UNITED STATES PATENT OFFICE.

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

OXYPURIN AND PROCESS OF MAKING SAME.

SPECIFICATION forming part of Letters Patent No. 631,708, dated August 22, 1899.

Application filed January 31, 1898. Serial No. 668,646. (Specimens.)

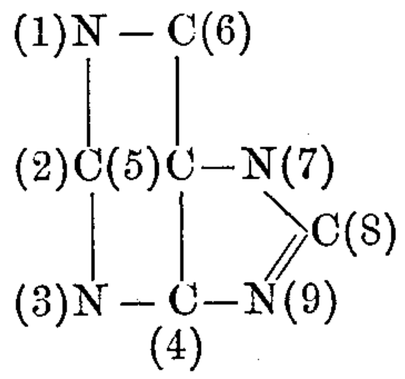
To all whom it may concern:

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 the Manufacture of Oxypurins 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.

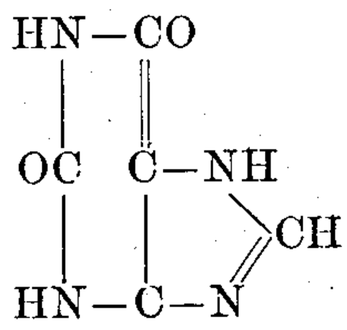
The present invention relates to the preparation of oxypurins and their alkyl derivatives, and particularly to the production of a series of bodies starting from trichloropurin, a compound which is described in Letters Patent of the United States No. 598,502, dated February 8, 1898.

The present invention has for its specific object the preparation of xanthin, synthetically, from trichloropurin and also the production of the intermediate new compound 8-chlorodiakyl-oxypurin.

Before proceeding with the description it should be stated that the nomenclature herein followed is that adopted by the article published in *Berichte der Deutschen Chemischen Gesellschaft*, Vol. 30, page 549. According to this nomenclature a large number of bodies—such as caffein, uric acid, guanin, adenin, &c.—are designated by the generic term "purins," and their nucleus, the "purin group," has its several carbon and nitrogen atoms numbered in the following manner:

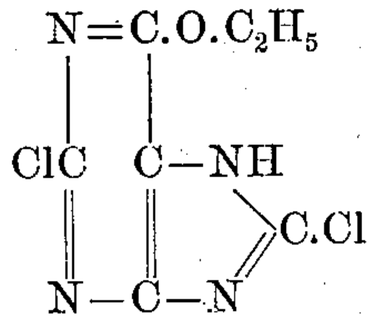


Bearing this nomenclature and system of numbering the position of the atoms in the molecule in mind, the use of terms in the following description will be readily understood. Thus, for example, the compound xanthin, which may be obtained synthetically by the application of my invention, is styled "2-6-oxy-purin" under the new nomenclature, since it has the structural formula:

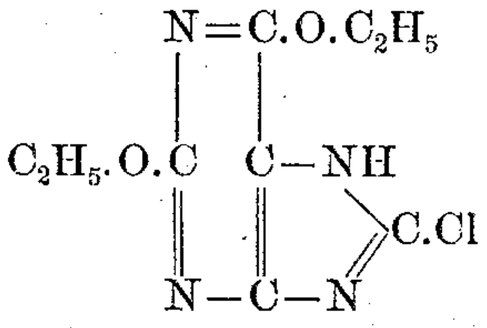


The two known methyl-trichloropurins described in *Berichte der Deutschen Chemischen Gesellschaft*, Vol. 17, page 331, and Vol. 28, page 2488, have hitherto not been susceptible of conversion into xanthin derivatives by the action of alkali, for the reason that the latter causes the chlorin atom in the position 8 to be split off. I have found, however, that the unmethylated trichloropurin, the trichloropurin proper, which, together with its method of preparation, forms the subject-matter of my Letters Patent of the United States No. 598,502, dated February 8, 1898, behaves in a radically different manner. This compound is a strong acid and forms stable alkali salts, the formation of the salts resulting in such a modification in the affinities of the three chlorin atoms that on heating with alkali the chlorin atom in the position 6 instead of the chlorin atom in the position 8 is first split off and replaced by oxygen.

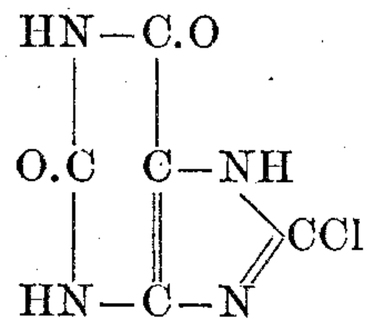
At ordinary temperature.—For example, when acting upon trichloropurin with alcoholic alkali at ordinary room temperature the former is converted into 6-ethoxy-2-8-dichloropurin having the formula:



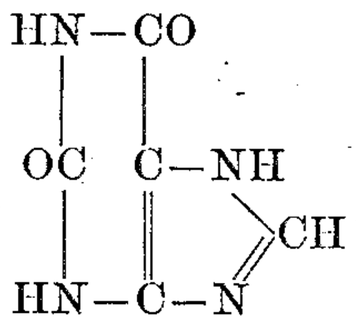
At higher temperature.—If the trichloropurin is acted upon with alcoholic alkali at higher temperature, a second chlorin atom is eliminated—namely, that occupying the position 2. As a result of this reaction we obtain 8-chloro-2-6-diethoxy-purin having the structural formula:



The latter body on treatment with hydrochloric acid loses the two ethyl groups, forming 2-6-dioxy-8-chloropurin, having the structural formula:



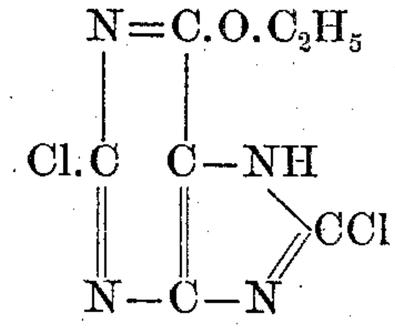
This latter body, which on account of its structure I term "chloro-xanthin," is by reduction converted into 2-6-dioxy-purin—



which is identical with natural xanthin. It is true of the 8-chloro-2-6-diethoxy-purin also that the elimination of the ethyl groups and the substitution of hydrogen for the chlorin atom may be simultaneously carried out by the action of hydriodic acid, xanthin being again obtained as above. If in lieu of ethyl-alcohol methyl-alcohol be substituted for the alcoholic solution, 8-chloro-2-6-dimethoxypurin will result. My invention, hence, involves the manufacture of chloro-dialkyl-oxypurins generally and of xanthin therefrom, directly or indirectly.

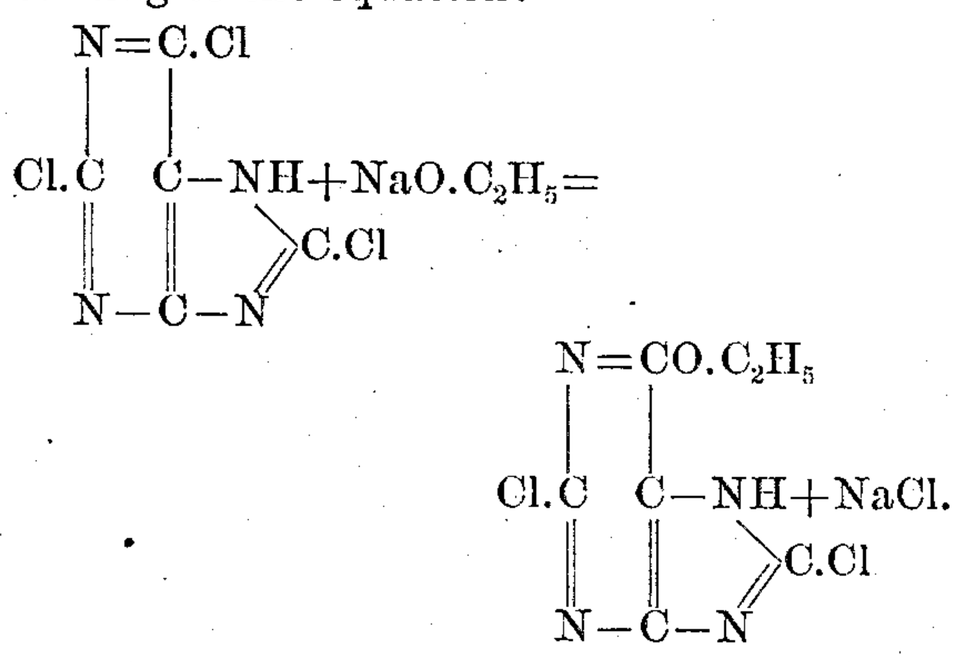
In the following detailed description I will first describe the preparation of 8-chloro-2-6-diethoxy-purin by proceeding either from the dichloro-alkyl-oxypurin or from trichloropurin and then the preparation of the xanthin from a chloro-dioxypurin without or with alkyl groups bound to the oxygens in the positions 2 and 6. This description will be preceded by the disclosure of the preparation of dichloro-alkyl-oxypurin, 2-8-dichloro-6-ethoxypurin. The proportions given are all understood to be by weight.

1. Preparation of 2-8-dichloro-6-ethoxy-purin.—Four parts dry trichloropurin, whose properties and mode of preparation are set forth in my aforesaid Patent No. 598,502, dated February 8, 1898, are dissolved in sixteen parts of alcohol, and this solution after being rapidly cooled to about 10° to 15° centigrade, and which as a rule has a tendency to throw out crystals of the trichloropurin, is added to a solution of one and two-tenths parts of sodium in twenty-four parts of alcohol cooled to room temperature. A clear pale yellow liquid results, whose temperature rises spontaneously to about 30° centigrade and soon becomes turbid by reason of a precipitation of sodium-chlorid. The mixture is allowed to stand at ordinary temperature for three hours, whereupon fifty parts of water are added and the whole is supersaturated slightly with acetic acid. The alcohol is then evaporated off, whereby the dichloro-ethoxypurin is precipitated in colorless very flexible acicular crystals. The same is then purified by recrystallization from hot benzol. Its formula is $C_7H_6Cl_2N_4O$, or



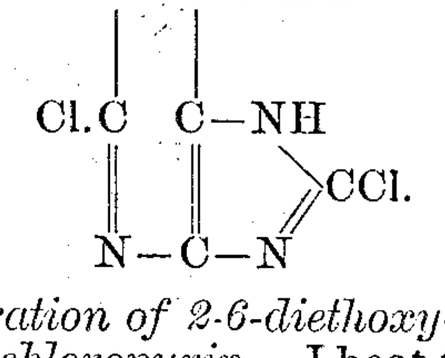
It softens at about 190° centigrade and melts completely at about 200° centigrade, the fusion being accompanied by decomposition. It is soluble only with difficulty in hot water, but dissolves readily in hot alcohol and aceton.

The above converting process proceeds according to the equation:



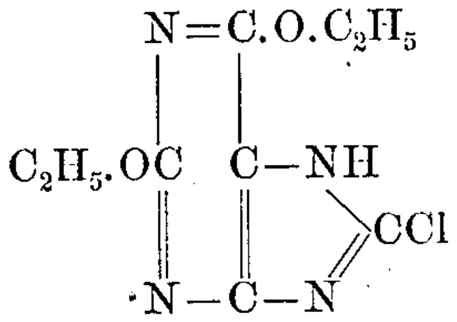
2. Preparation of 2-8-dichloro-6-methoxy-purin.—If in the place of the ethyl-alcoholic solution a methyl-acoholic solution of sodium is employed, the other ingredients and conditions of the above process remaining the same, I obtain 2-8-dichloro-6-methoxy-purin, which melts and decomposes at about 225° centigrade, and which is considerably less soluble in benzene than the ethoxy compound.

The generic formula for both of the oxy-alkyl-dichloro-purins is:

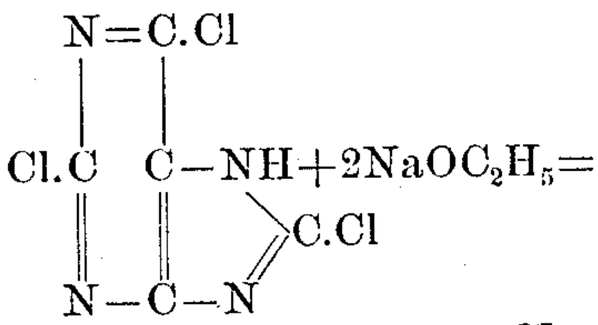


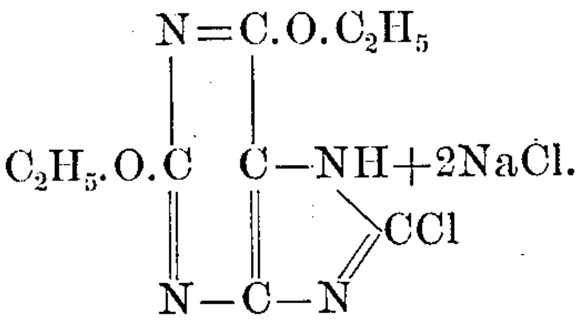
3. Preparation of 2-6-diethoxy-8-chloropurin from trichloropurin.—I heat trichloropurin (one part) together with a concentrated alcoholic solution of sodium-ethylate (containing one part of sodium) in a closed vessel to 100° centigrade, maintaining this tem-

perature for three hours. The sodium-ethylate must be in excess or at least two molecules more than sufficient to neutralize the trichloropurin. The alcohol is then evaporated and the residue is dissolved in water, the resulting yellow solution being then supersaturated with acetic acid, whereby the diethoxy-chloropurin is obtained as a copious precipitate, which forms fine needles. This new body has the formula $C_9H_{11}N_4ClO_2$, or, structurally expressed,



The reaction takes place according to the equation:

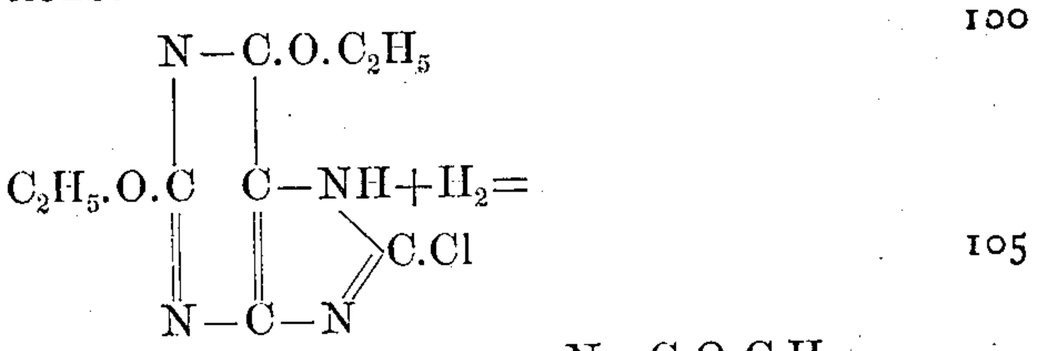




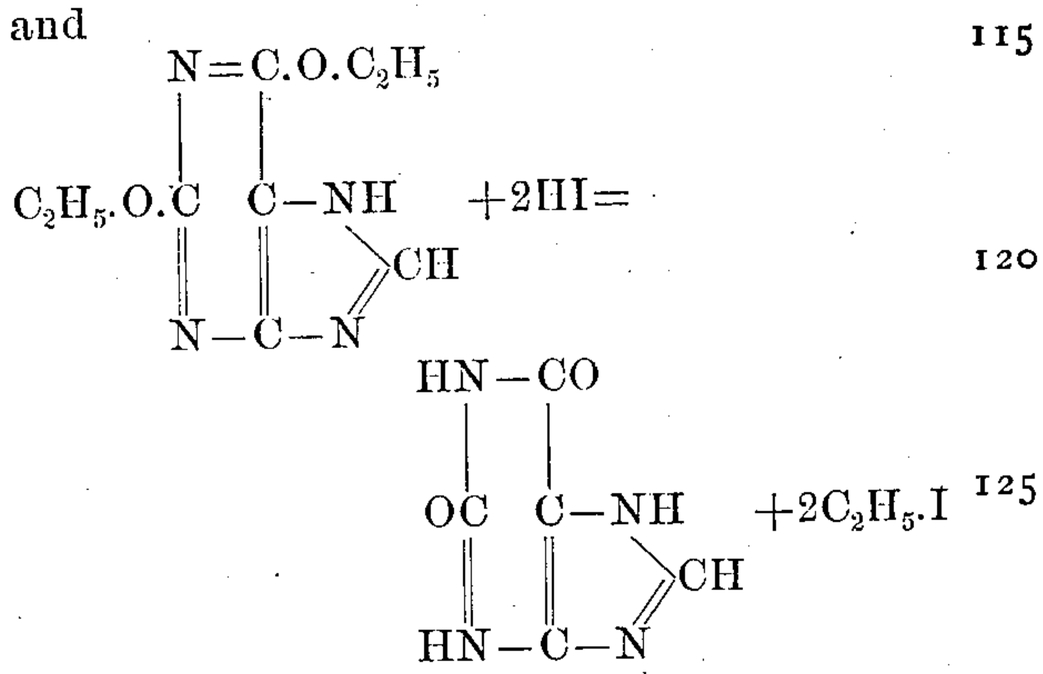
It is very similar in behavior to the monoethoxy compound described under example 1. Like the latter, it softens at about 190° centigrade and melts at about 205°, the melting-point being not sharply defined, and fusion being attended by decomposition and evolution of gas. In hot acohol it is very readily soluble, but very difficult of solution in benzol. It is readily soluble in alkalies, including ammonia and baryta-water. Boiling water dissolves the same only with difficulty, one thousand parts of the same being required for the solution of one part of the compound.

4. Preparation of 2-6-diethoxy-8-chloropurin from 2-8-dichloro-6-ethoxy-purin.—The diethoxy compound may also be obtained from the mono-ethoxy-chloro compound by heating the same with excess of sodium-ethylate under substantially the same conditions set forth under example 5.

5. Conversion of 8-chloro-2-6-diethoxy-purin into xanthin.—The chloro-diethoxy-purin may be converted into xanthin under the influence of reducing agents. Thus if the same is dissolved in ten times its weight of hydrogen-iodid or hydriodic acid of the specific gravity 1.96 at ordinary temperature the reduction begins promptly, iodin being liberated. The latter is again reduced by the addition of sufficient phosphonium-iodid or yellow phosphorus. The reduction is completed at the end of about an hour at ordinary temperature. In the course of this reaction the intermediate product 2-6-diethoxypurin is most probably formed, but remains dissolved in the hydrogen-iodid. This diethoxypurin, however, already undergoes a further conversion into 2-6-dioxypurin or xanthin in the course of the same reaction, the ethyl radicals being split off by the strong acid, particularly when dealing with large quantities. This second phase of the reaction is, however, only partial at ordinary temperatures, and consequently only a proportionately small quantity of hydriodate of xanthin is thrown out. If, on the other hand, the whole is subsequently heated on the water-bath, the conversion into xanthin becomes complete and its hydriodate is precipitated in the form of a thick crystalline mass. From this mass the hydriodic acid is evaporated and the residue is treated with dilute aqueous ammonia in slight excess and filtered. The residue is then dissolved in a large quantity of warm aqueous ammonia solution for purification. On boiling or evaporating the ammonia the xanthin is thrown out in the form of a colorless crystalline powder. The product thus obtained synthetically has all of the properties observed for natural xanthin. The reaction whereby the xanthin is formed under this head takes place according to the equations:

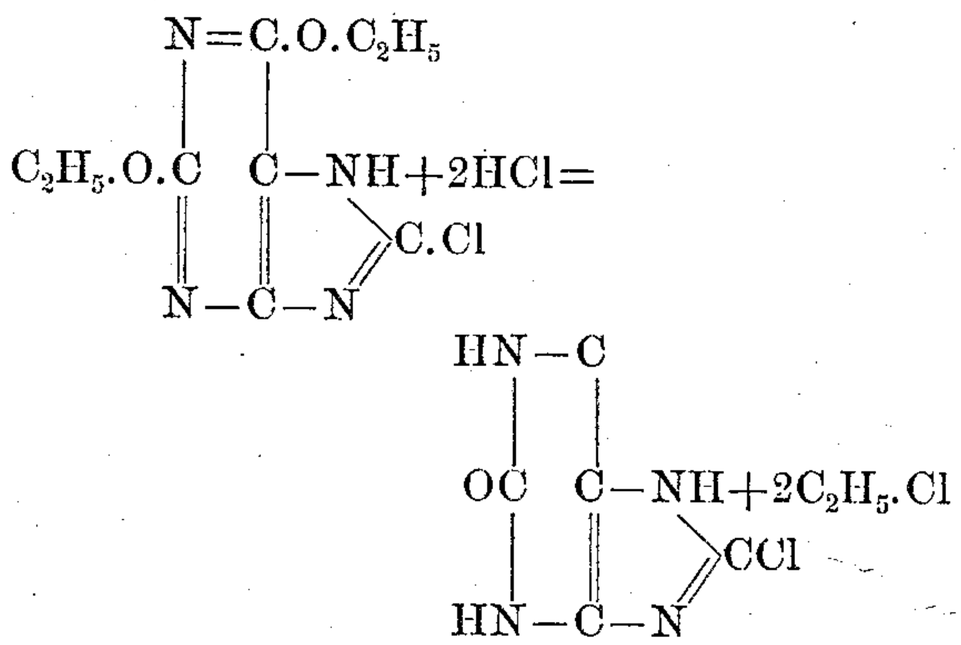


and

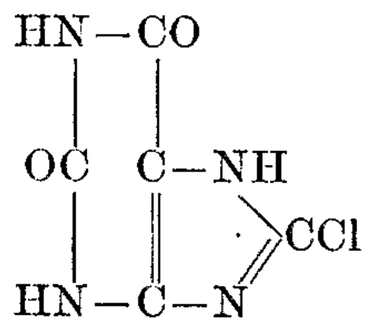


6. Conversion of 8-chloro-2-6-diethoxypurin into chloro-xanthin.—If instead of acting upon the chloro-diethoxypurin with a reducing agent it is submitted to the influence of hydrochloric acid, the chlorin atom remains

in the molecule, while the ethyl groups are split off, as under the fifth head of this description. If one part of the powdered chloro-diethoxypurin is heated on the water-bath with five times its weight of hydrochloric acid of the specific gravity 1.19, it first goes into complete solution, and a short time thereafter the 8-chloro-2-6-dioxy-purin or chloroxanthin, which is soluble only with great difficulty, begins to be precipitated. The decomposition is completed at the end of about half an hour. The reaction takes place according to the equation:



To completely purify, the chloro-xanthin is converted into the readily-crystallizing ammonium salt by dissolving in warm very dilute aqueous ammonia. On slowly cooling the ammonium salt is obtained in the form of small, but well-developed, apparently rectangular tablets. The said ammonium salt is then again decomposed by acid, such as hydrochloric acid, as will be readily understood. 8-chloro-xanthin has the composition $C_5H_3ClN_4O_2$ and the molecular structure:



It dissolves with difficulty in hot water and alcohol and glacial acetic acid. From the warm solution of its salts it is precipitated by mineral acids as a colorless granular crystalline mass. On heating it chars without melting. It dissolves readily in concentrated sulfuric acid, being precipitated from such solution by the addition of water. Its alkali salts are readily soluble in water. Its potassium salt crystallizes from strong potash-lye in the form of very fine pliable needles. Its ammonium salt is much less soluble. On slowly cooling of an aqueous solution of the same it crystallizes in small, but well-developed, apparently rectangular tablets.

Chloro-xanthin, like xanthin, gives a very strong murexide test. This chloro-dioxypurin is like the chloro-dioxypurin having alkyl combined with the oxygen, such as 8-chloro-2-6-diethoxypurin, readily converted into xanthin by the action of a reducing agent, such as hydrogen-iodid, under substantially the conditions set forth under 5.

The chloroxanthin may, as set forth in my application Serial No. 668,645, be converted into chlorocaffein by methylation and the latter by reduction into caffein or 1-3-7-trimethyl-xanthin. This mode of obtaining an alkylized xanthin by methylation and subsequent reduction of a chloro-oxypurin is, however, claimed generically and specifically in my applications Serial Nos. 668,644 and 668,645, filed concurrently herewith, and is herein only referred to as another illustration of the utility of my compound 8-chloro-2-6-diethoxy-purin.

The present application is designed to cover the preparation of xanthin by the reduction of a chloro-dioxypurin either with or without alkyl groups combined with the oxygen atoms. More specifically my present application covers the 8-chloro-2-6-diethoxy-purin and its mode of preparation, as also the preparation of xanthin therefrom by reduction.

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

1. The process which consists in heating trichloropurin having chlorin in the places (2), (6) and (8) with an alcoholic alkali.

2. The process which consists in heating trichloropurin with excess of sodium-ethylate.

3. The process which consists in heating trichloropurin with a concentrated alcoholic solution of sodium-ethylate in excess, evaporating the alcohol, dissolving the residue in water and supersaturating the solution with acetic acid.

4. As a new chemical compound, 8-chloro-2-6-diethoxypurin, having the formula above given which trickles at about 190°, centigrade, and melts at about 205°, centigrade, the fusion being attended by decomposition, which is soluble in hot alcohol, in alkalies, but soluble with difficulty in hot water and benzene and which crystallizes in fine needles.

5. The process of preparing xanthin which consists in acting on 8-chloro-dioxy-purin with a reducing agent.

6. The process of preparing xanthin which consists in submitting 8-chloro-2-6-diethoxy-purin to the action of a reducing agent.

7. The process of preparing xanthin which consists in dissolving 8-chloro-2-6-diethoxy-purin in hydriodic acid at ordinary temperatures then adding phosphonium-iodid to reduce the liberated iodin, then heating the whole on the water-bath, whereby the hydro-iodate of xanthin is precipitated, then evaporating the hydriodic acid and treating the residue with aqueous ammonia in slight excess.

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

EMIL FISCHER.

Witnesses:

CHAS. H. DAY,

HENRY HASPER.