

UNITED STATES PATENT OFFICE.

RUDOLF KNIETSCH, ARTHUR HENRY STALAY HOLT, AND ERWIN OBERREIT,
OF LUDWIGSHAFEN, GERMANY, ASSIGNORS TO THE BADISCHE ANILIN
AND SODA FABRIK, OF SAME PLACE.

PROCESS OF MAKING AROMATIC ISATIN COMPOUNDS.

SPECIFICATION forming part of Letters Patent No. 646,841, dated April 3, 1900.

Application filed January 26, 1899. Serial No. 703,504. (No specimens.)

To all whom it may concern:

Be it known that we, RUDOLF KNIETSCH, a subject of the King of Prussia, Emperor of Germany, ARTHUR HENRY STALAY HOLT, a subject of the Queen of Great Britain and Ireland, and ERWIN OBERREIT, a subject of the King of Saxony, all doctors of philosophy, and residing at Ludwigshafen-on-the-Rhine, in the Kingdom of Bavaria and Empire of Germany, have invented new and useful Improvements in the Manufacture of Aromatic Isatin Compounds, of which the following is a specification.

We have invented a new process for the manufacture of isatin, its homologues, and its analogues of the aromatic series, any one or all of which we hereinafter designate by the term "isatin bodies."

Isatin has hitherto been prepared from a benzene derivative containing an aliphatic side chain—as, for instance, nitro-phenyl-propionic acid. (*Berichte* 13, p. 2259; 12, p. 350.) Also isatin has been obtained from bodies containing the indol ring already formed. Thus it is produced by the oxidation of indigo-blue, of indigo-red, of indol, of oxy-indol-carboxylic acid, and of amido-oxy-indol. (See *Berichte* 29, p. 658; 11, p. 1228.)

Prior to our invention isatin has never been obtained from indoxyllic acid and derivatives thereof by direct oxidation.

As is well known, if indoxyl or indoxyllic acid be oxidized by the oxygen of the air in alkaline solution indigo is produced, and the same is the case if an acid solution be oxidized by ferric chlorid. Therefore in case it was desired to prepare isatin from indoxyl or indoxyllic acid or the like it was heretofore necessary either to oxidize these products to indigo and then prepare the isatin from this or to adopt some such indirect process as the conversion of the indoxyl into ethyl-indoxyllic acid, nitrosing this body, and reducing the nitroso-indoxyl thus obtained to the amido compounds and oxidizing these. (See *Berichte* 15, p. 784.)

The new process which we have invented is based upon the fact that indoxyl, indoxyllic acid, and their alkali derivatives, as also the

homologues and analogues of these bodies, yield isatin and its corresponding homologues and analogues on direct suitable oxidation. This conversion into the isatin compounds takes place directly without any previous conversion into nitroso or amido derivatives or any previous production or intermediate formation of indigo itself. The process is simple and gives very good yields. Almost all the usual oxidizing agents can be used, and either acid, neutral, or alkaline solution. Only such weak oxidizing agents as ferric chlorid or oxygen cannot be used successfully, because they result in the formation of indigo itself. The oxidation can be effected at the ordinary temperature, but is preferably carried out at temperatures from 70° to 100° centigrade.

The following instances of the oxidizing agents which can successfully be employed will illustrate the wide choice that there is in the oxidizing agents for use in this invention: (a) when oxidizing in acid solution, potassium bichromate, lead nitrate, mercuric nitrate, or dilute nitric acid; (b) when oxidizing in neutral solution, potassium permanganate under conditions when the solution is maintained neutral, for instance, by the addition of magnesium sulfate; (c) when oxidizing in alkaline solution, ammonium persulfate, potassium chromate, manganic oxidizers, such as potassium permanganate or manganese peroxid, potassium ferricyanid, iodine, bromine, chlorine; ferric sulfate, cupric sulfate, or mercuric chlorid, precipitated with caustic soda; lead peroxid.

The initial materials which have been successfully used are indoxyl and indoxyllic acid, (or the melts containing the same or analogues thereof, obtained in accordance with the examples of Heumann's indigo patents; see, for instance, United States Letters Patent No. 534,560 and English Letters Patent Nos. 8,726 and 10,509, of 1890,) ethyl-indoxyl, acetylindoxyl, indoxyllic ester, acetyl-indoxyllic ester, (*Berichte* 14, p. 1742,) para-methyl-indoxyl-ester, beta-naphthindoxyllic-ester, and the corresponding acids, all of which are hereinafter referred to as "indoxyl compounds."

The following examples will serve to illustrate the manner in which the invention can best be carried into effect. The parts are by weight:

5 *Example 1—Oxidation of indoxyllic acid with potassium permanganate, and caustic soda.*—Prepare a solution of about six parts of potassium permanganate in fifty parts of water and containing ten parts of solid caustic
10 soda. Heat this solution to about 80° centigrade and add about seven parts of indoxyllic acid. When the color of the permanganate disappears, filter from the precipitated manganese peroxid, neutralize the filtrate exactly, and evaporate down to a small volume.
15 Then add an excess of hydrochloric or sulfuric acid and allow the isatin to crystallize out.

In the above example instead of seven parts
20 of indoxyllic acid rather more than eight parts of indoxyllic-ethyl-ester can be used and the reaction proceeds in a similar manner; or if the equivalent quantity of ortho- or para-methyl-indoxyllic-ester be used then the corresponding ortho- or para-methyl-isatin results.
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Example 2—Oxidation of naphthindoxyl-ethyl-ester with potassium ferricyanid and caustic soda.—Dissolve about eight parts of
30 potassium ferricyanid in about one hundred and sixty parts of water and add about ten parts of caustic-soda lye, (containing about thirty-five per cent. NaOH.) Heat the solution to about 90° centigrade and add gradually about two parts of naphthindoxyl-ethyl-
35 ester, (alpha or beta.) Stir while adding and continue stirring the mixture subsequently. After a short time the oxidation is concluded. Filter in order to separate from a small quantity of pitchy matter. Add hydrochloric acid
40 to the filtrate. A deep-red crystalline precipitate of naphthisatin is obtained. Collect by filtration and work up in the usual way.

Example 3—Oxidation of indoxyl with manganese peroxid and caustic soda.—Prepare a mixture of twenty parts regenerated
45 manganese peroxid, thirty parts of water, and seven parts of caustic-soda lye, (containing about twenty per cent. NaOH.) Boil this mixture and add slowly an aqueous solution
50 of eight parts of indoxyl. When the oxidation is completed, collect the isatin, as described in the foregoing Example 1.

Example 4—Oxidation of indoxyllic acid with cupric sulfate and caustic soda.—Dissolve about four parts of crystallized copper
55 sulfate in sixteen parts of boiling water and precipitate by adding about three parts caustic-soda lye, (containing about thirty-five per cent. NaOH.) Stir continually and add about
60

one part of indoxyllic acid. The oxidation takes place almost immediately. Boil this mixture and filter off the precipitate of cuprous oxid and add an excess of hydrochloric acid to the filtrate. The isatin will in a short
65 time separate out in the crystalline form.

Example 5—Oxidation of indoxyllic acid with potassium ferricyanid and caustic soda.—Dissolve about seven parts potassium
70 ferricyanid in about two hundred parts of boiling water and add about ten parts of caustic-soda lye, (containing about thirty-five per cent. NaOH.) To this solution add gradually nine parts of indoxyllic acid. The solution
75 obtained contains the isatin.

Example 6—Oxidation of a melt containing indoxyllic acid with nitric acid.—Prepare a mixture of three parts of nitric acid (containing about sixty-one per cent. HNO₃) and
80 one hundred parts of water. To this mixture sufficient acetic acid must be added to rather more than neutralize the alkali from the melt to be added with the indoxyl body, so that the oxidation liquid remains acid all the time while adding the melt. Add the melt gradually in the form of a fine powder, and continue
85 adding this melt until a sample withdrawn and rendered alkaline on treatment with air shows that there is a slight excess of indoxyl body present, in that indigo is
90 formed. This indicates that the oxidation agent is used up. Neutralize the solution exactly with sodium carbonate, filter and concentrate by evaporation, and precipitate the
95 isatin with sulfuric acid.

Now what we claim is—

1. The process for the production of an isatin body of the aromatic series by the direct oxidation of an indoxyl compound substantially as described. 100
2. The process for the production of an isatin body of the aromatic series by the direct energetic oxidation of the corresponding indoxyl compound, substantially as described.
3. The process of making an isatin body
105 by direct energetic oxidation of the corresponding indoxyllic-acid body, all substantially as described.
4. The process of making isatin by oxidation of indoxyllic acid with a manganic oxidizer, all substantially as described. 110

In testimony whereof we have hereunto set our hands in the presence of two subscribing witnesses.

RUDOLF KNIETSCH.
ARTHUR HENRY STALAY HOIT.
ERWIN OBERREIT.

Witnesses:

ERNEST F. EHRHARDT,
HOWARD E. J. INGLEY.