RESERVE COPY.

PATENT SPECIFICATION

NO DRAWINGS

894382

Date of Application and filing Complete Specification: March 18, 1960.

No. 9687/60.

Application made in United States of America on March 24, 1959.

Complete Specification Published: April 18, 1962.

Index at acceptance:—Class 2(4), PD1D.

International Classification:—C09b.

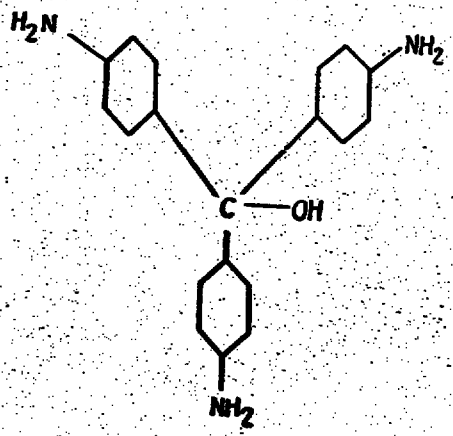
COMPLETE SPECIFICATION

Triphenylmethane Dye Salts and methods for their production

We, PARKE, DAVIS & COMPANY, a corporation organized under the laws of the State of Michigan, one of the United States of America, of Joseph Campau at the River, Detroit, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

The present invention relates to novel salts of pararosaniline and pamoic acid, and to methods for their production.

Pararosaniline, a compound of the formula

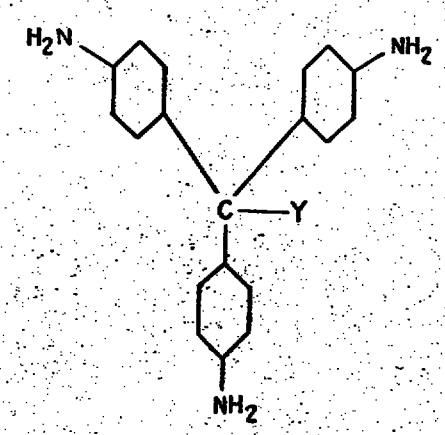


and its known salts and derivatives are valuable agents in the treatment of schistosomiasis. One of their important advantages is that they do not exhibit the high degree of toxicity shown by other substances used in the treatment of schistosomiasis. Nevertheless pararosaniline and its known salts and derivatives exhibit a certain degree of gastrointestinal irritation including in some subjects vomiting, diarrhoea and loss of appetite.

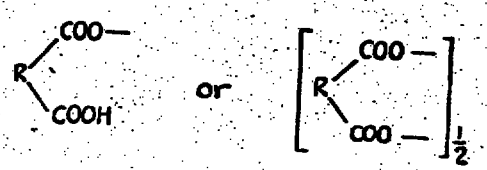
One of the objects of the present invention is to provide pararosaniline salts having therapeutic properties superior to those of pararosaniline itself and to those of its known salts and derivatives.

Another object of the present invention is to provide novel pararosaniline salts which have high antischistosomal activity associated with a very low incidence of gastrointestinal irritation, and reduced staining properties.

These, as well as other objects which will appear hereinafter, are achieved by providing certain novel salts comprising the tris(*p*-aminophenyl)carbonium cation (pararosaniline cation) and an anion of pamoic acid which is 2,2¹ - dihydroxy - 1,1¹ - dinaphthyl methane - 3,3¹ - dicarboxylic acid. Such salts can be represented by the formula



where Y is one equivalent of an anion of pamoic acid, i.e. if R represents the pamoic acid residue, Y represents



Such salts include bispararosaniline pamoate, a salt comprising 2 moles of the pararosaniline cation to 1 mole of the divalent pamoate anion, and pararosaniline acid pamoate, a salt comprising 1 mole of the pararosaniline cation to 1 mole of the monovalent acid pamoate anion.

In accordance with the invention the pararosaniline salts of pamoic acid can be formed by reaction of a soluble salt of pararosaniline with a soluble salt of pamoic acid, or by the reaction of pararosaniline with pamoic acid. When a soluble salt of pararosaniline is reacted with a soluble salt of pamoic acid, the process is suitably carried out in an unreactive medium such as water or an aqueous alkanol whereupon the desired pamoate salt either precipitates from the reaction mixture or can be obtained by concentration of the mixture or by dilution with water or with a non-polar solvent. When pararosaniline is reacted with pamoic acid the process is suitably carried out in an unreactive, approximately neutral solvent such as dimethylformamide or an aqueous alkanol.

The novel salts of this invention produce an anti-schistosomal effect upon oral administration, with a much lower incidence of gastrointestinal irritation and toxicity than that associated with pararosaniline and its known salts and derivatives. Moreover, they display reduced staining properties when compared with simple pararosaniline salts such as the hydrochloride. They are active against immature as well as mature schistosomes. They are also effective against other trematodes and are useful in the treatment of paragonimiasis, effecting a strong inhibition in the production of ova in the latter disease.

The invention is illustrated but not limited by the following examples:

EXAMPLE 1:

A mixture of 235 g. of pararosaniline hydrochloride (containing 1.8% of water) and 160 g. of disodium pamoate monohydrate in 3 liters of methanol is heated and stirred for 3 hours and then filtered slowly with vigorous stirring into 15 liters of water. The insoluble product is washed with water and dried *in vacuo* at 50—60° C. The product obtained in this manner is hydrated bispararosaniline pamoate, a salt comprising two moles of the tris(*p*-aminophenyl-carbonium cation (pararosaniline cation) to one mole of the divalent pamoate anion; m.p. about 220—225° C.

EXAMPLE 2:

A filtered solution of 11.5 g. of pararosaniline hydrochloride in 200 ml. of water heated to the boiling point is added to a hot, filtered solution of 8.0 g. of disodium pamoate monohydrate in 100 ml. of water. The gummy product which precipitates solidifies on cooling and is collected on a filter. It is resuspended in water, again collected and then dried *in vacuo* at 50° C. This compound is hydrated bispararosaniline pamoate, substantially identical with the product of the preceding example.

EXAMPLE 3:

To a hot, filtered solution of 3.88 g. of pamoic acid in 150 ml. of N,N-dimethylformamide is gradually added a solution of 6.10 g. of pararosaniline in 100 ml. of hot N,N - dimethylformamide. The resulting deeply-colored solution is heated for one hour at 90—100° C. and then poured with stirring into 1 liter of cold water. The insoluble product is collected on a filter, washed with water and dried *in vacuo*. This compound is dark-green bispararosaniline pamoate, substantially identical with the product of the preceding examples.

EXAMPLE 4:

To a hot, filtered solution of 3.88 g. of pamoic acid in 125 ml. of N,N-dimethylformamide is added a solution of 3.05 g. of pararosaniline in 50 ml. of hot N,N-dimethylformamide. A dark-red solution which results is heated for one hour at 90—100° C. and then poured with vigorous stirring into 2 liters of cold water. The reddish-brown product is collected on a filter, washed well with water and dried *in vacuo* at 45° C. Purification by recrystallization from methanol affords pararosaniline acid pamoate, a salt comprising one mole of the tris(*p*-aminophenyl)carbonium cation (pararosaniline cation) to one mole of the monovalent acid pamoate anion; m.p. 205—210° C.

WHAT WE CLAIM IS:—

1. Salts of pararosaniline and pamoic acid.
2. Salt comprising 2 moles of pararosaniline cation to 1 mole of pamoate anion.
3. Process for the production of salts of pararosaniline and pamoic acid characterized in that a soluble salt of pararosaniline is reacted with a soluble salt of pamoic acid, or pararosaniline is reacted with pamoic acid.
4. Process according to Claim 3 wherein pararosaniline hydrochloride is reacted with an alkali metal salt of pamoic acid.
5. Process according to Claim 3 or Claim 4 wherein the product obtained is a salt comprising 2 moles of pararosaniline cation to 1 mole of pamoate anion.
6. A process for the production of salts of pararosaniline and pamoic acid, substantially as described in any one of the foregoing Examples.

HASELTINE LAKE & CO.,
28, Southampton Buildings, London, W.C.2,
Agents for the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1962.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

Such salts include bispararosaniline pamoate, a salt comprising 2 moles of the pararosaniline cation to 1 mole of the divalent pamoate anion, and pararosaniline acid pamoate, a salt comprising 1 mole of the pararosaniline cation to 1 mole of the monovalent acid pamoate anion.

In accordance with the invention the pararosaniline salts of pamoic acid can be formed by reaction of a soluble salt of pararosaniline with a soluble salt of pamoic acid, or by the reaction of pararosaniline with pamoic acid. When a soluble salt of pararosaniline is reacted with a soluble salt of pamoic acid, the process is suitably carried out in an unreactive medium such as water or an aqueous alkanol whereupon the desired pamoate salt either precipitates from the reaction mixture or can be obtained by concentration of the mixture or by dilution with water or with a non-polar solvent. When pararosaniline is reacted with pamoic acid the process is suitably carried out in an unreactive, approximately neutral solvent such as dimethylformamide or an aqueous alkanol.

The novel salts of this invention produce an anti-schistosomal effect upon oral administration, with a much lower incidence of gastrointestinal irritation and toxicity than that associated with pararosaniline and its known salts and derivatives. Moreover, they display reduced staining properties when compared with simple pararosaniline salts such as the hydrochloride. They are active against immature as well as mature schistosomes. They are also effective against other trematodes and are useful in the treatment of paragonimiasis, effecting a strong inhibition in the production of ova in the latter disease.

The invention is illustrated but not limited by the following examples:

EXAMPLE 1:

A mixture of 235 g. of pararosaniline hydrochloride (containing 1.8% of water) and 160 g. of disodium pamoate monohydrate in 3 liters of methanol is heated and stirred for 3 hours and then filtered slowly with vigorous stirring into 15 liters of water. The insoluble product is washed with water and dried *in vacuo* at 50—60° C. The product obtained in this manner is hydrated bispararosaniline pamoate, a salt comprising two moles of the tris(*p*-aminophenyl-carbonium cation (pararosaniline cation) to one mole of the divalent pamoate anion; m.p. about 220—225° C.

EXAMPLE 2:

A filtered solution of 11.5 g. of pararosaniline hydrochloride in 200 ml. of water heated to the boiling point is added to a hot, filtered solution of 8.0 g. of disodium pamoate monohydrate in 100 ml. of water. The gummy product which precipitates solidifies on cooling and is collected on a filter. It is resuspended in water, again collected and then dried *in vacuo* at 50° C. This compound is hydrated bispararosaniline pamoate, substantially identical with the product of the preceding example.

EXAMPLE 3:

To a hot, filtered solution of 3.88 g. of pamoic acid in 150 ml. of N,N-dimethylformamide is gradually added a solution of 6.10 g. of pararosaniline in 100 ml. of hot N,N - dimethylformamide. The resulting deeply-colored solution is heated for one hour at 90—100° C. and then poured with stirring into 1 liter of cold water. The insoluble product is collected on a filter, washed with water and dried *in vacuo*. This compound is dark-green bispararosaniline pamoate, substantially identical with the product of the preceding examples.

EXAMPLE 4:

To a hot, filtered solution of 3.88 g. of pamoic acid in 125 ml. of N,N-dimethylformamide is added a solution of 3.05 g. of pararosaniline in 50 ml. of hot N,N-dimethylformamide. A dark-red solution which results is heated for one hour at 90—100° C. and then poured with vigorous stirring into 2 liters of cold water. The reddish-brown product is collected on a filter, washed well with water and dried *in vacuo* at 45° C. Purification by recrystallization from methanol affords pararosaniline acid pamoate, a salt comprising one mole of the tris(*p*-aminophenyl)carbonium cation (pararosaniline cation) to one mole of the monovalent acid pamoate anion; m.p. 205—210° C.

WHAT WE CLAIM IS:—

1. Salts of pararosaniline and pamoic acid.
2. Salt comprising 2 moles of pararosaniline cation to 1 mole of pamoate anion.
3. Process for the production of salts of pararosaniline and pamoic acid characterized in that a soluble salt of pararosaniline is reacted with a soluble salt of pamoic acid, or pararosaniline is reacted with pamoic acid.
4. Process according to Claim 3 wherein pararosaniline hydrochloride is reacted with an alkali metal salt of pamoic acid.
5. Process according to Claim 3 or Claim 4 wherein the product obtained is a salt comprising 2 moles of pararosaniline cation to 1 mole of pamoate anion.
6. A process for the production of salts of pararosaniline and pamoic acid, substantially as described in any one of the foregoing Examples.

HASELTINE LAKE & CO.,
28, Southampton Buildings, London, W.C.2,
Agents for the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1962.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.