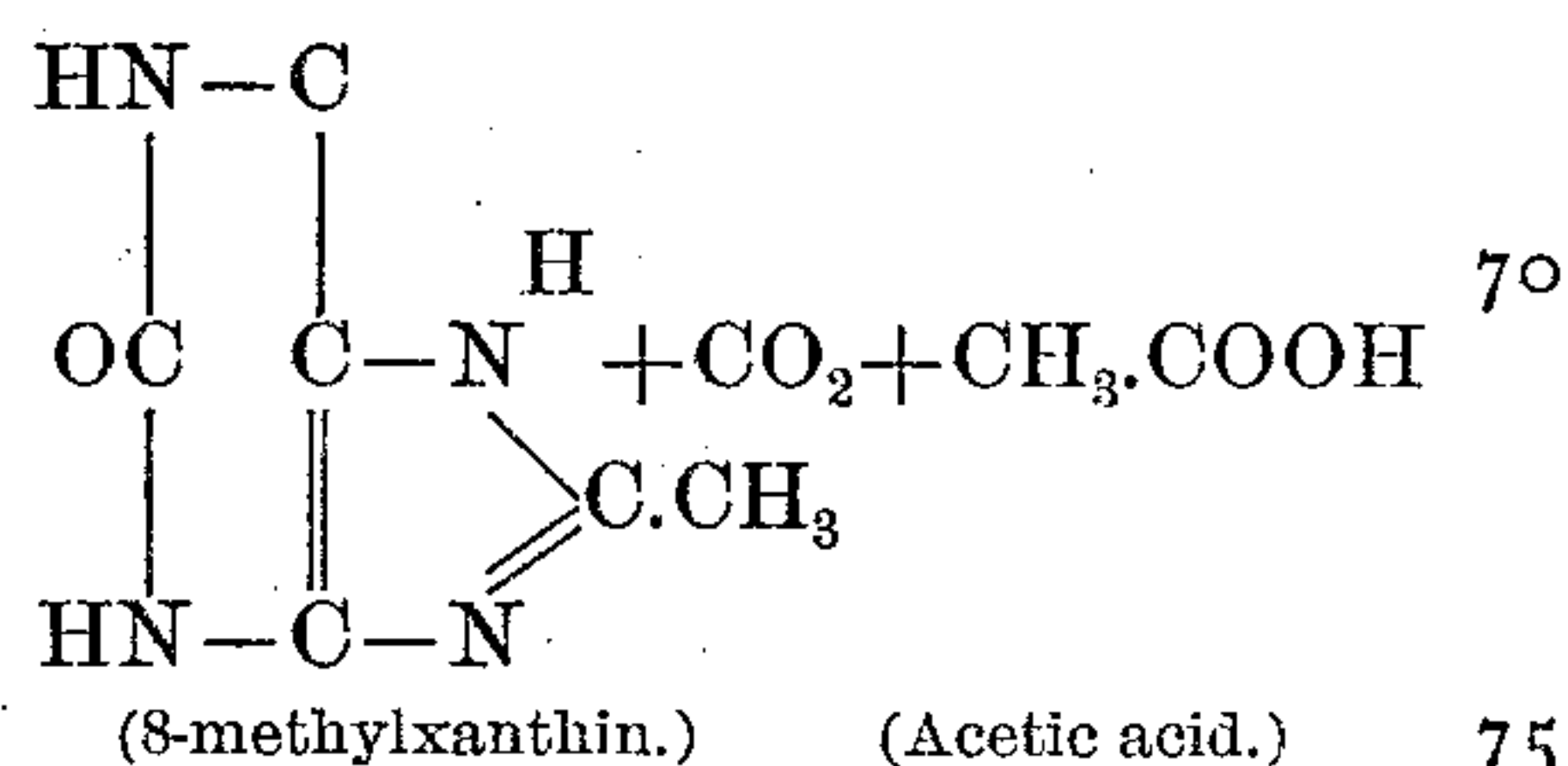
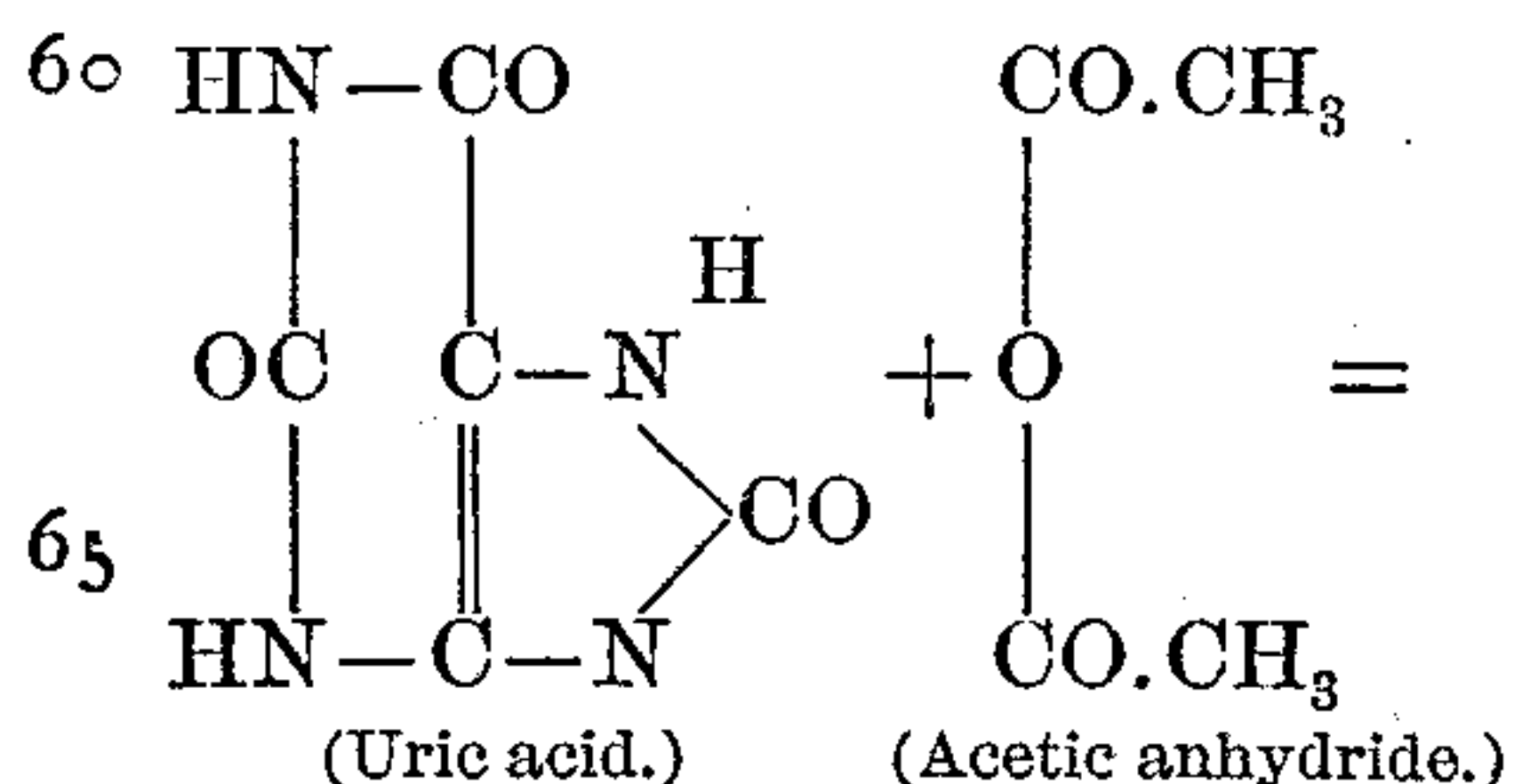
The new xanthin homologues are by the above methods obtained in an almost pure condition, and in general they possess the properties characteristic of xanthins—viz., complete stability and indifference with respect to ammoniacal silver solutions, the formation of murexid when they are treated with chlorate of potassium and hydrochloric acid, and the formation of a yellow residue when evaporated together with concentrated nitric acid.

In order to enable those skilled in the art to practice my invention, I will now describe the same in detail with the aid of several examples constituting the preferred embodiment of the same. The proportions are all given by weight.

1. *Preparation of 8-methylxanthin from uric acid proper.*—One part of uric acid proper is boiled, together with ten parts of acetic-acid anhydride, in a reflux apparatus. Carbon-dioxid is very soon liberated steadily, while at the same time the uric acid is converted into 8-methylxanthin without going into solution. The conversion is complete after the lapse of about eighty hours' continued boiling. To ascertain whether this condition has taken place, the slightly-yellowish brown product, which is insoluble in the anhydride, is tested with ammoniacal silver solution. If the latter ceases to be reduced by the product, the process has been completed. The whole is now allowed to cool and is then drained by siphoning or by other means and finally washed with alcohol. From seventy-five to eighty per cent. of the theoretical yield of almost pure methylxanthin is thus obtained. To obtain the same as a colorless product, the xanthin thus obtained is advantageously converted into the mono-potassium salt, which crystallizes in the form of fine colorless needles. This salt is dissolved in water and precipitated from the solution by acetic acid or by a dilute mineral acid. The base is thus thrown out in the form of a fine granular powder. The 8-methylxanthin so obtained is free of water. An analysis of the same gives values corresponding to the equation $C_8H_6N_4O_2$ or, structurally,



The reaction of its formation, as described above, proceeds according to the equation:



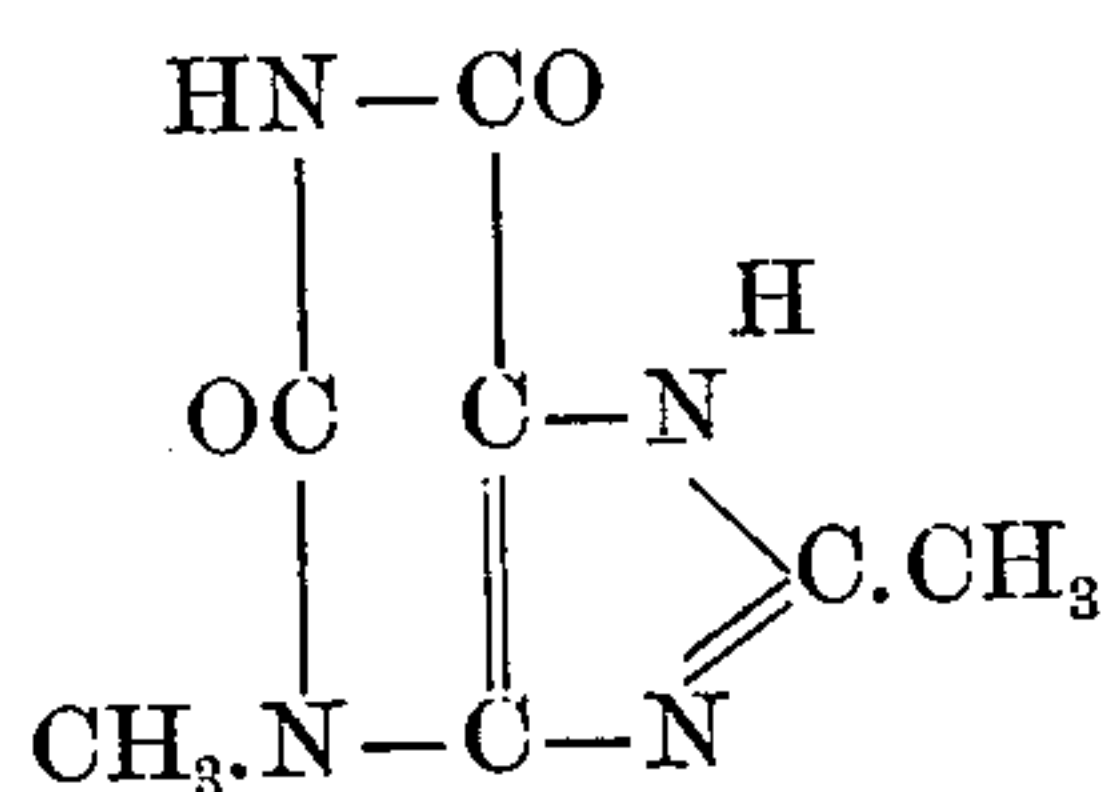
This new xanthin is soluble in the usual solvents only with extreme difficulty. While the solubility of xanthin in water is usually considerably increased under the influence of the methyl radical, in the present case the addition of methyl to the carbon atom 8 strongly reduces such solubility. Thus, for example, xanthin proper requires about fifteen hundred parts of boiling water for complete solution, while 8-methylxanthin requires about three thousand three hundred parts, crystallizing from such solution on slowly cooling the same in the form of colorless short prisms or tablets. 8-methylxanthin as a base is soluble with tolerable ease in dilute mineral acids on heating or warming. When dissolved in concentrated hydrochloric acid and allowed to cool, a hydrochlorate of the same is thrown out in the form of colorless shining prismatic crystals, which hydrochlorate, however, gives up its hydrochloric acid on being treated with water. From a solution in concentrated sulfuric acid the 8-methylxanthin, like xanthin proper, is not precipitated by water. It is readily soluble in alkalis and ammonia. On adding to a solution of the same in ammonia nitrate of silver a gelatinous colorless silver salt is precipitated, which remains unchanged on boiling. From a solution of the 8-methylxanthin in nitric acid a flaky double salt is thrown out by nitrate of silver. On treating the 8-methylxanthin with chlorine water murexid is formed. On evaporating the same with nitric acid of a specific gravity of 1.4 a pale-yellow residue is left, which, on being heated with potash-lye (KHO solution) gives an intensely orange-colored solution.

8-methylxanthin has no melting-point. At substantially 380° centigrade it begins to turn brown, and at a temperature above 400° centigrade it is decomposed.

The above reaction of acetic-acid anhydride or uric acid may be accomplished in a briefer period of time than stated above if the reagents are caused to act upon each other either under pressure—e. g., in a digester—or in the presence of a condensing agent. For example, if one part of uric acid proper is heated together with from five to six parts acetic acid in a closed vessel, such as an autoclave, while constantly stirring or agitating the mass, to a temperature of 180° centigrade and maintained at this temperature for twenty-four hours the conversion into 8-methylxanthin will be completed. After cooling a considerable pressure exists in the autoclave, while the methylxanthin will be obtained in the form of a rather brown powder, which

may be isolated and purified in the manner above given. The same acceleration of the reaction may be obtained when a condensing agent is added to the mixture of uric acid proper and acetic-acid anhydride. Thus, for example, I may add 0.5 parts of pyridin to one part of uric acid proper and ten parts of acetic anhydride. Under these conditions the formation of 8-methylxanthin will have been accomplished after the boiling for from forty to forty-five hours in a reflux apparatus. The new product is thereby obtained in a very pure condition and may be isolated in the manner above given.

2. Preparation of 3-8-dimethylxanthin from 3-methyl-uric acid.—One part of 3-methyl-uric acid, which is identical with 8-methyl-uric acid, as described—*e. g.*, in *Berichte der Deutschen Chemischen Gesellschaft*, Vol. 32, page 2726—is heated to ebullition with ten parts of acetic-acid anhydride in a reflux cooler and with the addition of 0.5 parts pyridin. The conversion into the corresponding xanthin takes place without apparent solution of the methyl-uric acid. After the lapse of about forty hours' continued boiling the difficultly-soluble product ceases to reduce ammoniacal silver solution. The whole is thereupon allowed to cool and the liquid is drained from the resultant slightly-colored granular powder by filtration, and the same is then crystallized from boiling water having animal charcoal added thereto for decolorizing purposes. The new body 3-8-dimethylxanthin is thus obtained in the form of fine colorless crystals in the form of needles which are matted or felted asbestos-like and which contain one molecule of water of crystallization. This water escapes at 110° centigrade. Analysis of the compound thus dried yields figures, which show its composition to be $C_7H_8N_4O_2$. Its structural formula is:



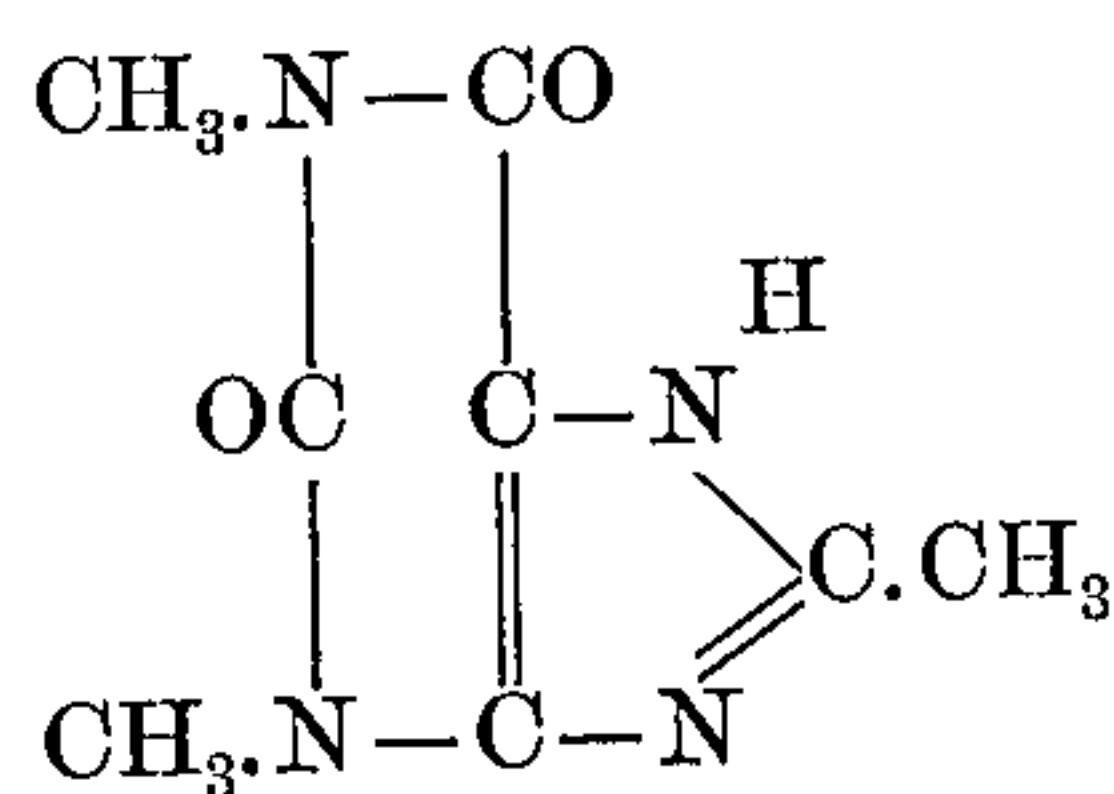
The addition of the methyl radical to the carbon-atom 8 greatly enhances the solubility of the 3-methylxanthin in water. While 3-methylxanthin requires three hundred and fifty parts of boiling water for complete solution, (*Berliner Berichte*, Vol. 31, page 1986,) 3-8-dimethylxanthin requires only seventy-five parts of boiling water and crystallizes from such solution in the form of fine colorless needles matted together like asbestos and containing one molecule of water of crystallization.

3-8-dimethylxanthin is readily soluble in dilute alkalis, including ammonia. When concentrated soda-lye (NaHO solution) is added, a sodium salt of the same, which crys-

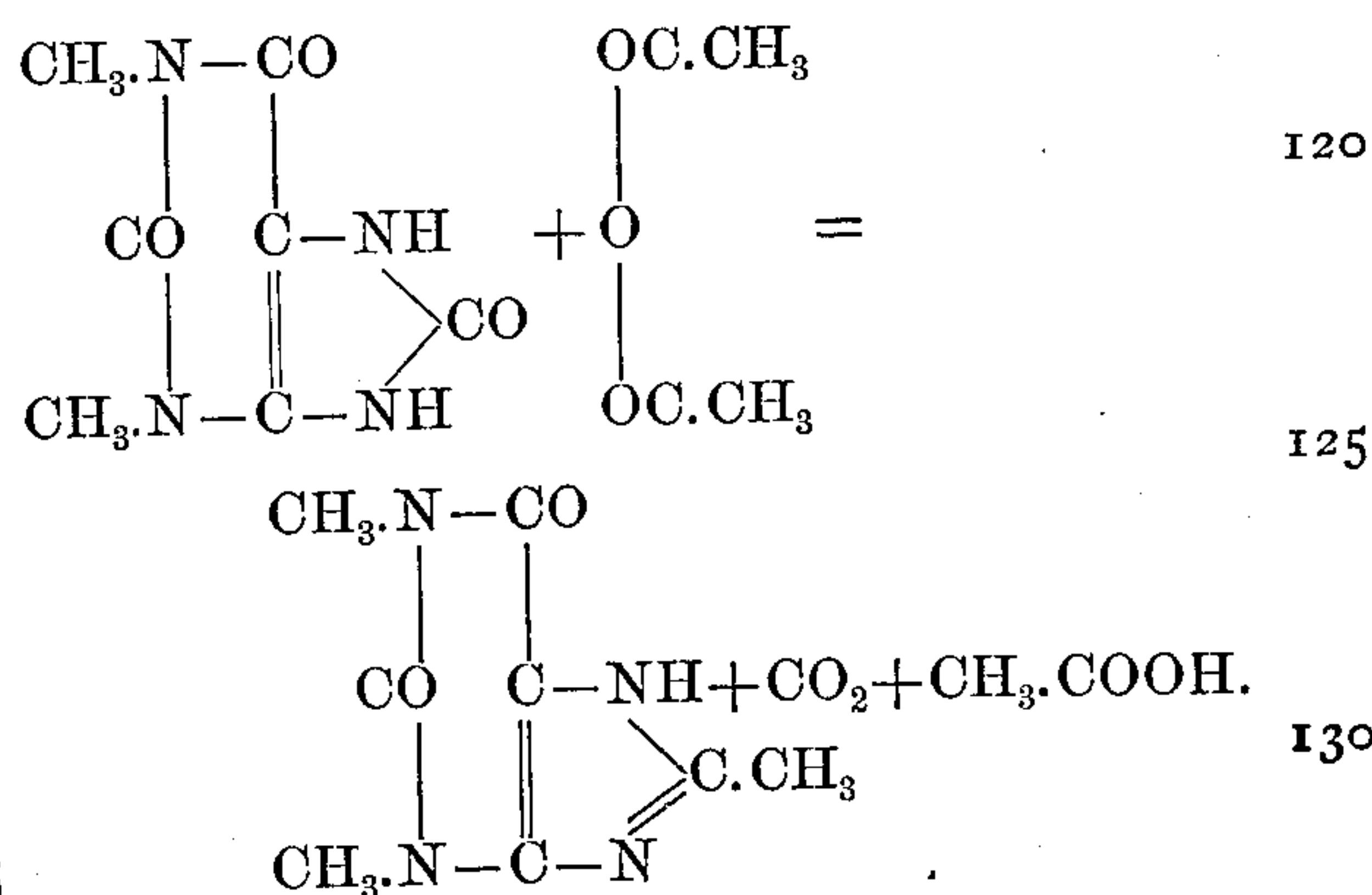
tallizes in fine needles, is soon separated from the whole. Dilute mineral acids readily take up 3-8-methylxanthin on heating. From a solution of the same in dilute nitric acid a double salt, crystallizing in fine needles, is thrown out by nitrate of silver. On adding silver nitrate to an ammoniacal solution of the same a colorless gelatinous silver salt is thrown out, which remains unchanged on boiling.

3-8-dimethylxanthin assumes a brownish color on being heated to above 320° centigrade, and at about 350° centigrade it melts with decomposition.

3. Preparation of 1-3-8-trimethylxanthin from 1-3-dimethyl-uric acid.—One part of 1-3-dimethyl-uric acid free from water is heated with ten parts of acetic anhydride and 0.5 parts pyridin in a reflux apparatus to boiling temperature. The dimethyl-uric acid will thereby be gradually dissolved. After boiling the mixture for twenty hours the formation of the new xanthin will be accomplished. The product, which on cooling crystallizes from the clear anhydride solution, is not reducible by a silver solution—a fact which indicates the end of the reaction. From the trimethylxanthin which separates in the form of fine needles the mother-liquor is drained by siphoning or any desired method, and the residual trimethylxanthin is then purified by dissolving in boiling water or alcohol and recrystallizing from such solution. The resultant fine acicular or prismatic crystals, for the most part aggregated in the form of fagots, contain no water of crystallization. The product when dried at 120° centigrade and analyzed gives figures from which the formula of the same is ascertained to be $C_8H_{10}N_4O_2$. Its structural formula is:



The reaction to which its formation is due is indicated in the equation:

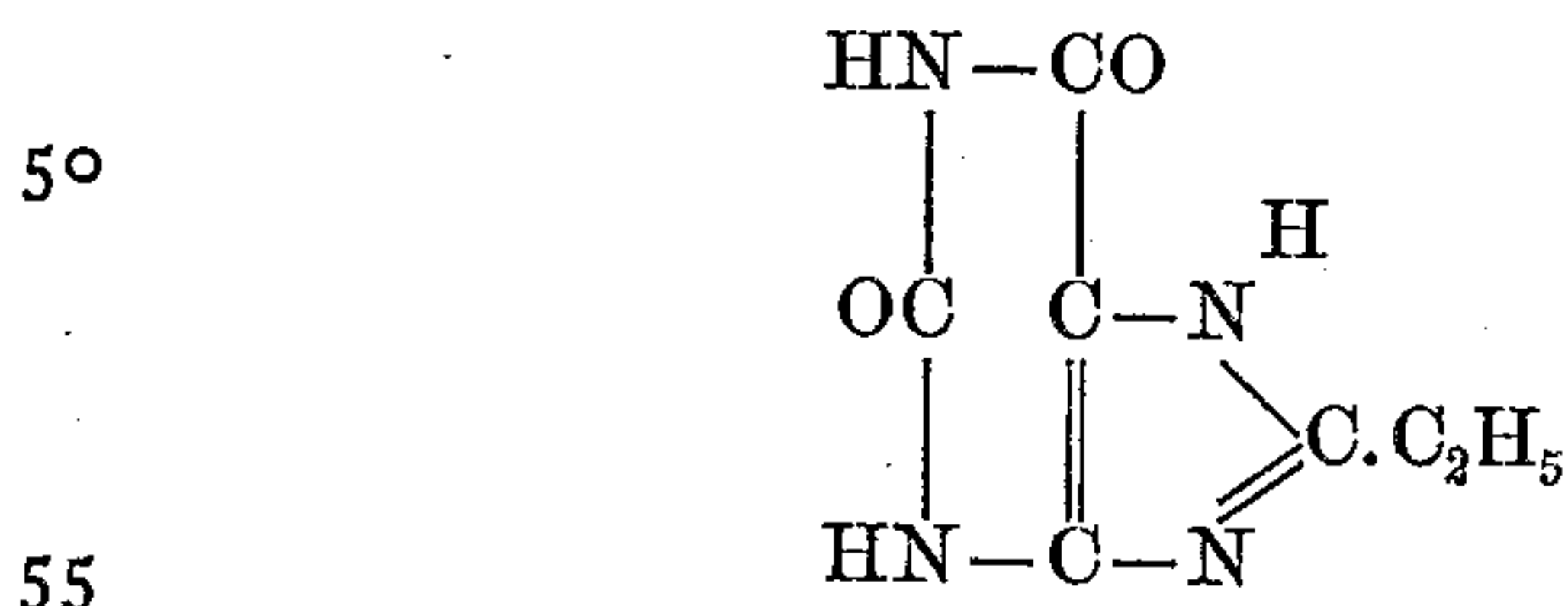


This new trimethylxanthin is soluble in about forty parts of boiling water. Hence by the formation of this body the solubility of 1-3-dimethylxanthin, which is the same as theophyllin and which requires only eight parts of water for solution, (see *Berichte*, Vol. 28, page 3189,) has been very materially reduced by the 8-methyl.

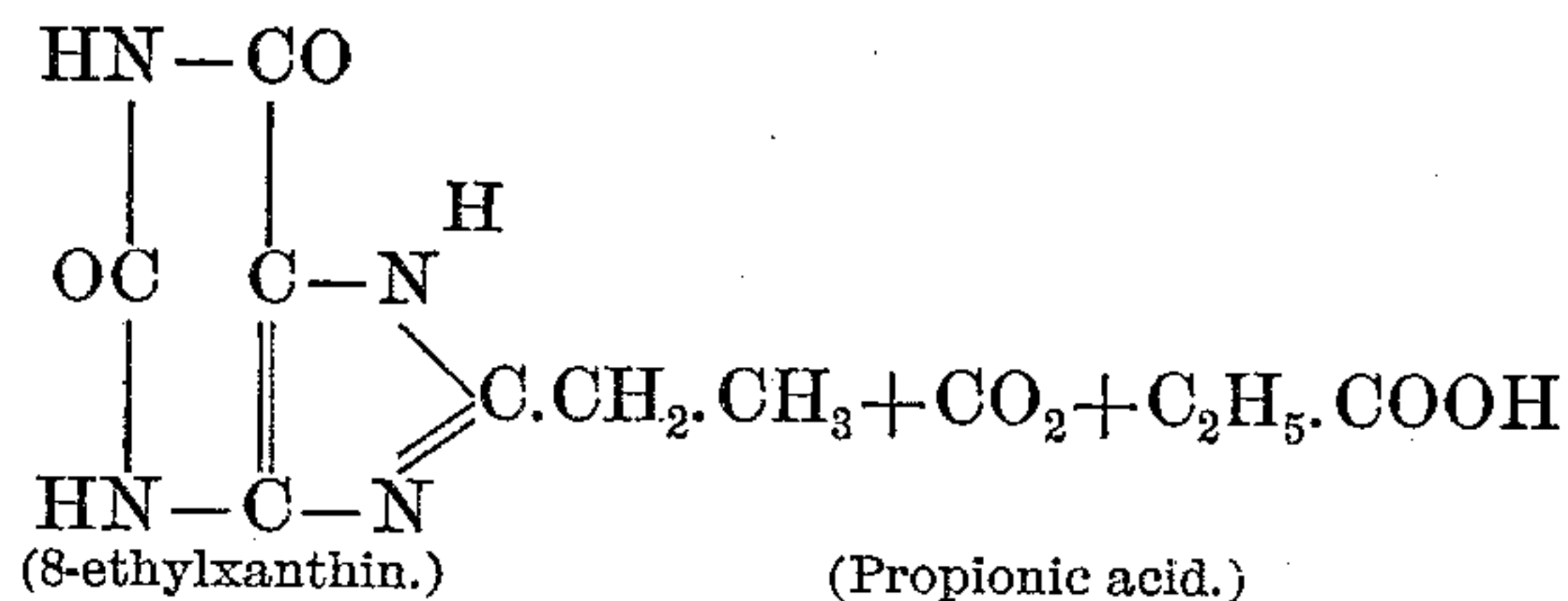
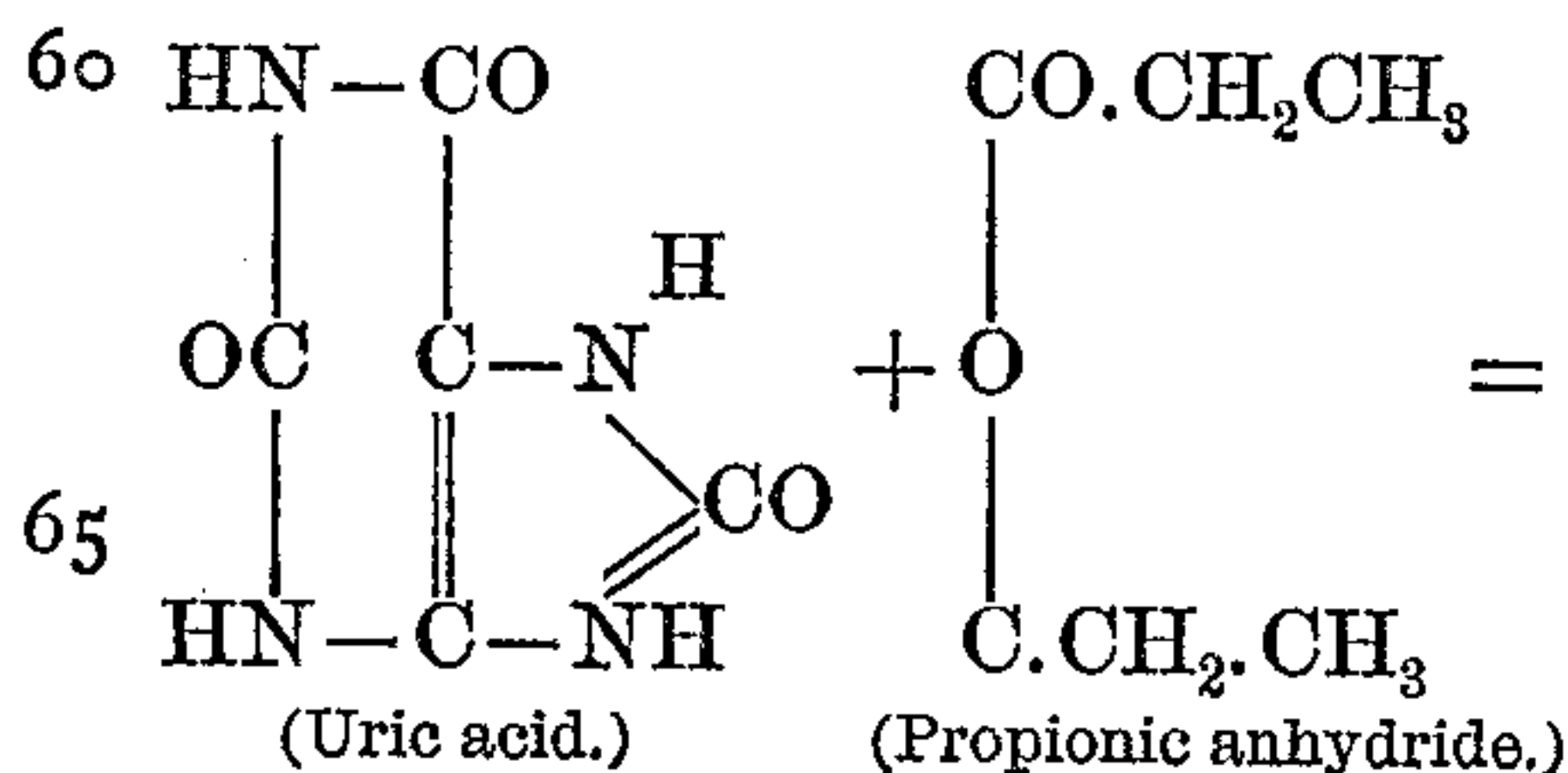
1-3-8-trimethylxanthin is rather soluble in boiling alcohol and moderately so in boiling chloroform. Moreover, it is readily soluble in ammonia and dilute alkalies. From concentrated alkali solutions the corresponding alkali salts are immediately thrown out in the form of fine acicular crystals. It is readily soluble in dilute mineral acids. With nitrate of silver in nitric-acid solution a double salt, crystallizing in fine needles, is formed. An ammoniacal solution of the same forms with nitrate of silver a silver salt, which is very difficultly soluble in ammonia and which is perfectly stable when boiling.

1-3-8-trimethylxanthin melts to a pale-colored liquid at 325° centigrade and sublimes almost without decomposition when continuously heated to a higher temperature in the form of fine colorless needles.

4. *Preparation of 8-ethylxanthin from uric acid proper.*—One part of uric acid proper is heated to boiling temperature, together with ten parts of propionic-acid anhydride and 0.5 parts of pyridin in a reflux apparatus. After boiling for twenty hours the conversion of the uric acid into 8-ethylxanthin will be completed—a stage of the process which is indicated by the fact that the product which remains undissolved in the anhydride ceases to reduce an ammoniacal silver solution. The resultant slightly-colored crystalline powder is dissolved in dilute alkali and treated with carbon (such as animal carbon or bone-black) for the purposes of decoloration. From such solution the 8-ethylxanthin is precipitated by dilute acids as a colorless fine granular powder, whose analysis gives figures corresponding to the formula $C_7H_8N_4O_2$ or, structurally,



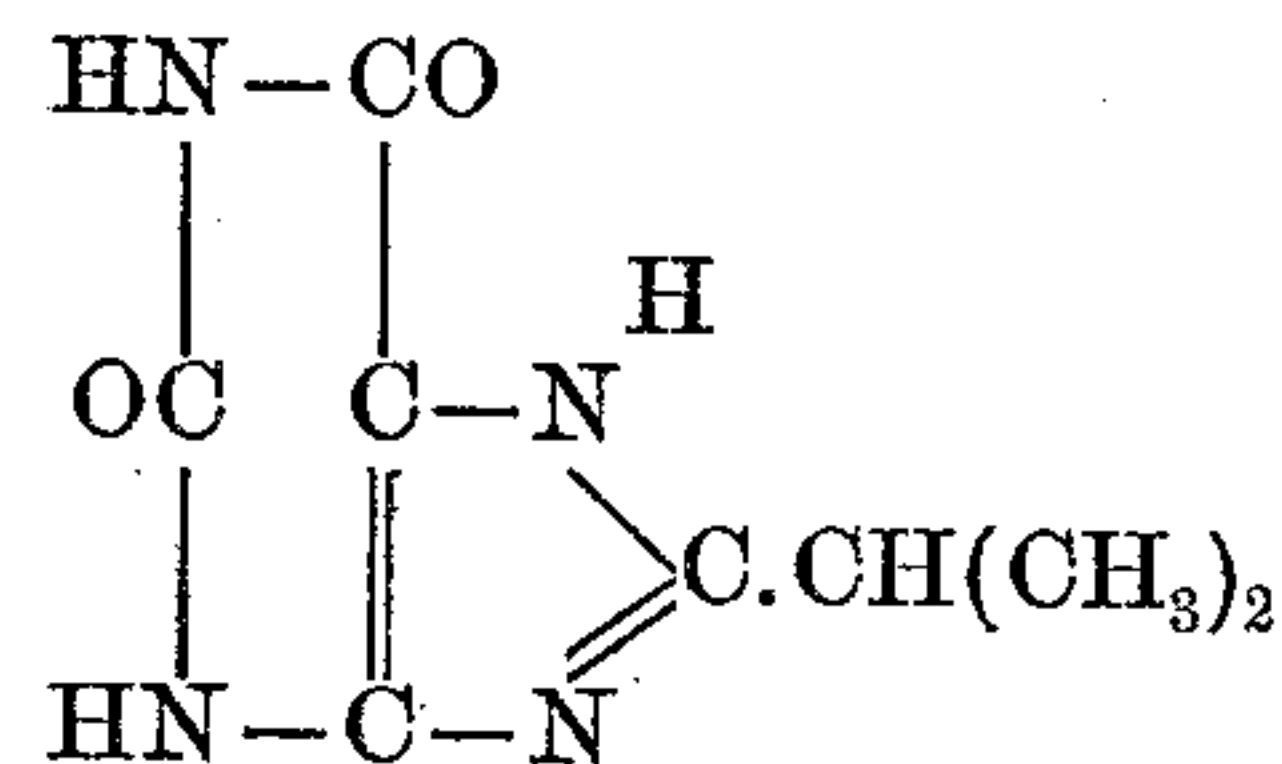
The reaction to which the formation of this new compound is due proceeds according to the equation:



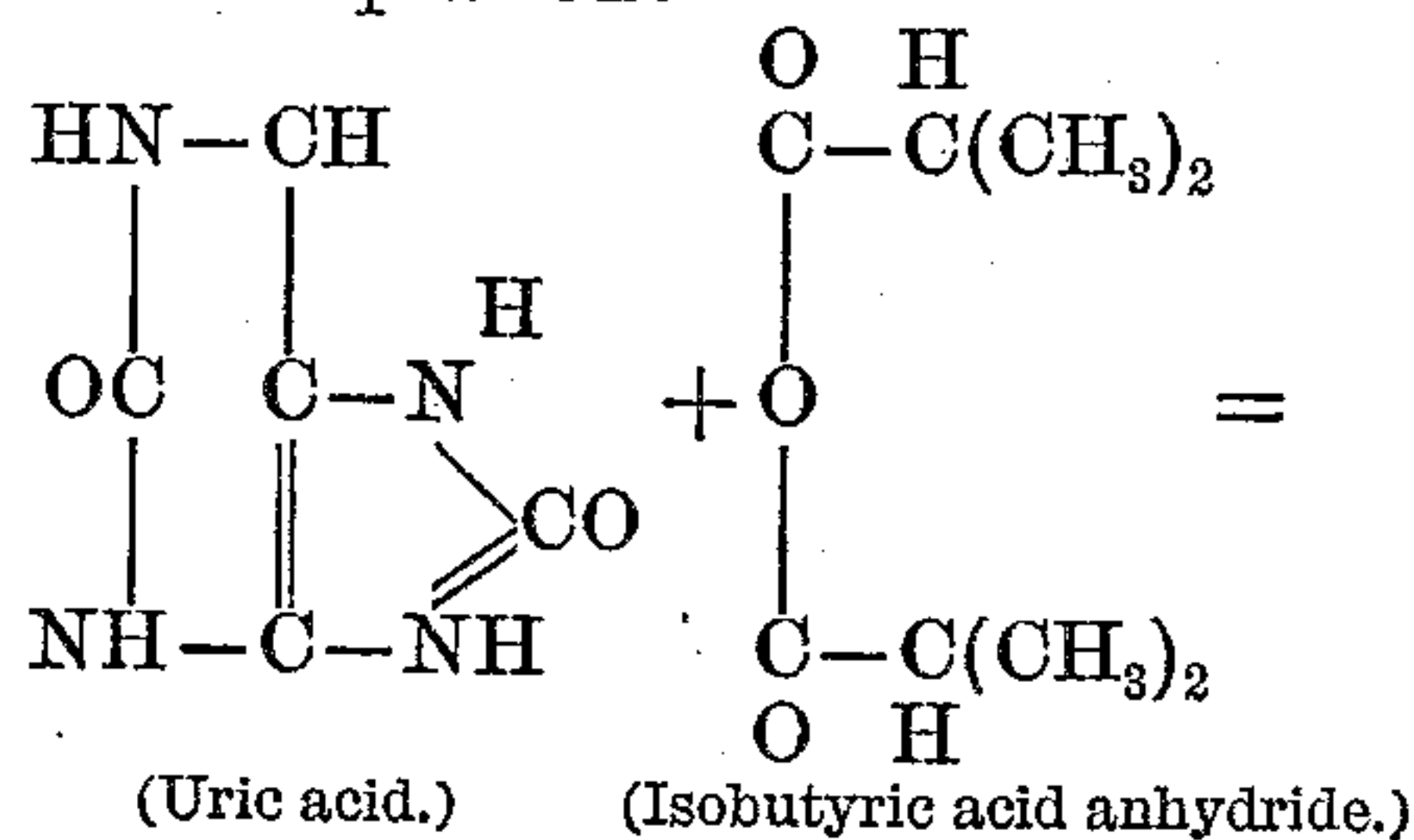
Eight hundred and fifty to nine hundred parts of boiling water are required to dissolve one part of 8-ethylxanthin. From such solution the new xanthin crystallizes in the form of small colorless tablets. It is readily soluble in alkalies, including ammonia, and on heating also in dilute acids. A solution of the same gives rise to a colorless gelatinous silver salt when nitrate of silver is added thereto, said silver salt being soluble only with difficulty in excess of ammonia and remaining unchanged on boiling. If the new base be dissolved in dilute nitric acid and silver nitrate be added to such solution, a colorless double salt, which crystallizes in fine needles, is precipitated.

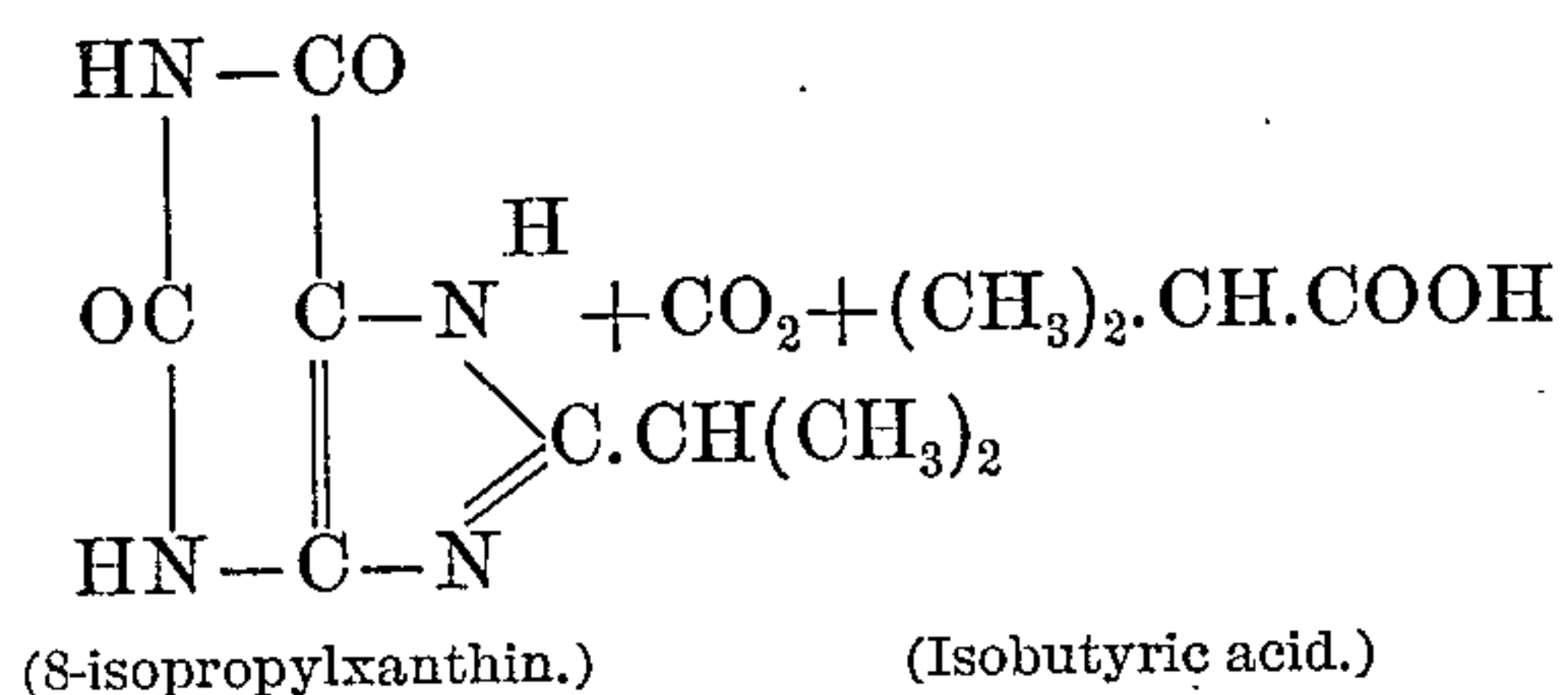
8-ethylxanthin on being heated above 350° centigrade assumes a brownish color, and at about 390° centigrade it is decomposed with effervescence or frothing.

5. *Preparation of 8-isopropylxanthin from uric acid proper.*—One part of uric acid, together with six parts of isobutyric acid anhydride and 0.4 parts of pyridin are heated to 170° to 175° centigrade in a closed tube and maintained at this temperature for thirty-six hours, the mass being continuously agitated during this treatment. On thereafter allowing the mass to cool strong pressure will exist in the tube, and the almost colorless resultant undissolved product will not reduce a silver solution on boiling. The liquor is then drained from the solid product, and the latter is dissolved in dilute alkali and treated with carbon in the ordinary manner and acidulated with a dilute mineral acid. Thereby a colorless powder, consisting of compact granular crystals, is obtained, which on analysis has been found to have the formula $C_8H_{10}N_4O_2$ or, structurally expressed,



The formation of the 8-isopropylxanthin under the above reaction proceeds according to the equation:





10 This new alkylxanthin is soluble in about four hundred and fifty parts boiling water, crystallizing therefrom in well-developed short prisms obliquely truncated at both ends, when the solution is allowed to cool slowly.

15 It is readily soluble in alkalies, including ammonia, and also in dilute mineral acids when gently warming the latter. From an ammoniacal solution of the same a colorless gelatinous silver salt is precipitated with a

20 solution of nitrate of silver, which precipitate is unchanged on boiling.

On heating the 8-isopropylxanthin above 340° centigrade it assumes a gold-brown color, and at about 380° centigrade it melts with effervescence or frothing.

25 Having thus fully described my invention, what I claim as new, and desire to secure by Letters Patent, is—

1. The process of preparing xanthin homologues, which consists in heating a uric acid together with an organic-acid anhydride.

2. The process of preparing xanthin homologues, which consists in heating a uric acid together with an organic-acid anhydride under pressure.

3. The process of preparing xanthin homologues, which consists in heating a uric acid together with an organic-acid anhydride and a condensing agent.

40 4. The process of preparing xanthin homologues, which consists in heating a uric acid together with an organic-acid anhydride and a condensing agent under pressure.

5. The process of preparing an 8-alkyl-
45 xanthin which consists in heating uric acid

proper together with an organic-acid anhydride.

6. The process of preparing an 8-alkylxanthin which consists in heating under pressure uric acid proper together with an organic-
50 acid anhydride.

7. The process of preparing an 8-alkylxanthin which consists in heating uric acid proper together with organic-acid anhydride and a condensing agent.

8. The process of preparing an 8-alkylxanthin which consists in heating under pressure uric acid proper and an organic-acid anhydride together with a condensing agent.

9. The process of preparing an 8-alkyl-
60 xanthin which consists in heating a uric acid and an organic-acid anhydride together with pyridin.

10. The process of preparing an 8-alkylxanthin which consists in heating under pres-
65 sure a uric acid and an organic-acid anhydride together with pyridin.

11. As a new chemical compound, a homologue of xanthin having an alkyl radical bound to the position 8, and having the prop-
70 erties of xanthin proper.

12. As a new chemical compound, 8-alkylxanthin whose formula differs from that of xanthin proper by having an alkyl radical substituted for the H in the position 8, which
75 is readily soluble in alkalies including ammonia, and in dilute acids and difficultly soluble in boiling water, which is precipitated from the alkaline solution by dilute acids in the form of a granular powder, which
80 becomes colored on heating to a high temperature and which has no melting-point but decomposes with frothing on heating to a still higher temperature.

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

FRITZ ACH.

Witnesses:

J. ADRIAN,

MAX BONHUEB.