# PATENT SPECIFICATION

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(72) Inventor ANDRE ESANU ·

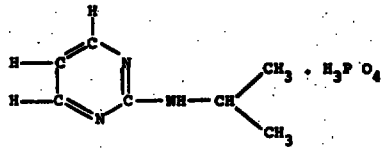

(19)

## (54) AMINOPYRIMIDINE SALT ·


(71) We, SOCIETE D'ETUDES DE PRODUITS CHIMIQUES, a company organised and existing under the laws of France, of 4, Rue Théodule Ribot, 75017 Paris, 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:—


The invention relates to a new salt of a substituted 2-aminopyrimidine. The new salt is useful as an active agent in medicines for the treatment of neuropathies of various origins, and the invention accordingly provides pharmaceutical preparations containing the salt.

The new salt according to the invention is 2-isopropylamino-pyrimidine orthophosphate, which has the formula:




It is a white crystalline powder which melts at 125°C and is soluble in water. Its formula is $C_7H_{14}O_4N_3P$ and its molecular weight it 235.17.

This compound may be obtained according to the invention by reacting 2-isopropylamino-pyrimidine with orthophosphoric acid, preferably in a slight stoichiometric excess, suitably in a polar solvent for example an alcohol having up to 5 carbon atoms.

The invention also provides a therapeutic composition comprising 2-isopropylamino-pyrimidine orthophosphate together with a therapeutically acceptable diluent or carrier.

The invention is illustrated by the following Example:

### Example

6 litres of ethanol and 685 g (5 moles) of 2-isopropylamino-pyrimidine were added to a 10 litre reactor and stirred. To the solution were added 600 g (5.2 moles) of phosphoric acid and the mixture was boiled under reflux for one hour. There was obtained a dark green solution which was treated with 30 g of carbon black. After separation and crystallization whilst stirring overnight, the crystallized product was separated, washed with ethanol and dried at 50°C. There was obtained 1.027 g (87% yield) of a white powder melting at 125°C. The analysis of the compound showed a good correspondence with the formula $C_7H_{14}O_4N_3P$.

### TOXICITY

The acute toxicity of the product was determined on mice i.p. and *per os* and is given in Table 1 below, together with the corresponding values for 2-isopropylamino-pyrimidine dichloroacetate which presents an activity in the same therapeutical field.

TABLE 1

| | LD 50 in g/kg Dichloroacetate | LD 50 in g/kg Orthophosphate |
|---|---|---|
| i.p. | 0.630 | 1.530 |
| *per os* | 1.700 | 2.830 |

Accordingly the compound of the invention appears far less toxic than this previous compound. The comparison of the subacute toxicities on rats for both compounds confirms a lower toxicity and a better tolerance for the compound of the invention. At similar doses, marked differences between the action of the same two salts were noticed, as set out in Table 2. Each experiment used 10 rats, with a control of 10 further rats.

TABLE 2

| Treatment | Weight Loss Compared to Controls, at 37th day | Death at the End of Treatment |
|---|---|---|
| Dichloroacetate *per os* 6 days a week for 5 weeks at 570 mg/kg | 23.1% | 2 |
| Orthophosphate *per os* 7 days a week for 6 weeks at 600 mg/kg | 7.3% | 0 |

Moreover a 40% to 45% incidence of heptamegalia was noticed after the above treatment with dichloroacetate, but not after the treatment with the orthophosphate of the invention.

## PHARMACOLOGY

The pharmacological activity of the compound of the invention is illustrated by the results of comparative experiments undertaken on the regeneration of sciatic nerves of male adult rats (Wistar). Each experiment was carried out as follows:

A lesion was made on the sciatic nerve of a rat by a thermosound at –20°C applied 20 minutes on the nerve.The rat was then treated *i.p.* by a comparison product or by the compound of the invention for a predetermined duration. At the end of the treatment, the rat was killed, the sciatic nerve was separated and placed in contact with a series of 70 thin parallel platinum wires (interval 1 mm) and an electric signal was applied upstream the lesion point to test the regenerated length of the nerve. The more distant wire where the signal could be collected gives the regenerated length. For each tested composition and each duration of treatment there was used a batch of at least 5 rats.

Four compositions were tested i.p.: the base 2-isopropylamino-pyrimidine (87 mg/kg), its dichloroacetate (170 mg/kg, corresponding to 87 mg/kg of the base), its orthophosphate (145 mg/kg, corresponding to 87 mg/kg of the base) and a mixture of vitamins B1 (500 mg/kg), B2 (500 mg/kg) and B6 (5 mg/kg) which is known in the art to be the most effective composition in this field. It has been demonstrated that, when using 2-isopropylamino-pyrimidine salts, the activity is principally bound with the amount of base actually comprised in the salts, each salt bringing only a slight modification with respect to the base. For that reason, the doses used for dichloroacetate and orthophosphate have been calculated for an equivalence of 87 mg/kg of the base. The interest of the comparison with the base is purely

theoretical as the base is not therapeutically administrable (too high pH).

The results of these experiments are summarized in Table 3 below, together with figures obtained for control animals (five batches respectively at 7, 11, 14, 17 and 21 days). In Table 3, *m* indicates the length in millimetres of regenerated nerve as an average value of the lengths measured for the *n* animals of the batch. When no figure appears (17 and 21 days) this means that the regenerated length exceeded the length of the sample taken.

TABLE 3

| Duration (Days) | | 7 | 11 | 14 | 17 | 21 |
|---|---|---|---|---|---|---|
| Controls | *m* | 5 | 10.6 | 13.2 | 21.8 | 26.8 |
| | *n* | 5 | 5 | 5 | 5 | 5 |
| Base 87 mg/kg | *m* | 6.3 | 13.8 | 25.1 | – | – |
| | *n* | 5 | 6 | 6 | – | – |
| Dichloroacetate (170 mg/kg) | *m* | 6.5 | 14.5 | 21.1 | – | – |
| | *n* | 6 | 6 | 6 | | |
| Orthophosphate (145 mg/kg) | *m* | 6.7 | 16.2 | 22.7 | – | – |
| | *n* | 7 | 5 | 7 | | |
| B1, B6, B12 | *m* | 9.4 | 13.2 | 16.2 | 21.4 | 25.5 |
| | *n* | 5 | 5 | 5 | 5 | 5 |

## PRESENTATION—POSOLOGY

This salt can be presented in any therapeutically acceptable form, for example in tablets or in gelatine capsules containing 50 mg per dosage unit together with an excipient such as lactose. For an injectable form the product may be dosed in phials containing at least 10 mg of active ingredient dissolved in water. For human use, oral administration requires from 250 mg to 2 g *per diem* whereas the injectable form may be administered at doses between 10 mg to 400 mg *per diem*. An example of the tablet form is given here under:

| | |
|---|---|
| 2-isopropylamino-pyrimidine orthophosphate | 250 mg |
| Microcrystalline cellulose | 170 mg |
| Corn starch | 115 mg |
| Talc | 47 mg |
| Silicic acid | 6 mg |
| Hydrogenated ricin oil | 5 mg |
| Magnesium stearate | 7 mg |
| | 600 mg |

WHAT WE CLAIM IS:—

1. A process for preparing the orthophosphate of 2-isopropylamino-pyrimidine, comprising reacting 2-isopropylamino-pyrimidine with orthophosphoric acid.

2. A process according to claim 1, wherein the orthophosphoric acid is used in a slight stoichiometric excess.

3. A process according to claim 1 or claim 2, wherein the preparation is carried out in solution in a polar solvent.

4. A process according to claim 3, wherein the solvent is an alcohol having up to 5 carbon atoms.

5. A process according to claim 1 substantially as described in the Example.

6. 2-isopropylamino-pyrimidine orthophosphate.

7. A therapeutic composition comprising 2-isopropylamino-pyrimidine orthophosphate together with a therapeutically acceptable diluent or carrier.

SERJEANTS,
Chartered Patent Agents,
25 The Crescent,
Leicester.

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