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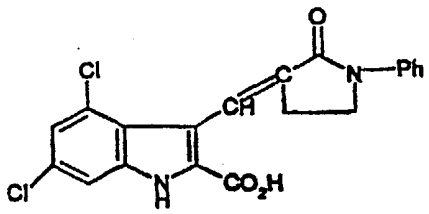
(54) Titre: Crystalline hydrated sodium salt of (E)-4,6-dichloro-3-(2-oxo-1-phenylpyrrolidin-3-ylidene methyl)-1H-indole-2-carboxylic acid.

(57) Abrégé: A crystalline hydrated form of the sodium salt of the compound of formula (I), processes for its preparation and its use in therapy.

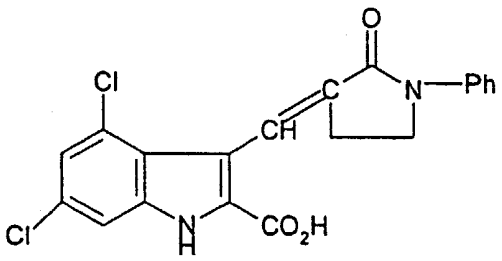


(I)

CRYSTALLINE HYDRATED SODIUM SALT OF (E)-4,6-DICHOLORO-3-(2-OXO-1-PHENYLPYRROLIDIN-3-YLIDENE METHYL)-1H-INDOLE-2-CARBOXYLIC ACID

The present invention is concerned with the sodium salt of the excitatory amino acid antagonist (E) 4,6-dichloro-3-(2-oxo-1-phenylpyrrolidin-3-yledine methyl)-1H-indole-2-carboxylic acid, its production, isolation and use in therapy.

WO 95/1057 describes inter alia the compound of formula (1).



(I)

and physiologically acceptable salts thereof, as a potent antagonist at the strychnine insensitive glycine binding site associated with the N-methyl-D-aspartate (NMDA) receptor complex. The compound of formula (I) and salts thereof e.g. the sodium salt are useful in the treatment or prevention of neurotoxic damage or neurodegenerative diseases. Thus the compounds are useful for the treatment of neurotoxic injury which follows cerebral stroke, thromboembolic stroke, hemorrhagic stroke, cerebral ischemia, cerebral vasospam, hypoglycemia, amnesia, hypoxia, anoxia, perinatal asphyxia cardiac arrest. The compounds are useful in the treatment of chronic neurodegenerative diseases such as: Huntingdon's disease, Alzheimer's senile dementia, amyotrophic lateral sclerosis, Glutaric Acidaemia type, multi-infarct dementia. They have further uses in the treatment or prevention of status epilecticus, contusive injuries (e.g. spinal cord injury and head injury), viral infection induced neurodengeration , (e.g. AIDS, encephalopaties), Down's syndrome, epilepsy, schizophrenia, depression, anxiety, pain, migraine, neurogenic bladder, irritative bladder disturbances, drug dependency, including withdrawal symptoms from alcohol, cocaine, opiates, nicotine, benzodiazepine, and emesis.

The sodium salt of the compound of formula (I) is of particular importance since it enables the compound to be conveniently formulated for administration to the patients. There is thus a need to produce the sodium salt of the compound of formula (I) in as pure and as highly crystalline a condition as possible in order to fulfil the exacting standards required for a pharmaceutical product.

The process by which the sodium salt of the compound of formula (I) also needs to be one which is convenient to carry out on a plant scale, and from which the product can be readily isolated.

The sodium salt of the compound of formula (I) has been prepared and isolated in solid form by lyophilisation of an aqueous solution of the sodium salt of a compound of formula (I) as described in WO 95/1057. This process is not particularly convenient for use on a plant scale and the product thus obtained is not the highly crystalline product desired.

It has now been found that the sodium salt of the compound of formula (I) can be advantageously prepared and isolated in a crystalline hydrated form which hydrated form can be readily obtained with the requred high degree of purity and good stability and thus fulfils the exacting criteria required for a pharmaceutical product.

The present invention thus provides a new crystalline hydrated form of the sodium salt of the compound of formula (I). More particularly the invention provides a crystalline hydrate which by analysis contains from 2.5 to 3.1% water by weight, and preferably 2.6 to 2.9% water by weight e.g. 2.6 to 2.8%.

The water content given above for the new crystalline hydrated form is that for the product which has been effectively dried to constant weight; for example dried under vacuum (1 to 5 mm Hg) at 40-45°C for up to 4 days.

The crystalline hydrated form of the sodium salt of the compound of formula (I) may be characterised by its infra red spectrum as a mull in mineral oil, and or its X-ray powder diffraction pattern.

The invention thus provides a crystalline hydrated form of the sodium salt of the compound of formula (1) characterised by an infra-red spectrum as a mull in mineral oil and with KBr discs showing the following peaks:

(cm^{-1})		
3308	1539	1349
3280	1500	1331
1668	1480	1305
1655	1482	1284
1639	1449	1244
1587	1435	834
1550	1407	814
		690

The invention also provides a crystalline hydrated form of the sodium salt of the compound of formula I characterised by the following - X-ray powder diffraction pattern expressed as 2 Theta (1θ) values and obtained on a Philips X^1 Part MPD Theta-2 Theta diffractometer utilising CuKα radiation (1.541 angstroms) with a step size of 0.04°/sec and count time of 1 sec.

Angle (°2θ)

5.170	18.325	25.395
5.435	18.775	26.535
9.585	19.225	26.920
11.745	20.820	27.630
14.635	21.195	28.230
15.590	22.925	30.370
16.365	23.970	30.870

A further aspect of the invention provides a process for the preparation of the new crystalline hydrated form of the sodium of the compound of formula (I) by crystallisation from a mixture of an alkanol (e.g. ethanol, IMS (ethanol/methanol 95/5) or isopropanol) and water. Preferably the crystallisation process is carried out at a temperature between 55° and reflux and conveniently 60-80°C.

Thus in one embodiment of the process the acid may be dissolved with heating in the alkanol e.g. isopropanol or IMS containing aqueous sodium hydroxide solution. If necessary, the hot solution may then diluted with water to effect crystallisation and then cooled.

In a further embodiment of the process the new crystalline hydrated form of the sodium salt of the compound formula (I) may be prepared and isolated directly by the hydrolysis of an alkyl ester e.g. C_{1-4}alkyl ester such as the methyl or ethyl ester of the compound of formula (I) by heating with aqueous sodium hydroxide and an alkanol e.g. ethanol, IMS (ethanol/methanol 95/5) or isopropanol, followed if necessary by addition of water.

Conveniently the alkyl ester of the compound of formula (I) may be prepared by reaction of the corresponding alkyl ester of 3-formyl-4,6-dichloroindole-2-carboxylic acid with tributyl (2-oxo-1-phenylpyrrolin-1-yl)phosphonium bromide in a solvent such as an alkanol e.g. ispropanol and in the presence of a base e.g. 1,8-diazabicyclo[5.4.0]undec-7-ene.

The invention also provides for the use of the new crystalline hydrated form of the sodium salt of compound of formula (I) for use in therapy and in particular use as medicine for antagonising the effects of excitatory amino acids upon the NMDA receptor complex.

The invention also provides for the use of the new crystalline hydrated form of the sodium salt of compound of formula (I) for the manufacture of a medicament for antagonising the effects of excitatory amino acids upon the NMDA receptor complex.

According to a further aspect the invention also provides for a method for antagonising the effects of excitatory amino acids upon the NMDA receptor complex, comprising administering to a patient in need thereof an antagonistic amount of the new crystalline hydrated form of the sodium salt of the compound of formula (I). Thus for example the inventon provides a method for the treatment or prevention of pain which comprises administering to a patient in need thereof an effective amount of the new crystalline hydrated form of the sodium salt of the compound of formula (I).

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms.

It will further be appreciated that the amount of the compound of the invention required for use in treatment will vary with the nature of the condition being treated the route of administration and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician. In general however doses employed for adult human treatment will typically be in the range of 2 to 800mg per day, dependent upon the route of administration.

Thus for parenteral administration a daily dose will typically be in the range 20-100mg preferably 60-80mg per day. For oral administration a daily dose will typically be within the range 100-800mg e.g. 200-600mg per day.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

While it is possible that, for use in therapy, the compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising the new crystalline hydrated form of the sodium salt of the compound of formula (I) together with one or more pharmaceutically acceptable carriers therefor and,

optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The compositions of the invention include those in a form especially formulated for oral, buccal, parenteral, inhalation or insufflation, implant, or rectal administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate, or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; solubilizers such as surfactants for example polysorbates or other agents such as cyclodextrins; and preservatives, for example, methyl or propyl p- hydroxybenzoates or ascorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition according to the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For administration by inhalation the compound according to the invention is conveniently delivered in the form of an aerosol spray presentation from pressurised packs, with the use of a suitable propellant, such as dichlorodifluoromethane, tirchlorofluoromethane, dichloro-tetrafluoroethane, carbon dioxide or other suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichloro-tetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compound according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable carrier such as lactose or starch. The powder composition may be presented in unit dosage form in for example capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

The composition according to the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The compositions according to the invention may contain between 0.1 - 99% of the active ingredient, conveniently from 30- 95% for tablets and capsules and 3-50% for liquid preparations.

The compound of formula (I) or an alkyl ester thereof may be prepared according to the processes described in WO95/1057. Alternatively an alkyl ester of the compound of formula (I) may be prepared by the process more specifically described herein in the Examples.

In order that the invention may be more fully understood the following examples are given by way of illustration only.

In the examples the temperatures are given in °C. The water content was determined by the Karl Fischer method.

Intermediate 1

Tributyl (2-oxo-1-phenylpyrrolidin-1-yl) phosphonium bromide

N,N,N^{1}N^1-Tetramethylethylene diamine (23.3ml) was added to a solution of N-phenylpyrrolidinone (5g) in dichloromethane (50ml). The solution was cooled to 0-5° and trimethylsilyl triflate (8.4ml) was added over *ca* 20 mins maintaining the temperature in the range 0-5°. The resultant solution was stirred for 10 mins and a solution of pyridinium bromide perbromide (13g) in acetonitrile (20ml) was added over *ca* 20 mins maintaining the temperature in the range 0-10°.The resultant suspension was stirred at 0-5° for *ca* 60 mins. Aqueous sodium bicarbonate solution (50ml) was added, cautiously. The mixture was stirred for *ca* 5 mins and the layers are separated.The aqueous phase was diluted with water (20ml) and back extracted with dichloromethane (20ml). The combined organic phases were washed with further sodium bicarbonate solution (50ml), 2M hydrochloric acid (2x50ml) and water (50ml), back extracting each wash with dichloromethane (10ml). The organic solution was dried ($MgSO_4$) and concentrated on a rotavapor. The red/brown solid was stirred with ethyl acetate (50ml) and warmed to give a solution which was then cooled and tributylphosphine (8.5ml) was added.The solution was heated to reflux and

maintained at reflux for 2.5 hours. The solution was allowed to cool to room temperature and was then cooled to 0-5°. The resulting suspension was aged at 0-5° for *ca* 60 min.The product was isolated by vacuum filtration and then washed with ethyl acetate:t-butylmethylether (1:1, 40ml) and dried in a vacuum oven at 45° to give the title compound as a white crystalline solid (10.12g), mp 127-128°.

Intermediate 2

Ethyl (E)-4,6-dichloro-3-(2-oxo-1-phenylpyrrolidin-3-ylidenemethyl)-1H-indole 2-carboxylate

1,8-Diazabicyclo[5.4.0]undec-7-ene (1.24ml) was added to a mixture of ethyl 3 formyl-4,6-dichloroindole-2-carboxylate (2g) and tributyl(2-oxo-1-phenylpyrrolin-1-yl)phosphonium bromide (3.7g) in isopropanol (20ml). The mixture was heated to reflux and refluxed for 8 hr before cooling slowly to room temperature.
The reaction mixture was cooled to approx. 5 ^{0}C using an ice/water bath and aged at 0-5^{0}C for 2 hr. The precipitate was filtered under vacuum and washed with isopropanol (7.5 ml). The product was dried in a vacuum oven at 40^{0}C to give the title compound as a white crystalline solid (1.95g).

Example 1
(E)-4,6-dichloro-3-(2-oxo-1-phenyl-pyrrolidin-3-ylidenemethyl)-1H-indole-2-carboxylic acid sodium salt, hydrate

Ethyl (E)-4,6-dichloro-3-(2-oxo-1-phenyl-pyrrolidin-3-ylidenemethyl)-1H-indole-2-carboxylate (494g) was added slowly, without stirring, to a two phase system composed of isopropanol (3458ml) and NaOH 32%w/w (640ml). The reaction mixture was heated to reflux (in 1hr 20min) and stirred for 1.5hrs. Water (10374ml) was added dropwise in 24 minutes (final temp. 55°C). The reaction mixture was stirred for 30min at 55/59°C, cooled to 15°C in 2hrs 15min then the reaction mixture was stirred for 45min, filtered (on a 27cm diameter teflon filter with polypropylene as support). And washed with a mixture of isopropanol/water 1/3 (988ml) and water (5928ml). The resulting solid was dried under vacuum at

40°C for 22hrs 15min to give the title compound .(475g) Water content 2.66% by weight.

^{1}H-NMR (400MHz) DMSO

2.78 δ (m, 2H), 3.81δ (m, 2H), 7.05 δ (d, 1H),7.13 δ (m, 1H), 7.38 δ (m, 2H), 7.36 δ (d, 1H), 7.78 δ (d, 2H), 7.83 δ (t, 1H), 11.72 δ (bs, 1H).

Example 2

(E)-4,6-dichloro-3-(2-oxo-1-phenyl-pyrrolidin-3-ylidenemethyl)-1H-indole-2-carboxylic acid sodium salt, hydrate

Ethyl (E) 4,6-dichloro-3-(2-oxo-1-phenyl-pyrrolidin-3-ylidenemethyl)-1H-indole-2-carboxylate (2g) was added to a 14ml of IMS (Ethanol/Methanol 95/5vol). A NaOH 32%w/w solution (2.58ml) was added to the obtained suspension. The reaction mixture was heated to reflux (in 50min) and stirred for 1.5hrs. Water (42ml) was added dropwise in 10 minutes. The reaction mixture was cooled to 15° and then stirred for 2hrs, filtered and washed with a mixture of IMS/water 1/3 (4mll) and water (42ml). The resulting solid was dried under vacuum at 40° for 20hrs to give the title compound desired carboxylic acid sodium salt (1.67g). Water content 2.7% by weight

^{1}H-NMR (500MHz) DMSO

2.78 δ (m, 2H), 3.81δ (m, 2H), 7.06 δ (d, 1H),7.14 δ (m, 1H), 7.40 δ (m, 2H), 7.40 δ (d, 1H), 7.78 δ (d, 2H), 7.83 δ (t, 1H), 11.82 δ (bs, 1H).

Pharmacy Example

Tablets

Active ingredient*	5.27-105.5mg
Lactose	340.0mg
Microcrystalline Cellulose	214.1mg
Sodium Starch Glycolate	13.6mg
Magnesium Sterate	6.8mg

The tablets may be manufactured using a standard dry blending and direct compression process followed by a conventional film coating and optionally followed by an enteric coating.

The active ingredient is the compound of Example 1 and the amount is equivalent to 5 to 100mg of the parent free acid.

Suitable conventional film coats include Opadry white and suitable enteric coatings include Sureteric Opadry enteric white.

Claims

1. (E)-4,6-Dichloro-3-(2-oxo-1-phenylpyrrolidin-3-ylidene methyl)-1H-indole 2-carboxylic acid, sodium salt, in a crystalline hydrated form.

2. A crystalline hydrated form as claimed in claim 1 wherein the water content is between 2.5 to 3.1% by weight.

3. A crystalline hydrated form as claimed in claim 1 or claim 2 wherein the water content is between 2.6 to 2.9 by weight.

4. A crystalline hydrated form as claim in any of claims 1 to 3 characterised by an infra-red spectrum as a mull in mineral oil showing the following peaks:

(cm^{-1})		
3308	1539	1349
3280	1500	1331
1668	1480	1305
1655	1482	1284
1639	1449	1244
1587	1435	834
1550	1407	814
		690

5. A crystalline hydrated form as claimed in any of claims 1 to 4 characterised by the following - X-ray powder diffraction pattern expressed as 2-Theta values (2θ) and obtained on a Philips X^1 Part MPD Theta-2 Theta utilisting CuKα radiation (1.541 angstroms) with a step size of 0.04°/sec and count time of 1 sec.

Angle (°2θ)		
5.170	18.325	25.395
5.435	18.775	26.535
9.585	19.225	26.920
11.745	20.820	27.630
14.635	21.195	28.230
15.590	22.925	30.370
16.365	23.970	30.870

6. A process for the preparation of the crystalline hydrated form as defined in any of claims 1 to 4 which comprises crystallising the sodium salt from a solution of an aqueous alkanol.

7. A process as claimed in claim 6 wherein the sodium salt of the compound of formula (I) is generated in situ by hydrolysis of the corresponding alkyl ester by reaction with aqueous sodium hydroxide in the presence of an alkanol, followed if necessary or desired by the addition of water.

8. A process as claimed in claim 7 wherein the alkyl ester is prepared by reacting the corresponding alkyl ester of 3-formyl-4,6-dichloroindole-2-carboxylic acid with tributyl (2-oxo-1-phenylpyrrolin-1-yl)phosphonium bromide.

9. A process as claimed in claim 8 wherein the alkyl ester is an ethyl ester.

10. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 5 in admixture with one or more physiologically acceptable carriers or excipients.

11. A method of treatment of a mammal including man for conditions where antagonising the effects of excitatory amino acids on the NMDA receptor complex is of therapeutic benefit, comprising administration of an effective amount of a compound as claimed in any of claims 1 to 5.

12. A method of treatment or prevention of pain which comprises administering to a patient in need thereof an effective amount of a compound as claimed in any of claims 1 to 5.