PATENT SPECIFICATION

NO DRAWINGS

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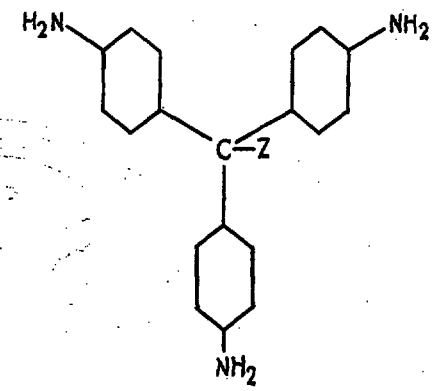
COMPLETE SPECIFICATION

Pharmaceutical Compositions containing Pararosaniline or Derivatives thereof

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 therapeutic compositions useful in the treatment of schistosomiasis and, more particularly, to antischistosomal compositions which furnish as their principal therapeutic ingredient pararosaniline or a mineral acid salt or monobasic organic acid salt thereof.

Pararosaniline compounds intended for use in the compositions of this invention can be represented by the structural formula



where Z is a hydroxyl group, one equivalent of an anion of a mineral acid or a monobasic organic acid, or a labile covalent group. When Z is a hydroxyl group, the compound is pararosaniline itself. Salts of the foregoing formula comprehended for use in the compositions of this invention include the hydrochloride (sometimes also known as the chloride or as parafuchsin), hydrobromide, hydroiodide, acetate, sulfate, palmitate, stearate, salicylate, hydroxynaphthoate, 2-hydroxy-6-naphthalenesulfonate, and salts formed with a variety of other inorganic and organic acids; the term "monobasic organic acid" being defined as an organic acid having a single carboxyl or sulfonic acid group. The specific pararosaniline derivative formulated into the compositions of this invention can be either a salt, as of the general type indicated hereinbefore, or a derivative, having a labile covalent group attached to the central carbon atom, which affords such a salt in its normal method of use. An example of such a derivative is the methyl ether of pararosaniline which, in consequence of the labile covalent bond binding the methoxyl group to the central carbon atom, is rapidly converted to an ionic salt when it is brought into contact with the normally acidic contents of the stomach.

The dosages and relative activities of pararosaniline compounds of the foregoing formula are conveniently expressed in terms of pararosaniline cation equivalent, which is defined as the quantity of pararosaniline cation or tris(*p*-aminophenyl)carbonium cation, which corresponds stoichiometrically with any given quantity of a pararosaniline derivative.

Schistosomiasis is a disease of great medical and economic importance in many areas of the world, particularly in tropical and semi-tropical climates. The great number and variety of therapeutic agents which have been proposed for the treatment of schistosomiasis reflect the difficulties which have been encountered in developing satisfactory means for the treatment and control of this disease. The development of satisfactory methods for the treatment and control of schistosomiasis is rendered more difficult by its prevalence in

[*Price 4s. 6d.*]

areas where adequate medical care is lacking and economic standards are low. Moreover, the disease is persistent and maintained at an epidemic level by relapse and reinfection.

Of the various agents that have been proposed for the treatment of schistosomiasis, the ones which presently have the most widespread use are compounds of trivalent and pentavalent antimony and certain derivatives of thioxanthone.

One of the objects of the present invention is to provide compositions for the treatment of schistosomiasis which have a higher degree of useful therapeutic activity with relative freedom from toxic side-effects than other compositions presently in use.

Another object of this invention is to provide compositions for the treatment of schistosomiasis which are therapeutically effective in cases where the presently-accepted medicaments fail to produce clinically-satisfactory results.

A further object of this invention is to provide compositions for the treatment of schistosomiasis which permit the eradication of disease-producing parasites from the body with a minimum incidence of subsequent relapse.

Still another object of this invention is to provide compositions for the treatment of schistosomiasis which act prophylactically against the development of the disease, such compositions being of particular value in circumstances where repeated reinfection of large segments of the population is likely to occur.

The compositions of this invention are characterized by their high degree of effectiveness against schistosomes, by their oral activity for such purpose, by their relative freedom from undesirable side-effects, and by their ease of administration and low cost; whereby they can be employed for mass control of the disease.

Pararosaniline and various of its salts have been known in the dye industry for many years. According to the present invention, it has been found that the employment of compositions containing such pararosaniline compounds affords a high degree of effectiveness in the treatment of schistosomiasis without the combinations of disadvantages that have rendered the prior art methods such as those involving the use of the antimony compounds and the thioxanthones of such limited utility in the treatment of this disease. Apart from, and in addition to, the beneficial results which this invention affords, the development of the invention is deemed noteworthy for two reasons: first, in that the commercial availability of pararosaniline and the unsolved problem of schistosomiasis have co-existed for many decades without the result of this invention being attained, in spite of the fact that pararosaniline was known to be active against other classes of parasites *in vitro* studies and in laboratory animals, and, second, in that the highly specific activity of pararosaniline compositions against schistosomiasis results although numerous other dyes of related structure, including substances as closely related as rosaniline, have no useful degree of curative activity against schistosomiasis. Consequently, the development of a useful anti-schostosomal agent in the pararosaniline compositions of this invention is entirely unexpected from the teachings of the prior art.

According to the present invention, schistosomacidal compositions are produced by formulating compositions furnishing pararosaniline or a mineral acid salt or monobasic organic acid salt thereof. Such compositions are constituted in dosage unit form with one or more pharmaceutically acceptable diluents and/or excipients.

By the term "dosage unit form" is meant "a physically discrete unit containing an individual quantity of the active material in association with a pharmaceutical diluent or carrier, the quantity of active material being such that one or more units are required for a single therapeutic administration" and it does not include mere solutions in common solvents except when such are packaged in ingestible containers.

In view of the oral activity of pararosaniline and its non-toxic salts, the dosage unit should be in a form suitable for oral administration. For this purpose, the pararosaniline compound can be incorporated, for example, into tablets, powders, capsules and solutions or suspensions from which dosage units are measured out. The medicament can be incorporated with pharmaceutically-acceptable solid or liquid diluents and/or excipients. Solid diluents and excipients are particularly suitable for use and include sugars such as lactose and sucrose; cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose and cellulose acetate phthalate; gelatin (including hard and soft gelatin capsules); talc; corn starch, stearic acid and magnesium stearate. Liquid diluents and excipients suitable for use include vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; polyethylene glycol, propylene glycol; glycerin; sorbitol; ethanol and water. Conventional preservatives and flavoring agents can also be incorporated in such compositions. In the production of dosage forms such as tablets, the use of an enteric coating or a sugar coating is also useful in minimizing a tendency toward nausea or staining. Other therapeutic agents can also be incorporated with a pararosaniline compound in these compositions; but other therapeutic agents if present are to constitute only a minor proportion of the total therapeutic components, so that the pararosaniline compound remains the principal therapeutic

ingredient in the composition. For the purposes of this invention the principal therapeutic ingredient is to be considered to be one which amounts to from 75% to 100% by weight of the total therapeutic components.

The aforementioned compositions can be administered in dosage unit form for the treatment and prophylaxis of schistosomiasis. The compositions are administered orally, with the dose adjusted to the needs and tolerances of the individual patient. The indicated total daily dose is within the range of approximately 0.5 to 4.0 g. (calculated as pararosaniline cation equivalent) optionally in divided portions. Within the indicated range, the dose is adjusted according to the size and age of the patient and the patient's response to the medication. For example, in the case of a child subject to gastrointestinal irritation, the proper dose would commonly be found near the lower limit of the indicated range whereas, in the case of an adult experiencing no side-effects, the proper dose would commonly be found near the upper limit of the indicated range. Treatment is continued for a period of from several days up to a few weeks or until the desired response is obtained.

In the preparation of dosage unit forms such as tablets and capsules the quantity of medicament furnished by each individual tablet or capsule is selected such that the proper total daily dose can be reached by administering either one or a reasonable number of the tablets or capsules. For convenience in manufacturing and ease of administration, it is preferable that such dosage forms contain at least 50 mg. of pararosaniline compound (calculated as pararosaniline cation equivalent) per unit. Dosage forms containing up to 1000 mg. and even more of pararosaniline compound (calculated as pararosaniline cation equivalent) per unit can be prepared and used, the limiting factor being ease of swallowing.

As previously indicated, the compositions of the invention are orally effective in the treatment and prophylaxis of schistosomiasis. They are active against immature as well as mature schistosomes whereas prior art materials such as tartar emetic and 1-di-ethylaminoethylamino-4-methylthioxanthone hydrochloride have been reported ineffective against immature worms. Moreover, the compositions of this invention are effective against other trematodes. They 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 bath of hydrated pararosaniline hydrochloride is prepared for tableting by treating it with 1% by weight of mineral oil to minimize dust formation. This product (1200 g.) containing about 5.7% by weight of water and 1% by weight of mineral oil is intimately mixed with 850 g. of sifted corn starch and 550 g. of sugar containing 3% by weight starch. This mixture is granulated with a 10% w/w solution of 68 g. of flake gelatin in distilled water. The granulation is dried and reduced. Sifted talc (75 g.) sifted corn starch (370 g.), and magnesium stearate (7 g.) are blended in and the mixture is processed through a tableting machine to provide about 9500 tablets each containing approximately 100 mg. of pararosaniline cation equivalent. If desired, these tablets can be given an enteric coating.

A quantity of pararosaniline affording an equal amount of pararosaniline cation can be substituted for the pararosaniline hydrochloride in the foregoing procedure.

EXAMPLE 2.

A batch of pararosaniline salicylate assaying 1.6% by weight of water is constituted into dosage units by encapsulation in 300 mg. portions into hard gelatin capsules. The yield from 600 g. of this lot of hydrated pararosaniline salicylate is about 1950 capsules, each containing approximately 200 mg. of pararosaniline cation equivalent.

EXAMPLE 3.

A mixture of 1060 g. of pararosaniline and 1440 g. of lactose is blended and filled into hard gelatin capsules so that each capsule contains 250 mg. of the mixture, equivalent to 100 mg. of pararosaniline cation equivalent. The yield is approximately 9800 capsules.

A quantity of pararosaniline hydrochloride affording an equal amount of pararosaniline cation can be substituted for the pararosaniline in the foregoing procedure.

EXAMPLE 4.

Novel pararosaniline salts useful in the compositions of this invention can be prepared by the reaction of pararosaniline with a mineral acid or a monobasic organic acid or by the reaction of their respective salts. Some examples of such preparations are as follows:

A hot, filtered solution of 32.4 g. of pararosaniline hydrochloride in 500 ml. of water is added to a hot, filtered solution of 16.0 g. of sodium salicylate in 100 ml. of water. The gummy product is collected and refrigerated until it turns solid. It is then triturated with water, collected on a filter and dried *in vacuo* over calcium chloride at room temperature and then at 50° C. This compound is hydrated pararosaniline salicylate, a salt comprising one mole of the tris(*p*-aminophenyl)carbonium cation to one mole of the salicylate anion.

A solution of 9.4 g. of 3-hydroxy-2-naphthoic acid in 100 ml. of water containing 2.0 g. of sodium hydroxide is added to a solution of 16.2 g. of pararosaniline hydrochloride in 600 ml. of warm methanol. The resulting solution is added slowly with stirring to 2.5 liters of cold water. The greenish solid is collected on a filter, washed with water and

dried at 45° C. *in vacuo*. This compound is a hydrated salt comprising one mole of the tris-(*p*-aminophenyl)carbonium cation to one mole of the 3-hydroxy-2-naphthoate anion.

WHAT WE CLAIM IS:—

1. A therapeutic composition useful in the treatment of schistosomiasis in a dosage unit form suitable for oral administration, said composition comprising one or more pharmaceutically acceptable diluents and/or excipients and, as the principal (as hereinbefore defined) therapeutically active ingredient, a compound selected from pararosaniline, mineral acid salts and monobasic organic acid salts (as hereinbefore defined) of pararosaniline and derivatives of pararosaniline having a labile covalent group attached to the central carbon atom thereof, or a mixture of two or more of said compounds.

2. A therapeutic composition according to Claim 1, wherein the dosage unit contains a quantity of therapeutically active ingredient corresponding to at least 50 milligrams of pararosaniline cation.

3. A therapeutic composition according to Claim 1 or 2, wherein the therapeutically active ingredient comprises pararosaniline hydrochloride.

4. A therapeutic composition according to any preceding claim, wherein the pharmaceutically acceptable excipient is gelatin and the dosage unit is in the form of a capsule.

5. A therapeutic composition, substantially as described in Example 1, 2 or 3 of the foregoing Examples.

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

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dried at 45° C. *in vacuo*. This compound is a hydrated salt comprising one mole of the tris-(*p*-aminophenyl)carbonium cation to one mole of the 3-hydroxy-2-naphthoate anion.

WHAT WE CLAIM IS:—

1. A therapeutic composition useful in the treatment of schistosomiasis in a dosage unit form suitable for oral administration, said composition comprising one or more pharmaceutically acceptable diluents and/or excipients and, as the principal (as hereinbefore defined) therapeutically active ingredient, a compound selected from pararosaniline, mineral acid salts and monobasic organic acid salts (as hereinbefore defined) of pararosaniline and derivatives of pararosaniline having a labile covalent group attached to the central carbon atom thereof, or a mixture of two or more of said compounds.

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3. A therapeutic composition according to Claim 1 or 2, wherein the therapeutically active ingredient comprises pararosaniline hydrochloride.

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