UNITED STATES PATENT OFFICE.

EMIL FISCHER, OF BERLIN, GERMANY, ASSIGNOR TO C. F. BOEHRINGER & SOEHNE, OF WALDHOF, GERMANY.

ALKYL-HYPOXANTHIN AND PROCESS OF MAKING SAME.

SPECIFICATION forming part of Letters Patent No. 618,045, dated January 17, 1899.

Original application filed September 7, 1897, Serial No. 650,826. Divided and this application filed January 3, 1898. Serial No. 665,463. (Specimens.)

To all whom it may concern:

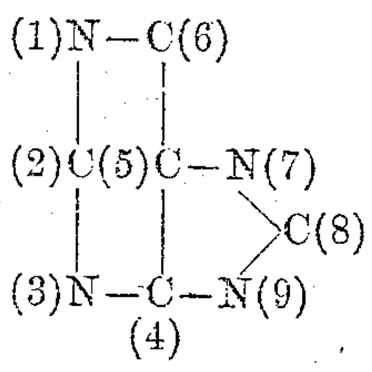
Be it known that I, EMIL FISCHER, a citizen of the German Empire, residing at Berlin, in the Empire of Germany, have invented certain new and useful Improvements in the Art of Preparing Methylized Hypoxanthins; and I do hereby declare the following to be a full, clear, and exact description of the invention, 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 alkylized oxypurins, and more particularly the synthetical production of methylized hypoxanthins which have been recognized as methylized oxypurins as the result of recent investigations.

Dimethyl-hypoxanthin has hitherto been obtained only by methylation of hypoxanthin, (Krüger, *Zeitschrift f. Phys. Chem. 18, 436.*) As to monomethyl-hypoxanthin I am the first to obtain the same in any manner.

My present invention consists in the methods of synthetically preparing these methylized hypoxanthins, in the monomethyl-hypoxanthin, and in such further features and subprocesses as will be hereinafter disclosed and pointed out in the claims.

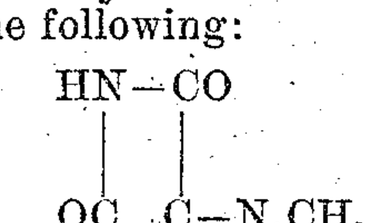
In explaining my invention the nomenclature recently proposed by me (*Sitzungs-Berichte der Königl. Preussischen Akademie*, 1897, No. 1, January 8, 1897, and *Berichte der Deutschen Chemischen Gesellschaft*, Vol. 30, No. 5, page 557) and the structural formulæ, adopted as the result of the most recent investigations, will be adopted. According to this nomenclature the various atoms of the purin molecule, which forms the basis of the uric acid and xanthin molecules and many others, are numbered as follows:



Bearing these numerals and their relative positions in mind, the designations of the equivalent terms hereinafter used in connection with theobromin, the primary starting material employed in my process, and of the hypoxanthins will be apparent and readily understood.

The structural formulæ and consequent additional designations which may be attached to these compounds are the following:

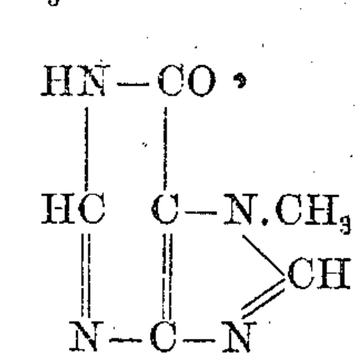
First. Theobromin



or 3-7-dimethyl-xanthin

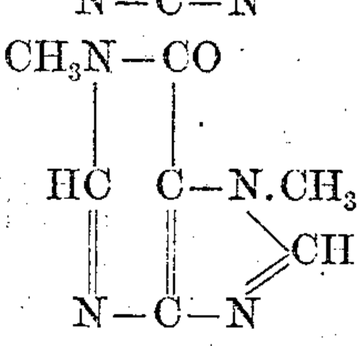
or 3-7-dimethyl-2-6-dioxypurin

Second. 7-methyl-hypoxanthin



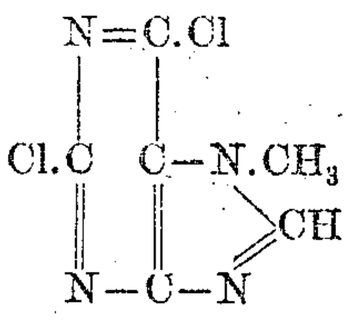
or 7-methyl-6-oxypurin

Third. 1-7-dimethyl-hypoxanthin



or 1-7-dimethyl-6-oxypurin

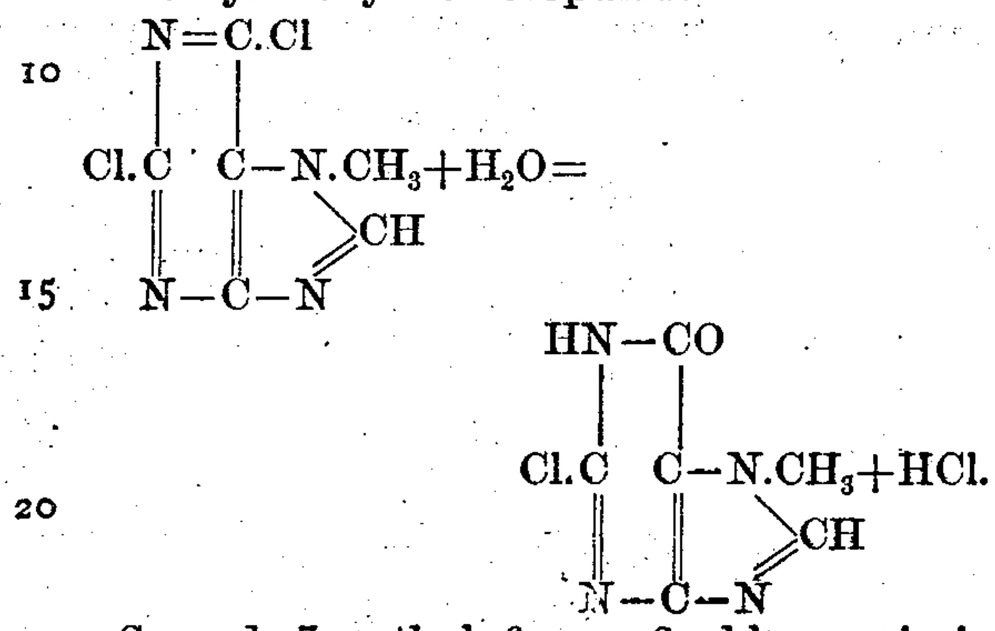
In preparing the hypoxanthins I start from theobromin, which is the same as 3-7-dimethyl-xanthin or 3-7-dimethyl-2-6-dioxypurin and whose formula is given above, treating the same with a phosphorus-oxyhalogen compound, such as phosphorus-oxychlorid. Under this treatment the oxygen atoms are replaced by chlorin and one methyl radical is split off, the resultant body being 7-methyl-2-6-dichloropurin:



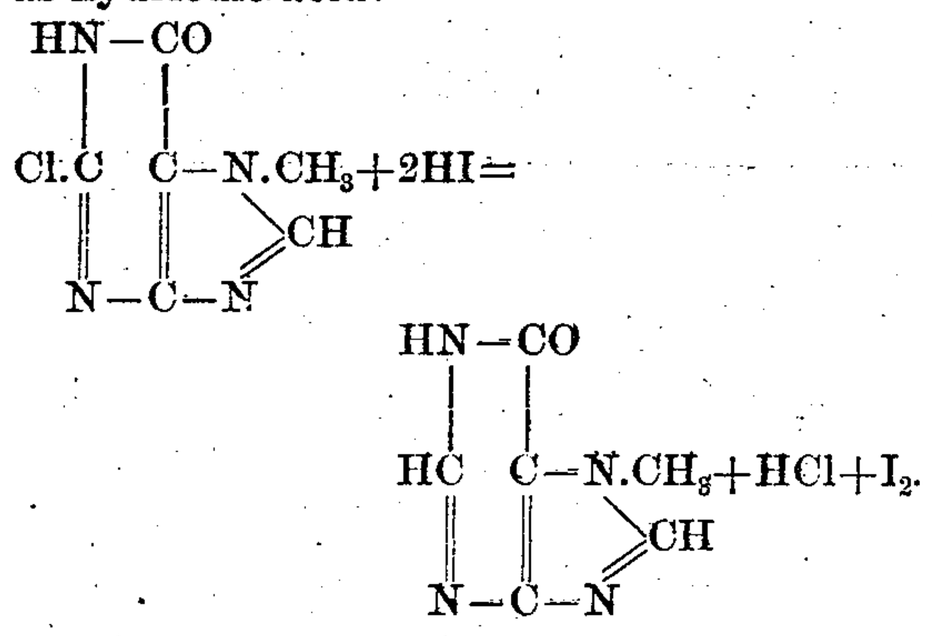
The two chlorin atoms of this new body, methyl-dichloropurin, are very mobile. They may be eliminated and replaced by hydroxyl simultaneously or separately. For the pur-

poses of the present invention I remove one only of the chlorin atoms. This substitution gives rise to the following reactions leading to the methylized hypoxanthins:

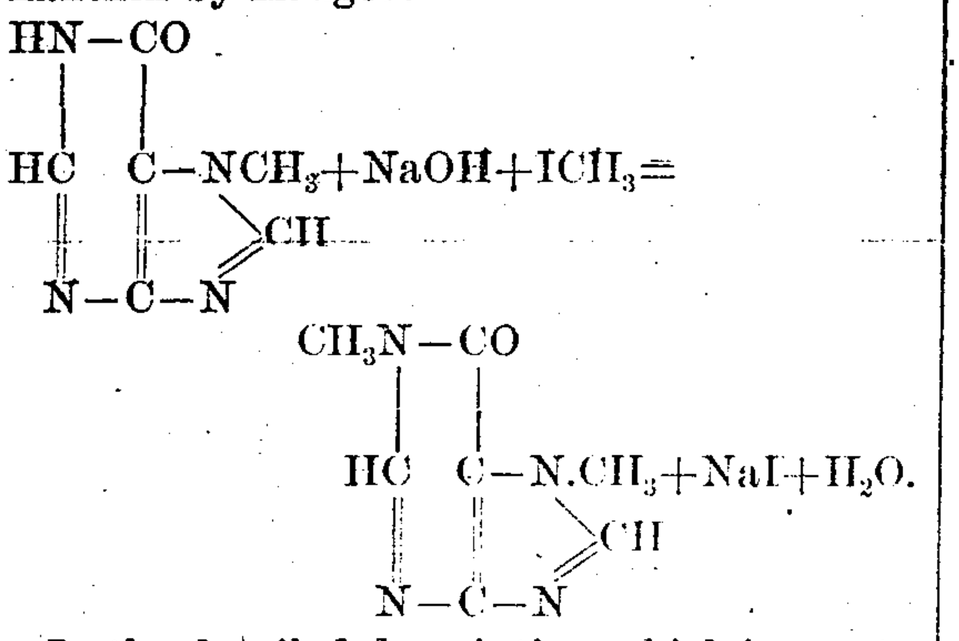
First. 7-methyl-2-6-dichloropurin on being treated with alkali exchanges only one chlorin atom for hydroxyl, the resultant body being 7-methyl-6-oxy-2-chloropurin:



Second. 7-methyl-6-oxy-2-chloropurin is converted into 7-methyl-hypoxanthin or 7-methyl-6-oxypurin by a reducing agent, such as hydriodic acid:

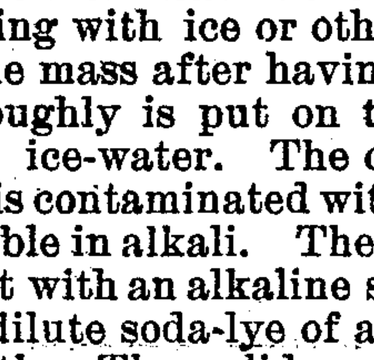


Third. The 7-methyl-hypoxanthin or 7-methyl-6-oxypurin by further methylation is converted into dimethyl-hypoxanthin, which has been prepared from natural hypoxanthin by Krüger:

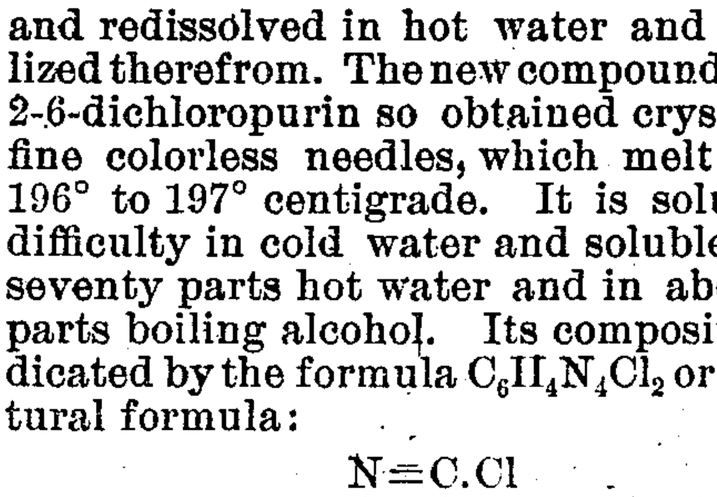


In the detailed description which is now to follow I will divide the subject into four heads, arranged in the order above indicated, giving a disclosure, first, of the method of converting the starting material, theobromin, into 7-methyl-2-6-dichloropurin; secondly, the method of preparing the 7-methyl-6-oxy-2-chloropurin; thirdly, the method of converting this into 7-methyl-hypoxanthin, and, fourthly, the preparation of 1-7-dimethyl-hypoxanthin.

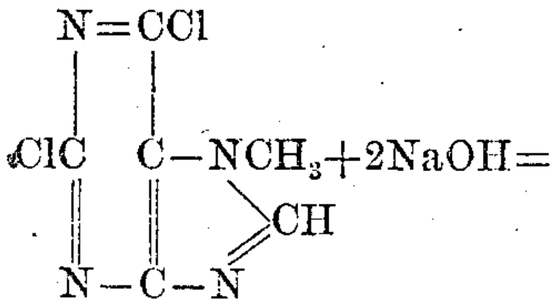
First. Preparation of 7-methyl-2-6-dichloropurin.—I take ten parts of theobromin and heat the same under pressure—*e. g.*, in a digester—together with one hundred parts of phosphorus-oxychlorid, to a temperature of 140° centigrade, this temperature being maintained for three hours and the mass constantly agitated. A clear liquid having a pale-brown color results. From this liquid the remaining phosphorus-oxychlorid is removed by distilling *in vacuo*. One hundred and fifty parts of cold water, having a temperature of between 0° and 5° centigrade preferably, are then poured over the amorphous residue. Under this treatment the mass is gradually converted into almost colorless crystals. This change is hastened by shaking. The generation of heat in the mass is obviated by cooling with ice or other refrigerant agency. The mass after having been finally cooled thoroughly is put on the filter and washed with ice-water. The crude product so obtained is contaminated with a substance which is soluble in alkali. The same is hence dissolved out with an alkaline solution, preferably very dilute soda-lye of about one-per-cent. strength. The solid residue is then drained on a filter and well washed thereon and redissolved in hot water and recrystallized therefrom. The new compound 7-methyl-2-6-dichloropurin so obtained crystallizes in fine colorless needles, which melt at about 196° to 197° centigrade. It is soluble with difficulty in cold water and soluble in about seventy parts hot water and in about thirty parts boiling alcohol. Its composition is indicated by the formula $C_6H_4N_4Cl_2$ or the structural formula:

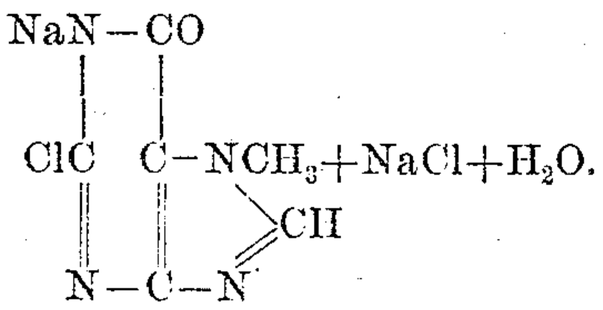


The reaction taking place in preparing the same from theobromin is indicated in the equation:



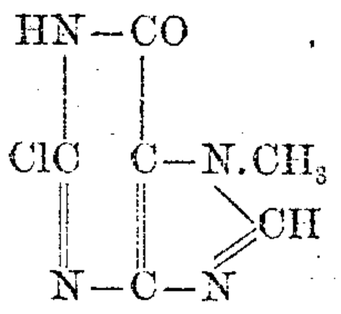
Second. Preparation of 7-methyl-6-oxy-2-chloropurin.—Ten parts of finely-pulverized 7-methyl-2-6-dichloropurin, which has been described under the first head, are suspended in one hundred parts of boiling water and a quantity of soda-lye sufficient to furnish two molecules of the alkali for each molecule of the methyl-dichloropurin. The mass is then stirred until a clear solution is formed, whereby the end of the process is indicated. The reaction takes place according to the following equation:





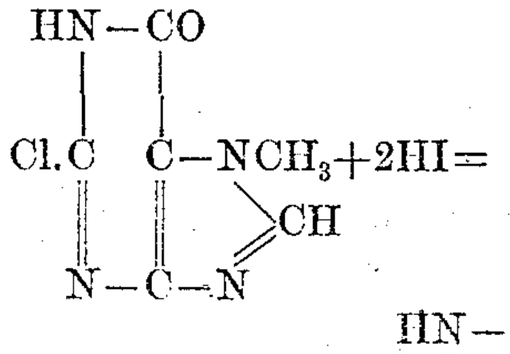
The liquid is then cooled and the same is then supersaturated with acetic acid, whereby the methyl-oxypurin is precipitated in crystalline form. This precipitate after being separated is boiled in one hundred and fifty parts of water, and after boiling it is filtered and the filtrate allowed to cool, when the new product will be thrown down in the form of columnar crystals of a yellow color. To completely purify the product, it is first converted into its barium salt, which forms fine crystals, and then reconverted into the methyl-oxychloropurin by redissolving the barium salt in fifty to sixty parts of hot water and supersaturating with acetic acid.

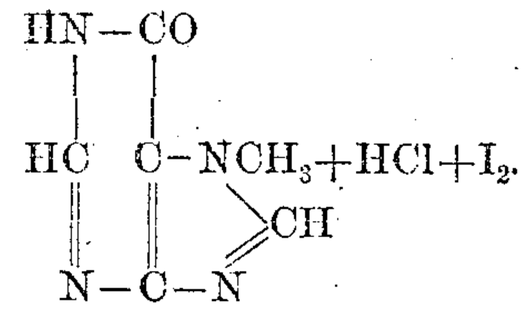
The analysis of the new product shows that its formula is $C_6H_5N_4OCl$ and that its structure corresponds to the formula:



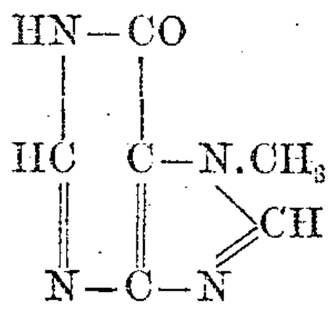
Pure methyl-oxychloropurin attains a yellow color when heated to about 310° centigrade. At a higher temperature its color becomes more and more dark, this darkening being attended by continuing decomposition. It dissolves in about one hundred and fifty parts of boiling water and in about two hundred and fifty parts of boiling alcohol.

Third. Preparation of 7-methyl-hypoxanthin.—One part of 7-methyl-6-oxy-2-chloropurin, which has been hereinabove described, is mixed with eight parts of colorless hydriodic acid of the specific gravity 1.96 by pouring the latter over the former. It is then heated to from 60° to 70° centigrade, after having first added a half part of phosphonium-iodid, and maintained at this temperature and frequently shaken until a clear colorless solution results. The liquid is then evaporated, when the hydriodate of the 7-methyl-hypoxanthin or 7-methyl-6-oxypurin remains as a colorless crystalline mass, which is readily soluble in water. The reaction proceeds according to the equation:





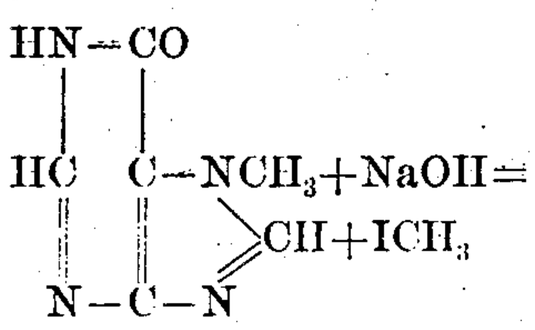
This new base, 7-methyl-hypoxanthin, is liberated from the above salt by dissolving the latter in water and boiling the same, then adding carbonate of lead to the boiling solution, and then filtering. Any traces or small quantities of lead remaining in the filtrate are then thrown out by means of hydrosulfuric acid and the liquid is again filtered, after which the filtrate is evaporated to dryness. The residue is methyl-hypoxanthin and forms a colorless crystalline mass, which is redissolved in and crystallized from alcohol for the purpose of purification. It is thus obtained in the form of fine colorless needles. Its analysis shows that its constitution corresponds to the formula $C_6H_6N_4O$. Its structural formula is

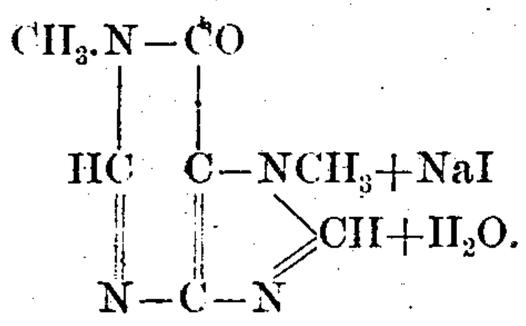


7-methyl-hypoxanthin when rapidly heated assumes a brown color at about 340° centigrade and melts at about 353° centigrade. The melting-point, however, is not quite fixed. It is readily soluble in water. On adding nitrate of silver to an aqueous solution of the same a white precipitate is formed, which on being dissolved in warm dilute nitric acid is obtained as a white crystalline powder.

Fourth. Preparation of 1-7-dimethyl-hypoxanthin.—Two parts of 7-methyl-hypoxanthin, which has been described, are mixed with twenty parts of water, twenty parts of methyl alcohol, two parts of methyl iodid, and 0.3 parts of sodium dissolved in methyl alcohol, (a quantity sufficient to replace the hydrogen represented by the one imido group

in the formula of 7-methyl-hypoxanthin.) The mixture is then heated in a closed vessel to from 75° to 80° centigrade, this temperature being maintained for three hours. The resulting liquid is then highly concentrated and allowed to cool. On cooling, the sodium-iodin compound of 1-7-dimethyl-hypoxanthin, which has been described by Krüger (*Berichte der Deutschen Chemischen Gesellschaft*, Vol. 26, page 1921) and having the formula $C_7H_8N_4O.NaI+3aq.$, is separated from the liquid in the form of needles. The base is separated from the sodium-iodin compound by dissolving in water and shaking with oxid of silver. After filtration of the iodid of silver the solution is evaporated and the base extracted from the residue with chloroform. After the solvent has evaporated the dimethyl-hypoxanthin remains as a crystalline mass in the form of fine needles. The former process proceeds according to the equation:





Dimethyl-hypoxanthin begins to soften at about 243° centigrade and melts at 246° centigrade without decomposition. Heated in small quantities it distils over without decomposition for the greater portion. From hot alcohol it crystallizes in the form of fine needles, which for the most part are massed together. In other respects this base is distinguished by the characteristic properties set forth by Krüger.

The 7-methyl-2-6-dichloropurin herein described, together with its method of manufacture, forms the subject-matter of the claims of my application, Serial No. 650,826, filed September 7, 1897, (of which this is is a divisional application,) and is there shown to be the starting material for the series of processes and compounds described in illustration of the invention. It is hence not claimed herein, being merely described for the purpose of a full and sufficient disclosure of my present invention.

Having thus fully described my invention, what I claim, and desire to secure by Letters Patent of the United States, is—

1. The process of preparing methyl-hypoxanthin which consists in treating 7-methyl-6-oxy-2-chloropurin with a reducing agent.

2. The process of preparing methyl-hypoxanthin which consists in heating 7-methyl-6-oxy-2-chloropurin together with hydriodic acid and phosphonium iodid.

3. The process of preparing methyl-hypoxanthin which consists in adding hydriodic acid to 7-methyl-6-oxy-2-chloropurin and heating the mixture after first adding phosphonium-iodid to the same, all in the proportions and under the conditions substantially as set forth.

4. The process of preparing methyl-hypoxanthin which consists in adding hydriodic acid to 7-methyl-6-oxy-2-chloropurin and heating the mixture after first adding phosphonium-iodid to the same, all in the proportions and under the conditions substantially as set forth and then separating the resultant hydriodate of the monomethyl-hypoxanthin and treating the said hydriodate with carbonate of lead.

5. The process of preparing methyl-hypoxanthin which consists in adding hydriodic acid and phosphonium-iodid to 7-methyl-6-oxy-2-chloropurin and heating and shaking the same, then evaporating and dissolving the residue in water and boiling, then adding carbonate of lead and boiling.

6. The process for the manufacture of monomethyl-hypoxanthin which consists in the following steps: treating theobromin with a phosphorus-oxyhalogen compound and isolating the resultant 7-methyl-2-6-dichloropurin; treating the latter with an alkali and then isolating the resultant 7-methyl-6-oxy-2-chloropurin and treating the latter with a reducing agent.

7. As a new chemical compound, 7-methyl-hypoxanthin, which has the formula hereinabove stated, whose melting-point is about 353° centigrade, which is readily soluble in water and which assumes a brown color when rapidly heated to about 340° centigrade.

8. The process in the manufacture of dimethyl-hypoxanthin which consists in treating 7-methyl-hypoxanthin with a methylating agent.

9. The process for the manufacture of dimethyl-hypoxanthin which consists in treating 7-methyl-hypoxanthin with methyl alcohol, methyl iodid, and sodium methylate.

10. The process for the manufacture of dimethyl-hypoxanthin which consists in mixing 7-methyl-hypoxanthin with water, methyl alcohol, methyl iodid and sodium methylate, heating the mixture under pressure, concentrating the resulting liquid and cooling, all in the proportion and under the conditions substantially as specified.

11. The process for the manufacture of dimethyl-hypoxanthin which consists in treating 7-methyl-6-oxy-2-chloropurin with a reducing agent and isolating the resultant 7-methyl-hypoxanthin and then methylating the latter.

12. The process for the manufacture of dimethyl-hypoxanthin which consists in the following steps: treating 7-methyl-2-6-dichloropurin with an alkali and isolating the resultant 7-methyl-6-oxy-2-chloropurin; treating

the latter with a reducing agent and separating the resultant 7-methyl-hypoxanthin, then methylating the latter product.

13. The process for the manufacture of dimethyl-hypoxanthin which consists in the following steps: treating theobromin with an oxyhalogen compound of phosphorus and isolating the resultant 7-methyl-2-6-dichloropurin; treating the latter with an alkali and isolating the resultant 7-methyl-6-oxy-2-chloropurin, then treating the latter with a reducing agent and separating the resultant 7-methyl-hypoxanthin, and methylating the latter.

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

EMIL FISCHER.

Witnesses:
CHAS. H. DAY,
HENRY HASPER.