

PATENT SPECIFICATION

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(54) 2-ANILINO-NICOTINIC ACID DERIVATIVES

(71) We, SCHERICO LTD., Topferstrasse 5, Lucerne, Switzerland, a body corporate constituted under the laws of Switzerland, 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 relates to 2-anilino-nicotinic acid derivatives. More specifically, this invention relates to a particular salt of a substituted 2-anilino-nicotinic acid, to its preparation, to compositions containing the said salt and the preparation of such compositions as well as to the use of the said salt as an analgesic agent.

In Belgian Patent Specification No. 679,271, and the corresponding United States Patent Specifications Nos. 3,337,570 and 3,689,653, there are disclosed certain 2-anilino-nicotinic acids and salts thereof. Reference is made therein to the analgesic and anti-inflammatory activity of the disclosed compounds.

We have now surprising found that a specific salt of a particular 2-anilino-nicotinic acid, namely the N-methyl-D-glucamine salt of 2-(2¹-methyl-3¹-trifluoromethylanilino)-nicotinic acid, exhibits unexpectedly high analgesic activity upon parenteral administration.

Accordingly, the present invention provides a novel compound, the N-methyl-D-glucamine salt of 2-(2¹-methyl-3¹-trifluoromethylanilino)-nicotinic acid. This compound may be made by methods known per se for the preparation of salts, which methods may in general be stated to comprise reacting 2-(2¹-methyl-3¹-trifluoromethylanilino)-nicotinic acid either as the free acid or in the form of a reactive derivative thereof, such as a salt capable of being transformed into the desired N-methyl-D-glucamine salt, with N-methyl-D-glucamine or a reactive derivative thereof. The preparation may be carried out in any convenient manner such as by reacting approximately equimolar

quantities of the starting materials in an inert medium, suitably an inert solvent, and then separating the so-obtained salt from the medium typically by precipitating the salt from the medium in any suitable manner. The precise reaction conditions such as temperature are not considered to be critical; temperatures of from ambient temperature up to the reflux temperature of the reaction mixture may suitably be used. Purification of the salt may be effected using any convenient technique such as recrystallisation.

The present invention further provides pharmaceutical compositions comprising as an active ingredient the N-ethyl-D-glucamine salt of 2-(2¹-methyl-3¹-trifluoromethylanilino)-nicotinic acid. The pharmaceutical compositions for parenteral use will typically be in the form of a sterile solution, suspension or emulsion suitable for use as an injectable. The specific form of the injectable composition will be dependent in known manner upon such factors as the route of injection, that is whether by intravenous, subcutaneous, intramuscular or other parenteral route. The precise carrier or vehicle employed in formulating the composition will be determined in accordance with well known procedures. Conveniently, however, for parenteral administration an aqueous vehicle is employed, but in certain instances water-miscible vehicles or non-aqueous vehicles are also envisaged as being appropriate.

The pharmaceutical composition may suitably be in a dosage form and, for parenteral administration, typically stored under sterile conditions in, for example, vials and ampoules ready for use as an injectable.

The present invention also encompasses the preparation of the said pharmaceutical compositions, this preparation being broadly definable as bringing the N-ethyl-D-glucamine salt of the present invention into a form suitable for administration.

The present invention will now be illustrated by way of the following Examples in

[P]

which Example 1 illustrates the preparation of the 2-(2¹-methyl-3¹-trifluoromethyl-anilino)-nicotinic acid starting material, Example 2 illustrates the preparation of the N-methyl-D-glucamine salt in accordance with the present invention and Examples 3 and 4 illustrate the preparation of pharmaceutical compositions of the present invention.

EXAMPLE 1

2-(2¹-Methyl-3¹-trifluoromethylanilino)-nicotinic acid

To 20 g. of 2-methyl-3-trifluoromethyl aniline heated at 200°C add in a dropwise fashion 11 g. of ethyl 2-chloro-nicotinate. Heat the reaction mixture at 200°C for 0.5 hours, then cool and pour the mixture onto ice. Extract the mixture with diethyl ether, concentrate the ether extracts, dry the concentrate and then fractionate *in vacuo* to give ethyl 2-(2¹-methyl-3¹-trifluoromethyl-anilino)-nicotinate, b.p. 143—146°C/0.15 mm; m.p. 44—46°C.

To a solution of 12 g. of the so-obtained ethyl 2-(2¹-methyl-3¹-trifluoromethylanilino)-nicotinate in 100 ml. of methanol add 4.6 g. of potassium hydroxide in 10 ml. of water. Reflux the solution for three hours, concentrate *in vacuo* and dissolve the residue in water. Acidify the aqueous solution to yield the desired 2-(2¹-methyl-3¹-trifluoromethyl-anilino)-nicotinic acid, m.p. 226—228°C after recrystallisation from acetone-hexane.

EXAMPLE 2

N-Methyl-D-glucamine salt of 2-(2¹-methyl-3¹-trifluoromethylanilino)-nicotinic acid

Dissolve 15 g. of 2-(2¹-methyl-3¹-trifluoromethylanilino)-nicotinic acid and 10.5 g. of N-methyl-D-glucamine in 70 ml. of hot ethanol. Add 300 ml. of diethyl ether and filter off the separated salt to give a product of colourless crystals, m.p. 135—137°C. (M.p. 136—139°C upon recrystallisation from acetonitrile or ethanol-diethyl ether.)

EXAMPLE 3

Intramuscular/subcutaneous parenteral solution (Quantities per 1 ml. of solution)

N-methyl-D-glucamine salt of 2-(2¹-methyl-3¹-trifluoromethylanilino)-nicotinic acid

Disodium ethylenediaminetetraacetate U.S.P.

Formopon

Phenol AR

Diethanolamine

Propylene Glycol, U.S.P.

HCl 2.0 Normal q.s. to pH 8.5

Water for Injection q.s. to

*Acid equivalent

Mg.

10—150*

0.1

2.5

5.0

4.0

100.0

1.0 ml.

Procedure

Charge about 80 to 85% of the required amount of water into a suitable compounding vessel and sparge with nitrogen for 10 minutes. Separately add and dissolve with agitation, in order, the following ingredients while sparging: propylene glycol, diethanolamine, phenol, disodium ethylenediaminetetraacetate and formopon. Discontinue

sparging and add sufficient 2.0 normal hydrochloric acid solution to adjust the pH to 8.5. Dissolve with agitation the N-methyl-D-glucamine salt of 2-(2¹-methyl-3¹-trifluoromethylanilino)-nicotinic acid and adjust the solution to the required final volume. Aseptically filter the solution through a suitable sterilising membrane equipped with a pre-filter. Fill the required amount into appropriate sterile containers.

EXAMPLE 4

Intravenous parenteral solution (Quantities per 1 ml. of solution)

N-methyl-D-glucamine salt of 2-(2¹-methyl-3¹-trifluoromethylanilino)-nicotinic acid

Disodium ethylenediaminetetraacetate U.S.P.

Sodium Bisulfite, U.S.P.

Benzly Alcohol, NF

Sodium Hydroxide 1.0 Normal q.s. to pH 8.5

Water for Injection, U.S.P. q.s. to

*Acid equivalent

Mg.

10—150*

0.1

1.625

15.0

1.0 ml.

Procedure

Charge about 80 to 85% of the required amount of water into a suitable compounding vessel and sparge with nitrogen for 10 minutes. Separately add and dissolve with agitation while sparging, in order, the following ingredients: benzyl alcohol, disodium ethylenediaminetetraacetate and sodium bisulfite. Discontinue nitrogen sparging and adjust the pH to 8.5 with 1.0 normal sodium hydroxide solution. Dissolve with agitation the N-methyl-D-glucamine salt of 2-(2'-methyl - 3' - trifluoromethylanilino) - nicotinic acid and adjust the solution to the required final volume. Aseptically filter the solution through a suitable sterilising membrane equipped with prefilter. Fill the required amount into appropriate sterile containers.

As previously stated the N-methyl-D-glucamine salt of the present invention has been found to exhibit unexpectedly high analgesic activity upon parenteral administration.

Comparative *in vivo* data obtained using the standard rat yeast paw test (Randall L. O. and Selitto J. J. [1957] Arch. Int. Pharmacodyn, III, 409) are given in Table I below, in which:—

Compound A is the N-methyl-D-glucamine salt of 2-(2'-methyl-3'-trifluoromethylanilino)-nicotinic acid 30

Compound B is the free acid 2-(2'-methyl-3'-trifluoromethylanilino)-nicotinic acid 35

Compound C is the sodium salt of 2-(2'-methyl - 3' - trifluoromethylanilino)-nicotinic acid.

In the test procedure groups of the stated number of rats were treated subcutaneously (the site of injection being the top of the rats' shoulder blade) with the drug under test one hour after the left paw had been inflamed by a sub-plantar injection of 0.1 ml. of 20 per cent Brewers Yeast suspension. The reaction time to elicit struggling in response to a linear increase in pressure of 20 mm Hg/sec applied to the paw by a rounded metal peg was determined at hourly intervals after the drug treatment. Reaction times both for the normal and inflamed paws were determined at each interval. Yeast induces a hyperesthesia, the reaction times of inflamed paws being generally one-third those of normal paws. The relative potency of the test compounds was determined and is shown in Table I. 40 45 50 55

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TABLE I			
Compound	No. of rats employed	Relative Potency	
A ...	40	1.00	
B ...	20	0.50	
C ...	10	0.35	

65

As will be seen, compound A is significantly more active than compounds B or C.

In contrast to the above results, comparison of the N-methyl-D-glucamine salts of either 2 - (2' - methyl - 3' - chloroanilino)-nicotinic acid (Clonixin) or 2 - (3' - trifluoromethylanilino) - nicotinic acid (Niflumic acid) with the corresponding free acid or corresponding sodium salt of the specified acid did not show any marked differences in subcutaneous analgesic activity using the above test procedure.

The analgesic activity of the compound of the present invention is considered comparable to that of such known analgesic drugs as morphine, meperidine and pentazocine and accordingly to provide a possible alternative to these narcotic analgesics.

Acute toxicity data for the N-methyl-D-glucamine salt of 2-(2'-methyl-3'-trifluoromethylanilino)-nicotinic acid are given in Table II below.

TABLE II

90

Species	LD ₅₀ (mg/kg) Oral Route
Guinea Pig ...	greater than 350

The compound of the present invention is considered to be of use for both clinical and veterinary applications and, while the actual dose range employed would be determined in standard manner in any particular instance, it may be said for guidance that a dose of from 0.25 to 10 mg/kg is indicated for parenteral administration (i.e. intravenous, subcutaneous, intramuscular and the like routes of administration). It may be mentioned that in addition to the above mentioned analgesic activity the compound of the present invention also exhibits anti-inflammatory activity. 95 100 105

WHAT WE CLAIM IS:—

1. The N-methyl-D-glucamine salt of 2-(2'-methyl - 3' - trifluoromethylanilino)-nicotinic acid. 110

2. A process for the preparation of the N-methyl-D-glucamine salt of 2-(2'-methyl-3'-trifluoromethylanilino) - nicotinic acid which comprises treating 2-(2'-methyl-3'-trifluoromethylanilino)-nicotinic acid or a reactive derivative thereof with N-methyl-D-glucamine or a reactive derivative thereof and isolating the so-obtained N-methyl-D-glucamine salt. 115 120

Procedure

Charge about 80 to 85% of the required amount of water into a suitable compounding vessel and sparge with nitrogen for 10 minutes. Separately add and dissolve with agitation while sparging, in order, the following ingredients: benzyl alcohol, disodium ethylenediaminetetraacetate and sodium bisulfite. Discontinue nitrogen sparging and adjust the pH to 8.5 with 1.0 normal sodium hydroxide solution. Dissolve with agitation the N-methyl-D-glucamine salt of 2-(2¹-methyl - 3¹ - trifluoromethylanilino) - nicotinic acid and adjust the solution to the required final volume. Aseptically filter the solution through a suitable sterilising membrane equipped with prefilter. Fill the required amount into appropriate sterile containers.

As previously stated the N-methyl-D-glucamine salt of the present invention has been found to exhibit unexpectedly high analgesic activity upon parenteral administration.

Comparative *in vivo* data obtained using the standard rat yeast paw test (Randall L. O. and Selitto J. J. [1957] Arch. Int. Pharmacodyn, III, 409) are given in Table I below, in which:—

Compound A is the N-methyl-D-glucamine salt of 2-(2¹-methyl-3¹-trifluoromethylanilino)-nicotinic acid

Compound B is the free acid 2-(2¹-methyl-3¹-trifluoromethylanilino)-nicotinic acid

Compound C is the sodium salt of 2-(2¹-methyl - 3¹ - trifluoromethylanilino)-nicotinic acid.

In the test procedure groups of the stated number of rats were treated subcutaneously (the site of injection being the top of the rats' shoulder blade) with the drug under test one hour after the left paw had been inflamed by a sub-plantar injection of 0.1 ml. of 20 per cent Brewers Yeast suspension. The reaction time to elicit struggling in response to a linear increase in pressure of 20 mm Hg/sec applied to the paw by a rounded metal peg was determined at hourly intervals after the drug treatment. Reaction times both for the normal and inflamed paws were determined at each interval. Yeast induces a hyperesthesia, the reaction times of inflamed paws being generally one-third those of normal paws. The relative potency of the test compounds was determined and is shown in Table I.

60

Compound		TABLE I	
		No. of rats employed	Relative Potency
A	...	40	1.00
B	...	20	0.50
C	...	10	0.35

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As will be seen, compound A is significantly more active than compounds B or C.

In contrast to the above results, comparison of the N-methyl-D-glucamine salts of either 2 - (2¹ - methyl - 3¹ - chloroanilino)-nicotinic acid (Clonixin) or 2 - (3¹ - trifluoromethylanilino) - nicotinic acid (Niflumic acid) with the corresponding free acid or corresponding sodium salt of the specified acid did not show any marked differences in subcutaneous analgesic activity using the above test procedure.

The analgesic activity of the compound of the present invention is considered comparable to that of such known analgesic drugs as morphine, meperidine and pentazocine and accordingly to provide a possible alternative to these narcotic analgesics.

Acute toxicity data for the N-methyl-D-glucamine salt of 2-(2¹-methyl-3¹-trifluoromethylanilino)-nicotinic acid are given in Table II below.

TABLE II

90

Species	LD ₅₀ (mg/kg)
	Oral Route
Guinea Pig ...	greater than 350

The compound of the present invention is considered to be of use for both clinical and veterinary applications and, while the actual dose range employed would be determined in standard manner in any particular instance, it may be said for guidance that a dose of from 0.25 to 10 mg/kg is indicated for parenteral administration (i.e. intravenous, subcutaneous, intramuscular and the like routes of administration). It may be mentioned that in addition to the above mentioned analgesic activity the compound of the present invention also exhibits anti-inflammatory activity.

WHAT WE CLAIM IS:—

1. The N-methyl-D-glucamine salt of 2-(2¹ - methyl - 3¹ - trifluoromethylanilino)-nicotinic acid.

2. A process for the preparation of the N-methyl-D-glucamine salt of 2-(2¹-methyl-3¹ - trifluoromethylanilino) - nicotinic acid which comprises treating 2-(2¹-methyl-3¹-trifluoromethylanilino)-nicotinic acid or a reactive derivative thereof with N-methyl-D-glucamine or a reactive derivative thereof and isolating the so-obtained N-methyl-D-glucamine salt.



(13)

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3. A process as claimed in claim 2 and substantially as hereinbefore described with particular reference to Example 2.

4. The N-methyl-D-glucamine salt of 2-(2¹ - methyl - 3¹ - trifluoromethylanilino)-nicotinic acid whenever obtained by a process as claimed in claim 2 or claim 3.

5. Pharmaceutical composition suitable for parenteral administration comprising as an active ingredient a compound as claimed in claim 1 or claim 4, in association with a suitable carrier or excipient.

6. Pharmaceutical composition suitable for parenteral administration comprising as an active ingredient a compound as claimed in claim 1 or claim 4 in association with an aqueous vehicle.

7. A composition as claimed in claim 5 or claim 6 in dosage form.

8. A pharmaceutical composition suitable for parenteral administration as claimed in claim 5 and substantially as hereinbefore described.

9. A process for the preparation of a pharmaceutical composition which comprises bringing a compound as claimed in claim 1 or claim 4 into a form suitable for parenteral administration.

10. A process as claimed in claim 9 which comprises admixing a compound as claimed in claim 1 or claim 4 with a suitable carrier or excipient.

11. A composition whenever prepared by a process as claimed in claim 9 or claim 10.

12. A method of inducing an analgesic effect in a non-human animal which comprises parenterally administering a therapeutically effective quantity of the N-methyl-D-glucamine salt of 2-(2¹-methyl-3¹-trifluoromethylanilino)-nicotinic acid.

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