UNITED STATES PATENT OFFICE.

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

THIO DERIVATIVE OF PURIN AND MAKING SAME.

SPECIFICATION forming part of Letters Patent No. 625,441, dated May 23, 1899.

Application filed August 1, 1898. Serial No. 687,456. (Specimens.)

To all whom it may concern:

Be it known that I, EMIL FISCHER, a citizen of the German Empre, residing at Beriln, in the Empire of Germany, have invented certain new and useful Improvements in Thio Derivatives of Purin and Preparing the Same; 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 same.

The present invention relates to the art of preparing purin-derivatives, and in particular to sulfur derivatives of the same.

The object of the invention is to prepare compounds analogous to the oxy-purins, but differing therefrom in that the thio- or mercapto-group or groups are bound in the purin molecule instead of the hydroxyl-group which characterizes the oxy-purins.

My said invention, broadly considered, consists in treating a halogen-purin-derivative with a sulfhydrate, such as the alkali-sulfhydrates.

My invention further consists in such features, methods, and details as will be hereinafter set forth, and pointed out in the claims.

As I have heretofore demonstrated, certain of the halogen atoms in the halogen substitution-products of purin may be exchanged for hydroxyl through the action of alkalies. Thus, for example, 7-methyl-trichloropurin, (*Berichte der Deutschen Chemischen Gesellschaft*, Vol. 28, page 2488,) 7-methyl-2-6-dichloropurin, (*Ibid*, Vol. 30, page 2406,) trichloropurin, (*Ibid*, Vol. 30, page 2227,) chlorocaffein, and bromotheobromin on being treated with alkaline lyes readily give up halogen and are thereby converted into the corresponding oxypurins.

I have now found that the halogen-derivatives of purin readily undergo a conversion into sulfur-derivatives of purin corresponding to the oxy-purins when acted upon by the sulfhydrates of the alkalies. These substitution-products I term "thiopurins."

The exchange of halogen for the group SH is readily effected when using sulfhydrate of potassium, for example. Such exchange takes place with less difficulty than the substitution of hydroxyl for halogen. Thus, for instance, it is easy under my invention to prepare thioxanthin from bromoxanthin, while, on the other hand, it has thus far been impossible to obtain from bromoxanthin the corresponding oxypurin—*i. e.*, uric acid. (See *Berichte der Deutschen Chemischen Gesellschaft*, Vol. 28, page 2486.)

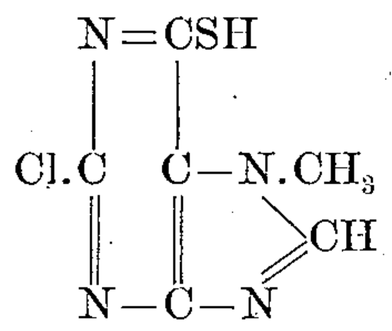
Regarding the constitution of the thiopurins, it is to be stated that as for the oxypurins (see *Liebig's Annalen*, Vol. 228, page 166, and *Berichte der Deutschen Chemischen Gesellschaft*, Vol. 30, page 550, *et seq*) the choice is left between the tautomerous formulæ NC.SH and HNC:S, although the preference seems to attach to the first scheme, since several thio-derivatives having a similar grouping have been proved to contain the sulfhydro or mercapto-group, and for the further reason that here also when methylating in the wet way the alkyl-radical does not unite with a nitrogen-atom, as is generally the case with the oxypurins, but is bound to the sulfur.

When employing di- and tri-halogen derivatives of purin, one, two, or three of the halogen-atoms may be replaced by the mercapto-group, according to the conditions under which the process is carried out. The intermediate products—the thio-halogen-purins, which are first formed—I have found show a great similarity to the corresponding oxychloropurins in their behavior with respect to the various reagents. Thus, for example, the residual chlorin-atom in 7-methyl-6-thio-2-chloropurin obtained from 7-methyl-2-6-dichloropurin may be exchanged for hydrogen, hydroxyl, ethoxyl, &c., in the same manner as in the case of 7-methyl-6-oxy-2-chloro-purin. (*Berichte der Deutschen Chemischen Gesellschaft*, Vol. 30, page 2400.)

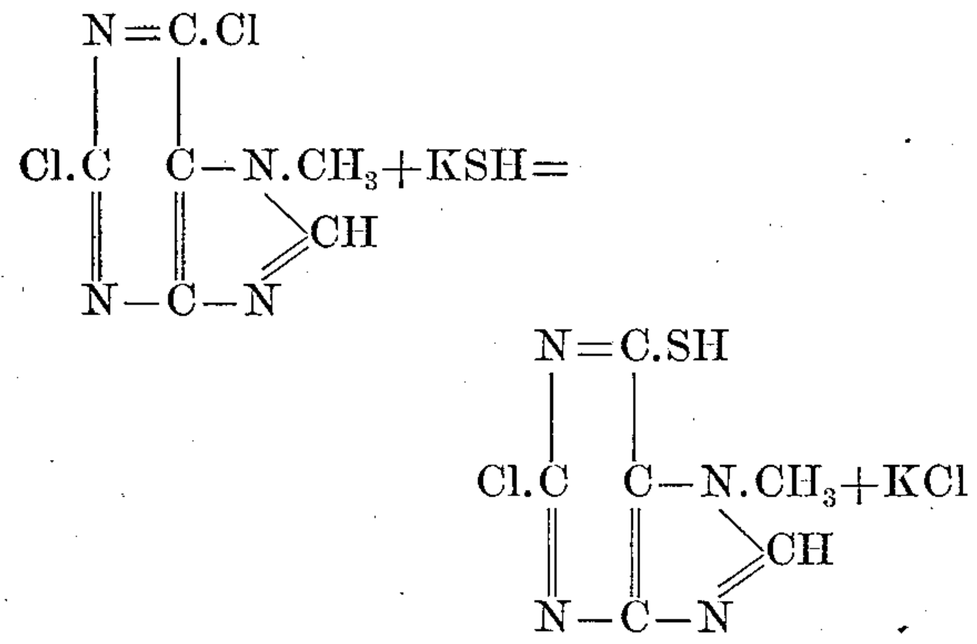
For the purpose of a full, clear, and exact disclosure of my invention I will now illustrate the same by giving a number of examples embodying the said invention.

I. *Preparation of 7-methyl-6-thio-2-chloro-purin from 7-methyl-2-6-dichloro-purin.*—I

take five parts of finely-powdered 7-methyl-2-6-dichloropurin, whose method of preparation and properties have been set forth in *Berichte der Deutschen Chemischen Gesellschaft*, Vol. 30, page 2406, and shake the same together with sixty parts, by volume, of a normal solution of sulfhydrate of potassium which has been obtained by saturating a normal solution of potassium-hydrate with hydrogen-sulfid. An energetic evolution of hydrogen-sulfid takes place immediately, a clear solution being obtained at the end of about from ten to eleven minutes. This indicates the end of the reaction. The clear yellow solution is then supersaturated with hydrochloric acid, whereby the 7-methyl-6-thio-2-chloropurin is precipitated as a colorless mass. After cooling the liquor is drained from the precipitate—*e. g.*, by filtration—and the said precipitate is then washed with water. For the purpose of purification this washed precipitate is dissolved in about eight hundred parts, by weight, of alcohol, the solution being then evaporated *in vacuo* and at about 30° centigrade to one-fourth its volume. It is then strongly cooled, (to about 0° centigrade.) The new compound is thereby crystallized in the form of fine light-yellow needles, which are for the most part united in globular or spheroidal aggregates. An analysis of the same after drying at 100° centigrade gives figures corresponding to the formula $C_6H_5N_4SCl$, or, structurally,



The reaction proceeds according to the equation:



This new body, 7-methyl-6-thio-2-chloropurin, has no melting-point, but at about 250° centigrade it begins to turn brown, and is decomposed when the temperature is raised above this point. It is still less soluble in water than in alcohol and is taken up by ether, acetone, benzene, or chloroform only with great difficulty. On the other hand, it is easily soluble in dilute alkalies. From these solutions the corresponding salts are precipitated by concentrated alkalies. Its ammonia-salt is readily soluble in water and forms a gelatinous precipitate with nitrate of silver, such precipitate being blackened on boiling.

The new compound is rapidly destroyed by potassium-chlorate and hydrochloric acid, giving no murexid reaction, however, on evaporating.

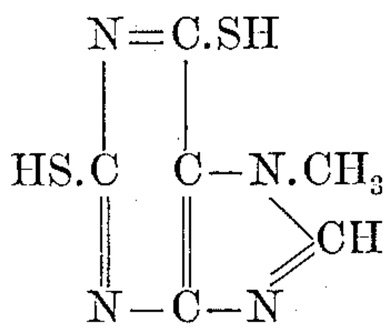
The behavior of methyl-thio-chloropurin with respect to nitric acid is characteristic. It is readily soluble at ordinary temperature in a solution of this acid having the specific gravity 1.4, a transient dark-brown coloration taking place during this action. On diluting such solution with a little water small shining crystals are then thrown out.

Methyl-thio-chloropurin dissolves in copious quantities in warm concentrated hydrochloric acid. At a higher temperature the hydrochloric acid acts as in the case of the sulfur-free-chloropurins—that is to say, the chlorin is replaced by oxygen. At the same time, however, the sulfur is partly split off with the halogen.

When acted upon by fuming hydriodic acid of the specific gravity 1.96, the methyl-thio-chloropurin is reduced to 7-methyl-6-thio-purin having the formula $C_6H_6N_4S$, which crystallizes in colorless prisms having the melting-point 306° to 307° centigrade. This compound is converted into 7-methyl-6-methyl-thio-purin having the formula $C_7H_8N_4S$ and crystallizing in the form of colorless flexible needles having the melting-point of from 207° to 208° centigrade on alkylizing the same in an aqueous alkaline solution. Finally, the 7-methyl-6-thio-purin is converted into 7-methyl-6-oxy-purin, which has been described in *Berichte der Deutschen Chemischen Gesellschaft*, Vol. 30, page 2409, when oxidizing the same with dilute nitric acid. By the preparation of the latter compound the molecular structure of the 7-methyl-6-thio-2-chloropurin is established.

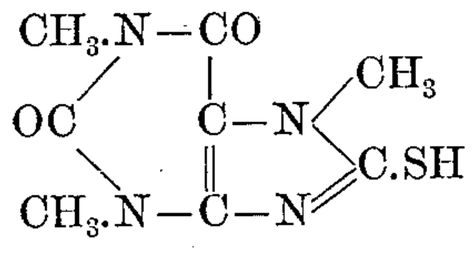
II. *Preparation of 7-methyl-2-6-dithio-purin from 7-methyl-2-6-dichloro-purin.*—By heating one part of the methyl-dichloro-purin with twenty-four parts, by volume, of a normal solution of potassium-sulfhydrate in the sealed tube to 100° centigrade both chlorin-atoms will be exchanged for the thio- or mercapto-group. By maintaining this temperature for about three hours the reaction will be completed. On acidulating the resultant clear yellow solution the 7-methyl-2-6-dithio-purin is thrown out in the form of a thick light-yellow crystalline precipitate. To purify the same, it is converted into the barium-salt by boiling with a cold-saturated aqueous solution of baryta hydrate and cooling the solution after filtering, whereby the barium-

salt crystallizes out. This salt is then recrystallized from water, when it forms colorless fine needles. The purified salt is then dissolved in water and the same is acidulated—*e. g.*, with hydrochloric acid—whereby the methyl-dithio-purin is precipitated in the form of an almost-colorless powder consisting of miscropic whetstone-like-shaped bodies. On drying this powder at 110° centigrade analysis of the same gives figures corresponding to the formula $C_6H_6N_4S_2$. The structural formula of the new compound is:

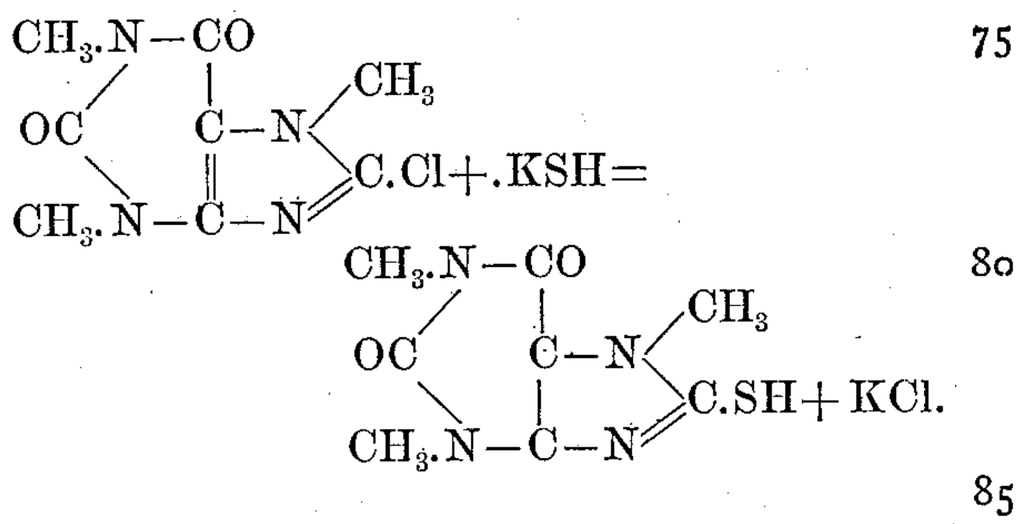


7-methyl-2-6-dithiopurin has no melting-point. At about 360° centigrade it turns brown, charring at a higher temperature. It is readily soluble in dilute alkalies, less soluble in dilute ammonia, soluble with difficulty only in hot concentrated hydrochloric acid and in boiling water. Its alkali-salts are readily soluble in water, but less readily soluble in concentrated lye. The sodium-salt crystallizes in fine felted or matted needles, the potassium-salt in needles or prisms. The ammonium-salt is somewhat less soluble in the above media. From an aqueous solution it crystallizes in the form of well-developed tablets. With nitrate of silver it forms a yellowish precipitate, which blackens on boiling. Methyl-dithiopurin on being heated with dilute nitric acid or with hydrochloric acid and potassium-chlorate is rapidly decomposed. Such solutions, however, on being evaporated give no or only a weak murexide reaction.

III. *Preparation of 1-3-7-trimethyl-2-6-dioxy-8-thiopurin or thio-caffein from 8-chlorocaffein.*—By boiling ten parts of 8-chlorocaffein, whose method of preparation and properties have been set forth in *Liebig's Annalen*, Vol. 215, page 262, with thirty parts, by volume, of potash-lye of twenty-five-per-cent. strength which has been saturated with hydrogen-sulfid a clear solution is obtained after about twenty minutes. On acidulating this solution—*e. g.*, with acetic acid—the thio-caffein is thrown out in the form of fine needles, which are for the most part united in globular aggregates. After cooling the liquor is drained from the precipitate—*e. g.*, by filtration—and the precipitate is then recrystallized from boiling water, about one hundred parts, whereby the 8-thio-caffein is obtained in the form of colorless fine very flexible needles. An analysis of the same after drying at 100° centigrade gives figures corresponding to the formula $C_8H_{10}N_4SO_2$, or, structurally,



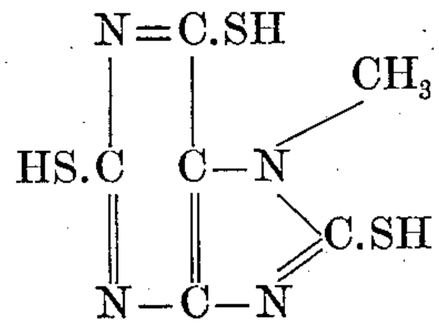
The reaction takes place according to the equation:



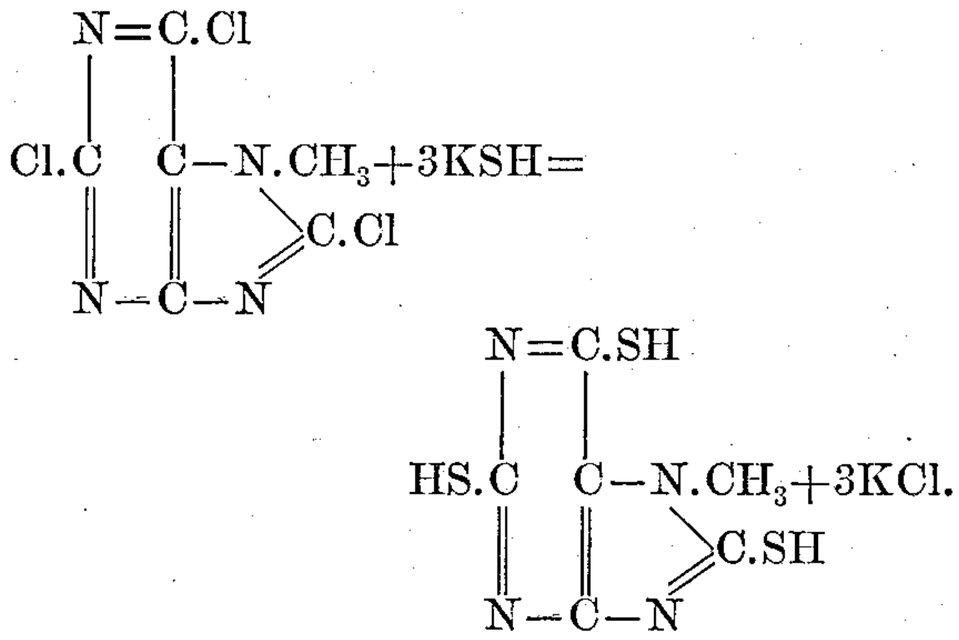
Thiocaffein begins to turn yellow at about 290° centigrade and melts at 308° centigrade to a brown liquor. It is easily soluble in hot alcohol, only with great difficulty in ether. It is readily dissolved in dilute alkalies, ammonia, and alkali-carbonates. From this solution thiocaffein is precipitated by supersaturating with acids. The ammonia-salt forms with nitrate of silver a gelatinous yellow precipitate, remaining unchanged on boiling. Thiocaffein gives the murexid test on heating with dilute nitric acid or with hydrochloric acid and potassium-chlorate.

IV. *Preparation of 7-methyl-2-6-8-trithiopurin from 7-methyl-2-6-8-trichloropurin.*—One part of 7-methyl-2-6-8-trichloropurin, whose method of preparation and properties have been set forth in *Berichte der Deutschen Chemischen Gesellschaft*, Vol. 28, page 2488, is shaken together with twenty-five parts, by volume, of a normal solution of sulfhydrate of potassium until a clear solution has taken place and then heated in a closed vessel to 100° centigrade for about six hours. On cooling the resultant clear yellow solution for a larger period with ice-water the acid-potassium-salt of 7 methyl-trithiopurin crystallizes out in the form of fine needles. By supersaturating the aqueous solution of the potassium-salt with hydrochloric-acid the methyl-trithiopurin is obtained in the form of a sulphur-yellow indistinctly crystalline powder, which on drying at 100° centigrade still contents one molecule of water of crystallization, giving the same off when heated on 130° centigrade.

7-methyl-2-6-8-trithiopurin has the formula $C_6H_6N_4S_3$, or, structurally,



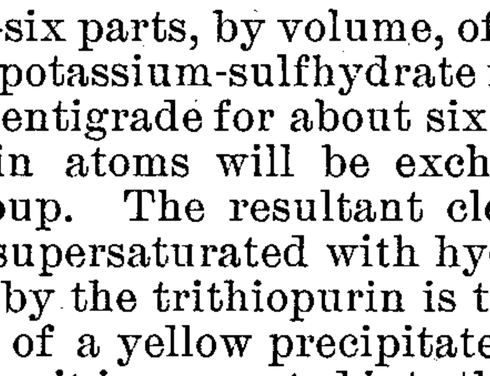
The reaction proceeds according to the equation:



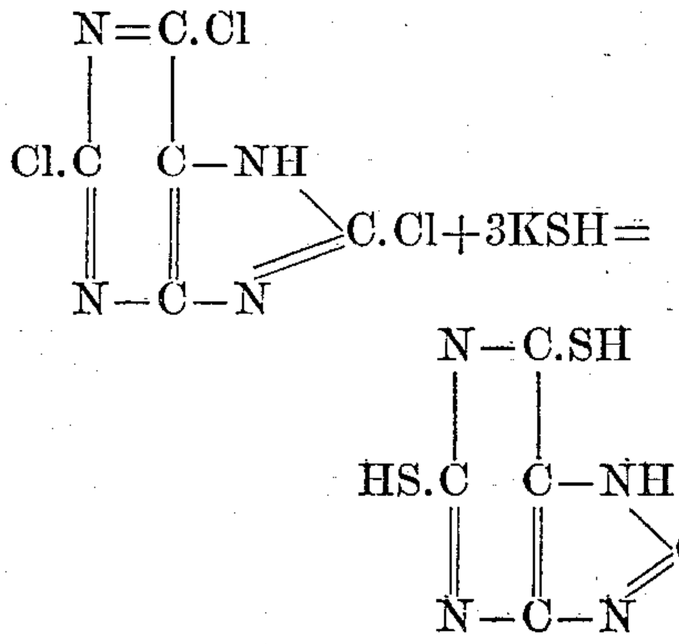
Methyl-trithiopurin turns brown at about 320° centigrade and chars when heated to a higher temperature without melting. It is soluble only with great difficulty in hot water, alcohol acetone, glacial acetic acid. It is readily dissolved from an excess of alkalies. From this solution by saturating with carbonic acid and concentrating, the acid-alkaline salts are thrown out—the potassium-salt in the form of fine needles, the sodium-salt in whetstone-like-shaped bodies.

The ammoniacal solution of methyl-trithiopurin forms with nitrate of silver a very fine yellow precipitate, which blackens on boiling for a longer time.

V. *Preparation of 2-6-8-trithiopurin from 2-6-8-trichloropurin.*—By heating one part of dry trichloropurin, whose properties and mode of preparation are set forth in my Letters Patent of the United States No. 598,502, with thirty-six parts, by volume, of a normal solution of potassium-sulfhydrate in a digester to 100° centigrade for about six hours the three chlorin atoms will be exchanged for the thio-group. The resultant clear yellow solution is supersaturated with hydrochloric acid, whereby the trithiopurin is thrown out in the form of a yellow precipitate. To purify the same, it is converted into the barium-salt by boiling with a cold-saturated aqueous solution of baryta hydrate and cooling after filtering, whereby the barium-salt crystallizes out in fine needles. This salt is then recrystallized from water, then redissolved in water, and the aqueous solution is acidulated—*e. g.*, with hydrochloric acid—whereby the trithiopurin is precipitated in the form of a canary-colored indistinctly-crystalline mass. Its formula is $C_5H_4H_4S_3$, or, structurally,

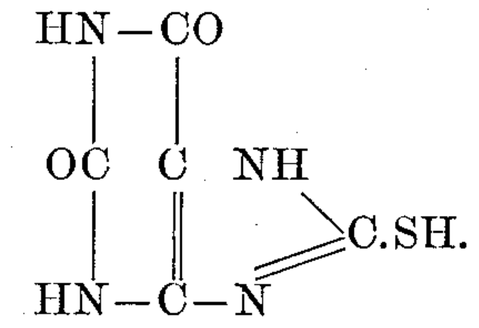


The reaction proceeds according to the equation:

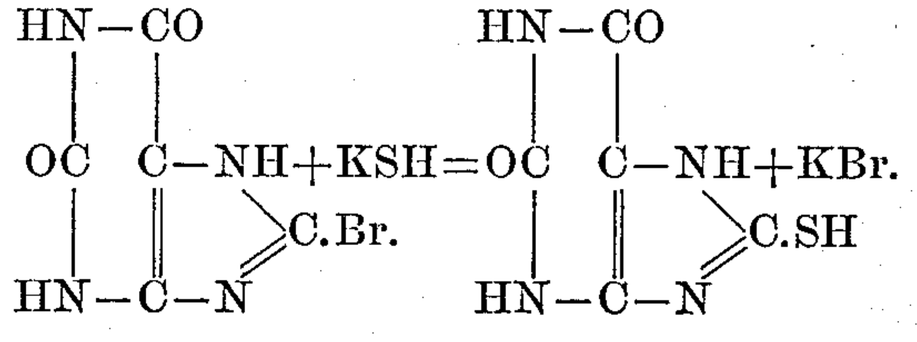


On heating it chars without melting. It dissolves with great difficulty in hot water and alcohol, readily in concentrated sulfuric acid, being precipitated from such solution by the addition of water. It is readily soluble in an excess of alkali or dilute ammonia. The ammoniacal solution forms with nitrate of silver a yellow amorphous precipitate.

VI. *Preparation of 2-6-dioxy-8-thiopurin or thioxanthin from 8-bromoxanthin.*—By heating three parts of bromoxanthin, whose method of preparation and properties are set forth in *Liebig's Annalen*, Vol. 221, page 343, with seventy-five parts, by volume, of a normal solution of potassium-sulfhydrate in a closed vessel to 120° centigrade and being maintained at this temperature and constantly agitated for about three hours a clear solution is formed. On cooling the potassium-salt of dioxythiopurin is thrown out in the form of a pale yellow voluminous mass. The salt is lixiviated with water, about seventy-five parts, dissolved by warming, and supersaturated by acids, such as hydrochloric acid, whereby the thioxanthin is thrown out in the form of a pale yellow crystalline powder containing one molecule of water of crystallization, which latter is completely driven off at a temperature of about 150° centigrade. An analysis of the substance thus dried gives figures corresponding to the formula $C_5H_4N_4SO_2$, or, structurally,



The reaction takes place to the following equation:



Thioxanthin chars at a higher temperature without melting. It is soluble only with great difficulty in hot water and in concentrated hydrochloric acid, easily soluble in concentrated sulfuric acid. It is readily dissolved by alkalies or ammonia. The ammoniacal solution with nitrate of silver gives rise to a yellow amorphous precipitate. On oxidizing with chlorate of potassium and hydrochloric acid the murexid test is obtained.

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

1. The process of preparing thiopurins which consists in treating halogen-purin derivatives with a sulfhydrate.

2. The process of preparing thiopurins which consists in treating a halogen-purin derivative with an alkali-sulfhydrate.

3. The process of producing thiopurins which consists in treating a halogen-purin derivative with the solution of an alkaline sulfhydrate and then acidulating the resultant solution.

4. The process which consists in heating under pressure a halogen-purin derivative together with the solution of an alkaline sulfhydrate and then acidulating the resultant solution.

5. The process which consists in boiling 1-3-7-trimethyl-2-6-dioxy-8-chloropurin or 8-chlorocaffein together with a solution of potassium-sulfhydrate in the proportions, substantially as set forth, and then acidulating the resultant solution to precipitate the thiocaffein.

6. The process which consists in boiling chlorocaffein together with a solution of potassium-sulfhydrate substantially as set forth and acidulating the resultant solution to precipitate the thiocaffein, then recrystallizing this thiocaffein from boiling water.

7. As a new compound a thiopurin which is characterized by having the group SH bound to one or more of the carbon-atoms of the purin molecule.

8. As a new chemical compound, 1-3-7-trimethyl-2-6-dioxy 8-thiopurin or thiocaffein having the formula above given, crystallizing in the form of colorless fine, very flexible needles, having the melting-point at 308°, centigrade, and which, on being heated with dilute nitric acid or with hydrochloric acid and potassium-chlorate, gives the murexid test.

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

EMIL FISCHER.

Witnesses:
C. H. DAY,
HENRY HASPER.