

PATENT SPECIFICATION

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COMPLETE SPECIFICATION

A new Diamidine Salt and process for its preparation

We, SOCIETE DES USINES CHIMIQUES RHONE-POULENC, a French body corporate, of 21 rue Jean-Goujon, Paris 8e, France, 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:—

This invention concerns a therapeutically useful diamine salt and a process for its preparation.

The diamidine salt of this invention is prepared by reaction together in an aqueous medium a water-soluble salt, for example, the sodium salt of the symmetrical urea of *m*-aminobenzoyl-*p*-methyl-*m*-aminobenzoyl-1-aminonaphthalene 4:6:8-trisulphonic acid, which urea is hereinafter referred to by its common name "suramin," and a water-soluble salt of 1:5-di(4¹-amidinophenoxy)pentane, for example, the isethionate or methane sulphonate, and isolating from the reaction mixture the

salt thus formed. The resulting salt is only sparingly soluble in water, and is conveniently isolated by crystallisation.

The salt as thus prepared has been proved to be of considerable value as a therapeutic agent. More particularly, it has been shown to possess a marked prophylactic and curative effect in the treatment of *trypanosome* infections. Both 1:5-di(4¹-amidinophenoxy)-pentane and suramin are known to possess in the form of certain water-soluble salts, such as the isethionate and sodium salts respectively trypanocidal activity but comparative experiments have demonstrated the fact (which is all the more surprising in view of the low solubility of the suramin salt of the diamidine) that the new salt is unexpectedly and substantially superior to either. Thus, in parallel toxicity experiments in rats to determine the maximum non-lethal dose on sub-cutaneous administration, the following figures were obtained:—

(a)	1:5-di(4 ¹ -amidino-phenoxy)-pentane	5 mg./100 g.
(b)	suramin - - - - -	40 mg./100 g.
(c)	the suramin salt of the diamidine	>500 mg./100 g.

The diamidine itself is known to possess a prophylactic action against rat *trypanosomiasis* and comparative tests of the diamidine and the new salt thereof were therefore conducted in this connection. In these tests the drugs were administered sub-cutaneously and after definite intervals (1, 2, 4, 8 and 12 weeks) the test animals were inoculated sub-cutaneously with the aforesaid strain of *T. brucei* and the blood examined every two or three days for a month. If in that period no evidence of infection was found protection was considered complete. Under these test conditions, it was found that the diamidine at maximum

non-lethal dose (5 mg./100 g.) gave protection for 4 weeks while the new salt at less than one thirtieth of the maximum non-lethal dose (15 mg./100 g.) gave protection for at least 8 months. Further, such tests in which all three products were compared showed that the maximum doses required to give complete protection for a period of 4 weeks were 5 mg./100 g. in the case of the diamidine, 2 mg./100 g. in the case of suramin, and 1.96 mg./100 g. of the new salt containing 0.7 mg. of the diamidine and 0.9 mg. of suramin.

The production of the new salt is illustrated in the following Example.

EXAMPLE.

To a solution of suramin sodium (14.3 g.) in water (30 c.c.) is added a solution of 1:5 - di(4¹-amidino-phenoxy)-pentane methane-sulphonate in water (300 c.c.) at 45° C. A white precipitate forms which is left to stand overnight and is then filtered off, washed with water (150 c.c.) and dried at 50° C. under 12 mm. of mercury. The suramin salt of 1:5-di(4¹-amidino-phenoxy)-pentane (26 gr.) is thus obtained which crystallises with 30 molecules of water.

We are aware that Guimaræs and Lourie, British Journal of Pharmacology and Chemotherapy (1951) Vol. 6, pages 514 to 530, have referred to the fact that a precipitate is liable to form in mixtures of dilute solutions of suramin and 1:5-di(4¹-amidino-phenoxy)-pentane also known as pentamidine and give reasons for attributing to the formation of an inactive salt complex the inhibitory effect observed by them in respect of a previous injection of suramin (or the presence of suramin) on certain actions of pentamidine, viz. fall of blood pressure, broncho-constriction, contraction of gut, "curare-like" action on the rat phrenic nerve diaphragm preparation, paralysis in frogs and toxicity for mice.

What we claim is:—

1. A therapeutic agent consisting of the salt of the symmetrical urea of *m*-aminobenzoyl - *p* - methyl - *m* - aminobenzoyl - 1 - amino-naphthalene 4:6:8-trisulphonic acid (suramin) and 1:5-di(4¹ - amidino-phenoxy)pentane uncontaminated with either the acid or the base from which it may be formed or another salt of said base or said acid.

2. A process for producing a therapeutically active salt which comprises reacting in aqueous medium a water-soluble salt of the symmetrical urea of *m* - aminobenzoyl - *p* - methyl-*m*-aminobenzoyl - 1-amino-naphthalene 4:6:8-trisulphonic acid with a water-soluble salt of 1:5 - di - (4¹-amidino-phenoxy)-pentane, and isolating from the reaction medium the diamidine salt thus formed.

3. A process as claimed in claim 2 when carried out substantially as described in the foregoing Example.

4. A therapeutically active diamidine salt when prepared by the process claimed in claim 2 or 3.

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