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(54) Title: A PROCESS FOR PREPARATION OF PRAZIQUANTEL

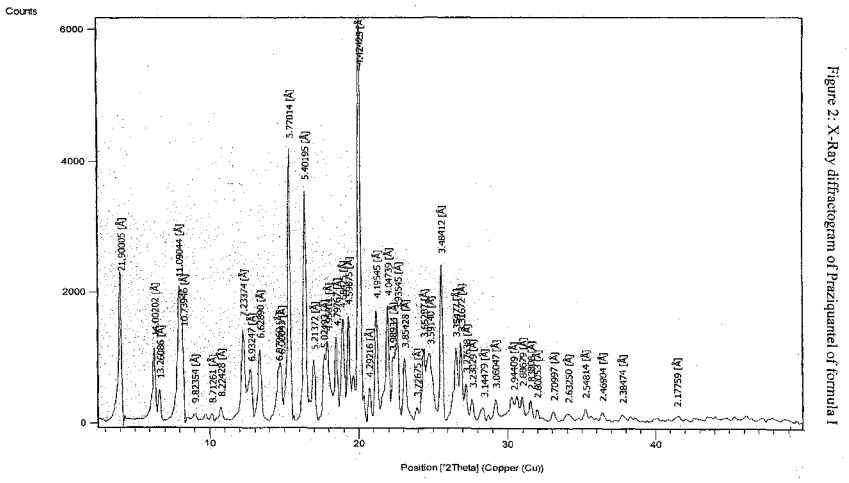

Figure 2: X-Ray diffractogram of Praziquantel of formula I

(57) Abstract: The present invention discloses a novel, cost-effective process for preparation of a 4- oxo- 1,2,3,6,7,11b-hexahydro-4H-pyrazino-[2, 1-a]isoquinoline derivatives. Specifically it discloses a process for the preparation of anthelmenthic drug praziquantel incorporating a novel intermediate 2-[(2,2-dimethoxyethyl)benzyl amino]-N- phenethylacetamide. This invention also discloses a novel crystalline form of 4-oxo- 1,2,3,6,7,11b-hexahydro-4H-pyrazino[2, 1-a]isoquinoline.

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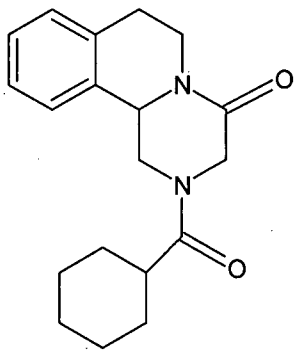
A Process for Preparation of Praziquantel

Field of Invention

The present invention relates to a novel, cost-effective process for preparation of a 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino-[2,1-a]isoquinoline derivatives. Specifically, it relates to a process for the preparation of praziquantel involving new intermediate.

Background of the Invention

Praziquantel having chemical name 2-cyclohexylcarbonyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline of formula I, is a member of the 2-Acyl-4-oxopyrazinoisoquinoline compounds, which are used as a drug indicated for the treatment of a variety of worm infections. Praziquantel is primarily used against parasites known as "cestodes" and it is also effective against flukes.



(I)

There are number of literatures available which describe the process for preparation of praziquantel. US patent 4001411 describes a process for preparation of praziquantel by acylating 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline with cyclohexanoylchloride in chloroform and triethylamine.

KR2002076486 describes a process for preparation of praziquantel by reacting phenylethylamine with chloroacetyl chloride to obtain 2-chloro-N-phenethylacetamide. Treating 2-chloro-N-phenethylacetamide with pthalimide to give 2-pthalimido-N-phenethylacetamide and treating further 2-pthalimido-N-phenethylacetamide with hydrazine monohydrate to give 2-amino-N-phenylethylacetamide, which on further treatment with bromoacetal gives 2-[(2,2-dimethoxyethyl)amino]-N-(2-phenylethyl)acetamide. This

compound on further cyclization and acylation using cyclohexanoylchloride forms praziquantel.

CN1683346 describes a similar above process except the first step where 2-amino-N-phenylethylacetamide is prepared by reacting 2-aminoacetylchloride hydrochloride with phenylethylamine.

WO2009115333 describes many processes in one of which 3-phenylpropanenitrile is reacted with aminoacetal in presence of formaldehyde to obtain 2-[(2,2-dialkoxyethyl)amino]-N-(2-phenylethyl)acetamide, which is further cyclised and acylated using cyclohexanoylchloride to form praziquantel.

Eur. J. Org. Chem. 2008, 895-913 describes a process comprising: a) reacting phenylethylamine with chloroacetyl chloride in presence of sodium bicarbonate to obtain 2-chloro-N-phenethylacetamide, b) treating 2-chloro-N-phenethylacetamide with aminoacetaldehyde dimethylacetal to give 2-[(2,2-dimethoxyethyl)amino]-N-(2-phenylethyl)acetamide, c) making hydrochloride salt of 2-[(2,2-dimethoxyethyl)amino]-N-(2-phenylethyl)acetamide, and d) cyclising using sulphuric acid to form praziquanamine (i.e.4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline).

A major drawback in above the known processes is use of very expensive raw material aminoacetaldehyde dimethylacetal. Moreover, it is used in two equivalents in which one equivalent is consumed in the reaction and the other equivalent is lost. It poses a lot of concern in terms of cost at the commercial scale production.

Thus there is a need to develop a process for the preparation of Praziquantel, which is cost effective and easy to handle on a commercial scale. Especially there is a need to develop a process which avoids the use of costly aminoacetaldehyde dimethylacetal compounds to reduce the overall cost of production.

Thus the present invention provides a cost effective process for preparing Praziquantel in good yield and good purity on a commercial scale.

Summary of the Invention

The principal aspect of the present invention is to provide a process for the preparation of 2-[(2,2-dimethoxyethyl)amino]-N-(2-phenylethyl)acetamide of formula III, which comprises:

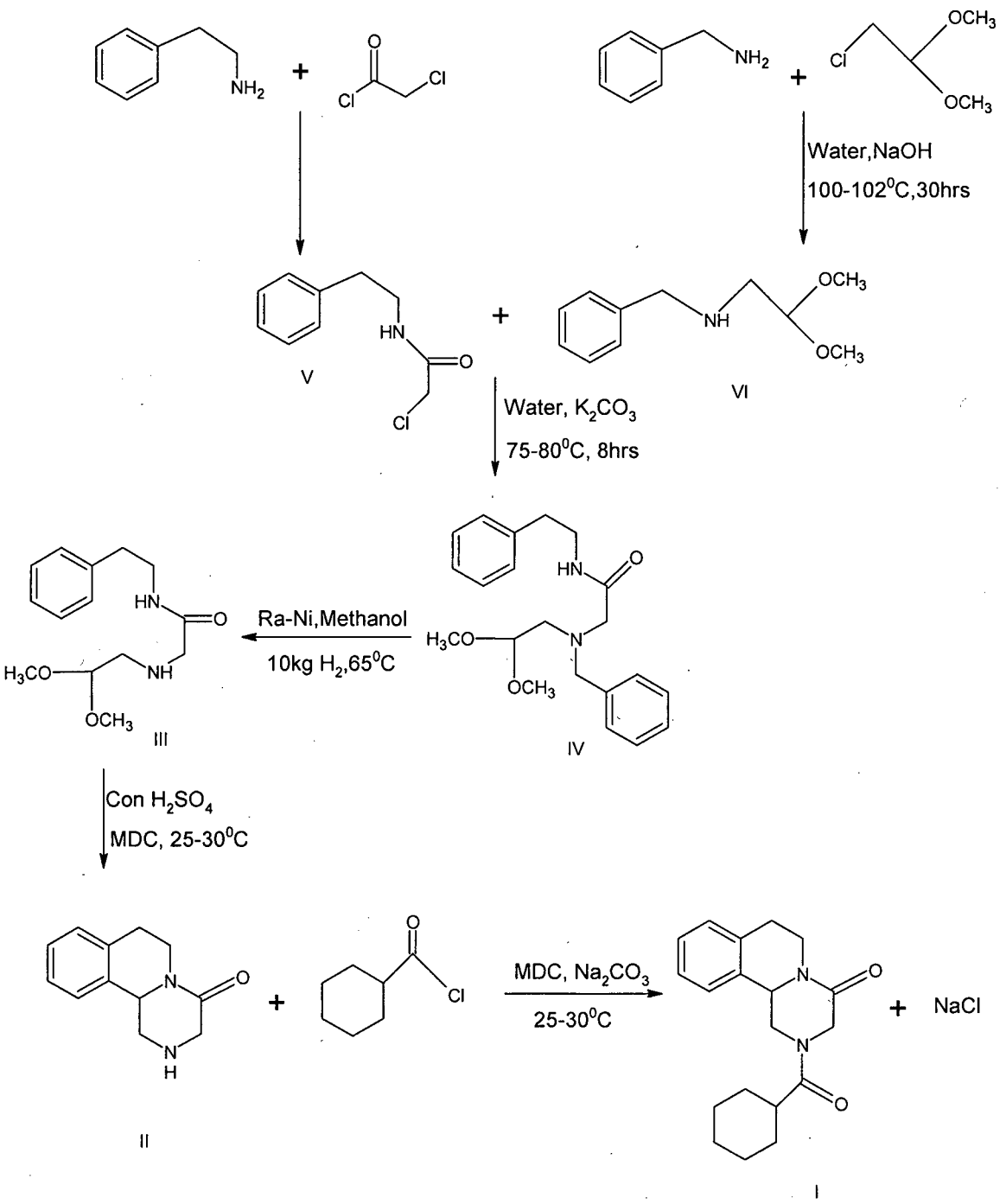
a) condensation of β-phenylethylamine with chloroacetylchloride in presence of a solvent and a base to obtain 2-chloro-N-phenethylacetamide of formula V;
b) condensation of Benzylamine with chloroacetaldehydedimethylacetal in presence of water and a base to obtain N-benzyl-2,2-dimethoxyethanamine of formula VI;
c) condensation of 2-chloro-N-phenethylacetamide of formula V prepared in step a) with N-benzyl-2,2-dimethoxyethanamine of formula VI prepared in step b) in presence of water and a base to obtain 2-[(2,2-dimethoxyethyl)benzylamino]-N-phenethylacetamide of formula IV; and
d) reduction of 2-[(2,2-dimethoxyethyl)benzylamino]-N-phenethylacetamide of formula IV using a reducing agent and a solvent in presence of hydrogen to obtain 2-[(2,2-dimethoxyethyl)amino]-N-(2-phenylethyl)acetamide of formula III.

The another aspect of the present invention is to provide a process for the preparation of Praziquantel of formula I, which comprises;

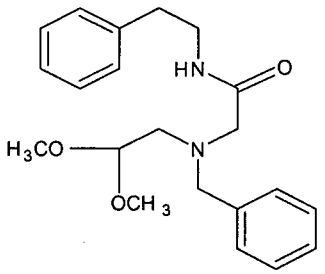
a) condensation of β-phenylethylamine with chloroacetylchloride in presence of a solvent and a base to obtain 2-chloro-N-phenethylacetamide of formula V;
b) condensation of Benzylamine with chloroacetaldehydedimethylacetal in presence of water and a base to obtain N-benzyl-2,2-dimethoxyethanamine of formula VI;
c) condensation of 2-chloro-N-phenethylacetamide of formula V prepared in step a) with N-benzyl-2,2-dimethoxyethanamine of formula VI prepared in step b) in presence of water and a base to obtain 2-[(2,2-dimethoxyethyl)benzylamino]-N-phenethylacetamide of formula IV;
d) reduction of 2-[(2,2-dimethoxyethyl)benzylamino]-N-phenethylacetamide of formula IV using a reducing agent and a solvent in presence of hydrogen to obtain 2-[(2,2-dimethoxyethyl)amino]-N-(2-phenylethyl)acetamide of formula III;
e) cyclisation of 2-[(2,2-dimethoxyethyl)amino]-N-(2-phenylethyl)acetamide of formula III prepared in step d) using an acid in presence of solvent to obtain 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline of formula II; and

f) acylation of 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline of formula II with cyclohexanoylchloride in presence of a base and solvent to obtain Praziquantel of formula I.

The process of the present invention may be illustrated as in the scheme below:



In another aspect of the present invention 2-[(2,2-dimethoxyethyl) benzyl amino]-N-phenethylacetamide of formula IV is novel, which is a valuable precursor for 2-[(2,2-dimethoxyethyl)amino]-N-(2-phenylethyl)acetamide of formula III and an important intermediate for Praziquantel I.



IV

In another aspect, this invention provides a novel crystalline form of 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline of formula II which is very stable. This novel crystalline form is characterised by the powdered X-Ray diffractogram substantially as given in figure 1 and having 2θ values 11.3224, 11.6010, 12.3040, 13.9389, 15.6595, 17.6684, 18.2167, 20.5348, 21.2141, 21.7543, 22.5259, 23.2597, 24.5423, 24.7190, 25.1168, 25.9533, 27.0875, 27.9823, 28.4783, 30.2130, 31.9009, 33.1835, 33.9561, 34.9936, 35.8283, 36.6569, 38.3095, 39.9195, 41.3981, 43.4197, 44.7071, 15.8443, 46.4157, and 47.5018±0.2.

Detail Description of the Invention

Accordingly in an embodiment of the invention, the condensation of β-phenylethylamine with chloroacetylchloride is carried out in presence of an organic solvent preferably an aromatic solvent more preferably selected from benzene or substituted benzene or toluene, most preferably toluene and a base selected from an alkali metal carbonate or bicarbonate preferably selected from sodium carbonate, sodium bicarbonate, potassium carbonate and potassium bicarbonate, more preferably sodium bicarbonate, in the temperature range -5 to 15 °C, preferably in the range 0 to 10°C.

In another embodiment of the invention, the condensation in step b) is carried out in an aqueous solvent, preferably water and a base selected from sodium hydroxide or

potassium hydroxide, preferably sodium hydroxide, in the temperature range 95 to 105°C, preferably at 100-102°C to obtain N-benzyl-2,2-dimethoxyethanamine.

In another embodiment of the invention, the condensation in step c) is carried out in an aqueous solvent, preferably water and a base selected from sodium carbonate or sodium bicarbonate or potassium carbonate preferably potassium carbonate, in the temperature range 70 to 90°C, preferably at 75 to 80°C.

In another embodiment of the invention, the reduction in step d) is carried out in an alcoholic solvent like methanol, ethanol, isopropanol, preferably in presence of methanol using a reducing agent selected from Raney nickel, Palladium on carbon or Platinum, preferably Raney nickel. The reduction is preferably carried out at 10 kg H_2 pressure and at temperature about 65°C to obtain 2-[(2,2-dimethoxyethyl)amino]-N-(2-phenylethyl)acetamide .

In another embodiment of the invention, the cyclization of 2-[(2,2-dimethoxyethyl)amino]-N-(2-phenylethyl)acetamide is carried out in presence of an acid, preferably mineral acid, more preferably concentrated sulphuric acid and in presence of an organic solvent selected from dichloromethane or dichloroethane or chloroform or carbon tetrachloride preferably dichloromethane. Preferably in the temperature range 25 to 30°C to obtain 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline of formula II.

In another embodiment of the invention, the acylation of 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline of formula II is carried out in presence of a base, preferably sodium carbonate and in presence of an organic solvent selected from dichloromethane or dichloroethane or chloroform or carbon tetrachloride preferably dichloromethane. Preferably in the temperature range 25 to 30°C to obtain Praziquantel.

In another embodiment of the invention, the novel crystalline form of 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline of formula II which is very stable. This novel crystalline 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline is represented by the X-ray diffractogram substantially as given in figure 1. The novel crystalline oxyclozanide is further characterised by its XRD 2θ values 11.3224, 11.6010, 12.3040, 13.9389, 15.6595, 17.6684, 18.2167, 20.5348, 21.2141, 21.7543, 22.5259,

23.2597, 24.5423, 24.7190, 25.1168, 25.9533, 27.0875, 27.9823, 28.4783, 30.2130, 31.9009, 33.1835, 33.9561, 34.9936, 35.8283, 36.6569, 38.3095, 39.9195, 41.3981, 43.4197, 44.7071, 15.8443, 46.4157, and 47.5018±0.2.

In yet another embodiment of the invention, praziquantel is crystalized preferably by acetone/water more preferably by methanol.

In yet another embodiment of the invention, the obtained praziquantel of formula I is crystalline in nature and is represented by the X-ray diffractogram substantially as given in figure 2. The crystalline praziquantel is further characterised by its XRD 2θ values 4.0347, 6.3125,6.6657, 7.9721, 8.2331, 9.0022, 10.1529, 10.7575, 12.2359, 12.7698, 13.3571, 14.5918, 14.7636, 15.3563, 16.4099, 17.0067, 17.6506, 17.9196, 18.4939, 18.9457, 19.3013, 20.0703, 20.6947, 21.1772, 21.9613, 22.2849, 22.5941, 23.0764, 23.8775, 24.3678, 34.7914, 25.5675, 26.5709, 26.8815, 27.2188, 27.6148, 28.3811, 29.1801, 30.3608, 30.9784, 31.5238, 31.9577, 33.0558, 34.0577, 35.2215, 36.3888, 37.7226, and 41.4325±0.2.

The present invention has advantage over prior art because it avoids the use of expensive raw material aminoacetaldehyde dimethylacetal which is used in prior art in two equivalents. Instead it makes a novel intermediate compound 2-[(2,2-dimethoxyethyl)benzylamino]-N-phenethylacetamide in water, which is very inexpensive. This reduces the overall cost of the praziquantel significantly. Apart from this the present process uses water as a solvent in most of the steps which makes the process green and environmentfriendly.

The present invention can be illustrated by the following examples, which are not to limit the scope of invention.

Example 1: Preparation of 2-cyclohexylcarbonyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline

(a) Preparation of 2-chloro-N-phenethylacetamide

β-phenylethylamine (0.68 kg) was taken in dry toluene(4.42L) and sodium bicarbonate (0.612 kg) was added at 30°C and cooled to 0-5°C. Chloroacetylchloride was

slowly added under nitrogen blanket at 0-10°C, stirred and maintained for 2 hr. After completion of the reaction, water was added slowly and reaction mass was allowed to attain 33±2°C and the layers were separated. To the aqueous layer toluene was added, stirred and two layers were separated. To the organic layer dil HCl solution (0.653L DM water + 0.272L con HCl) was added, stirred and two layers were separated. To the organic layer again sodium bicarbonate solution (0.653L DM water + 0.068kg sodium bicarbonate) was added, stirred and two layers were separated. Water was added to the organic layer, stirred and two layers were separated. From the organic layer toluene was distilled out, methanol was added, heated to 58°C,stirred.To the reaction mass water was added , temperature was maintained at 58°C,stirred for 1-1.5 hr, cool to 30±2°C for 3 hrs under stirring. Stirring was continued for 3 hrs at 0-5°C. The reaction mass was filtered, washed with water and dried.

Yield: 1kg.

(b) Preparation of N-benzyl-2,2-dimethoxyethanamine

Benzylamine (0.927kg), chloroacetaldehydedimethylacetal (0.909 kg) , sodium hydroxide solution (0.35 kg) in 2.72L of water were charged into the flask under stirring at 25-30°C for 10-15 min. Reaction mass was heated to 100-102°C under stirring for 30 hrs. After completion of reaction, reaction mass was allowed to settle for 30 min. Two layers are separated and upper product layer was collected, distilled under high vacuum.

Yield: 1.0 kg.

(c) Preparation of 2-[(2,2-dimethoxyethyl)benzylamino]-N-phenethylacetamide

Prazole-1 (0.589 kg), Prazole-2 (0.614 kg), potassium carbonate (0.522 kg) in 1.84L of water were charged into the flask under stirring at 25-30°C for 10-15 min. Reaction mass was heated to 75-80°C under stirring for 8 hrs. After completion of reaction, TLC was checked. The reaction mass was cooled, Toluene was added and reaction mass was allowed to attain 30±2°C for 15 min under stirring. Two layers were separated. To the toluene layer 10% acetic acid solution (0.55L DM water + 0.0614L acetic acid) was added, stirred and two layers were separated. To the organic layer again 10% acetic acid solution (0.55L DM water + 0.0614L acetic acid) was added, stirred and two layers were separated. To the organic layer 5% sodium bicarbonate solution (0.614L DM water + 0.0307 kg sodium bicarbonate) was added, stirred and two layers were separated. To the organic layer again 5% sodium bicarbonate solution (0.614L DM water + 0.0307 kg sodium bicarbonate) was added, stirred and two layers were separated. To the organic layer DM water was added,

stirred and two layers were separated. From the organic layer toluene was distilled out under vacuum below 60°C, material was collected.

Yield: 1.0kg.

(d) Preparation of 2-[(2,2-dimethoxyethyl) amino]-N-(2-phenylethyl)acetamide

Prazole-3 (1.47kg), methanol (4.41L) were treated with Raney nickel (0.147kg) at 25-30°C.Flush nitrogen and hydrogen. 10kg/cm^2 Hydrogen pressure was applied at 25-30°C. Reaction mass was heated to 65-67°C for 20 hrs at 10 kg hydrogen pressure. After completion of reaction, reaction mass was cooled to room temperature, filtered and washed with methanol. Methanol and toluene were distilled out under vacuum below 55°C, thick oil was collected.

Yield: 1.0kg.

(e) Preparation of 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline

Prazole-4 (2.0Kg), dichloromethane (4.0L) and sulphuric acid (2.33L) were stirred at 10-15°C for 30min, slowly allowed to attain 25-30°C and stirred for 2 hrs. After completion of reaction, reaction mass was quenched to pre-cooled DM water at 0-10°C.Two layers were separated. Aqueous layer was washed with dichloromethane, pH was adjusted to 6.5-7 using 20% sodium hydroxide solution (2.6kg sodium hydroxide + 13.0 L DM water), stirred for 10 min. Allowed the reaction mass to attain 25-30°C. Dichloromethane was added to the above solution, stirred and two layers were separated. Aqueous layers were twice extracted with Dichloromethane. Combined organic layers were washed with DM water, brine solution, dried. Carbon treatment was given to organic layer, stirred and Dichloromethane was distilled. Crude material was crystallized by ethyl acetate.

Yield: 1.0 kg.

(f) Preparation of Praziguantel

Prazole-5 (0.72kg), dichloromethane (4.32L) and sodium carbonate (0.4 kg) were stirred at 25-30°C for 15min, cooled to 0-5°C. Cyclohexanoyl chloride (0.54kg) was added dropwise, allow the reaction mass to attain 25-30°C under stirring for 2 hrs. After completion of reaction, reaction mass was quenched to DM water below 30°C, maintain the

pH in the range 8-8.5, stirred. Two layers were separated. Aqueous layer was extracted with dichloromethane. Combined organic layers were washed with 1% lye, DM water, dried. Acetone was added, carbon treatment was given to organic layer, stirred for 1hr at 40-45°C, filtered. Acetone was distilled. Crude material was crystallized by acetone and water, and wash with chilled acetone.

We claim:

1. A process for the preparation of 2-[(2,2-dimethoxyethyl)amino]-N-(2-phenylethyl)acetamide, which comprises:
   a) condensation of β-phenylethylamine with chloroacetylchloride in presence of a solvent and a base to obtain 2-chloro-N-phenethylacetamide;

   b) condensation of benzylamine with chloroacetaldehydedimethylacetal in presence of water and a base to obtain N-benzyl-2,2-dimethoxyethanamine;

   c) condensation of 2-chloro-N-phenethylacetamide prepared in step a) with N-benzyl-2,2-dimethoxyethanamine of formula VI prepared in step b) in presence of water and a base to obtain 2-[(2,2-dimethoxyethyl)benzylamino]-N-phenethylacetamide; and

   d) reduction of 2-[(2,2-dimethoxyethyl)benzylamino]-N-phenethylacetamide using a reducing agent and a solvent in presence of hydrogen to obtain 2-[(2,2-dimethoxyethyl)amino]-N-(2-phenylethyl)acetamide.

2. A process according to claim 1 wherein, the solvent in step a) is toluene and the base is sodium bicarbonate.

3. A process according to claim 1 wherein, the solvent in step b) and step c) is water and base is sodium hydroxide.

4. A process according to claim 1 wherein, the solvent in step d) is selected from methanol, ethanol, or isopropanol and the reducing agent is selected from Raney nickel or palladium on carbon.

5. A process for preparation of praziquental which comprises:

   a) cyclisation of 2-[(2,2-dimethoxyethyl)amino]-N-(2-phenylethyl)acetamide prepared according to claim 1, using an acid in presence of solvent to obtain 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline; and

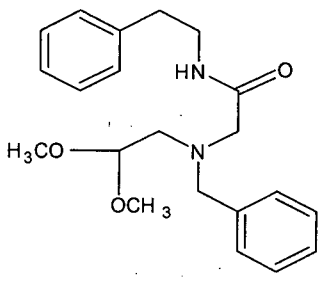
b) acylation of 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline of with cyclohexanoylchloride in presence of a base and solvent to obtain Praziquantel.

6. A process according to claim 5 wherein, cyclisation in step a) is carried out in presence of sulphuric acid and a chlorinated solvent like dichloromethane.

7. A process according to claim 5 wherein, acylation in step b) is carried out in presence of base sodium carbonate and solvent dichloromethane.

8. A process according to claim 5 wherein, the praziquantel obtained in step b) is purified by acetone and water.

9. A compound of formula IV



IV

10. Crystalline 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline represented by the powdered X-Ray diffractogram substantially as given in figure 1.

11. Crystalline 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline characterised by XRD 2θ values at 11.3224, 11.6010, 12.3040, 13.9389, 15.6595, 17.6684, 18.2167, 20.5348, 21.2141, 21.7543, 22.5259, 23.2597, 24.5423, 24.7190, 25.1168, 25.9533, 27.0875, 27.9823, 28.4783, 30.2130, 31.9009, 33.1835, 33.9561, 34.9936, 35.8283, 36.6569, 38.3095, 39.9195, 41.3981, 43.4197, 44.7071, 15.8443, 46.4157, and 47.5018±0.2.

Figure1: X-Ray diffractogram of 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a] isoquinoline of formula II

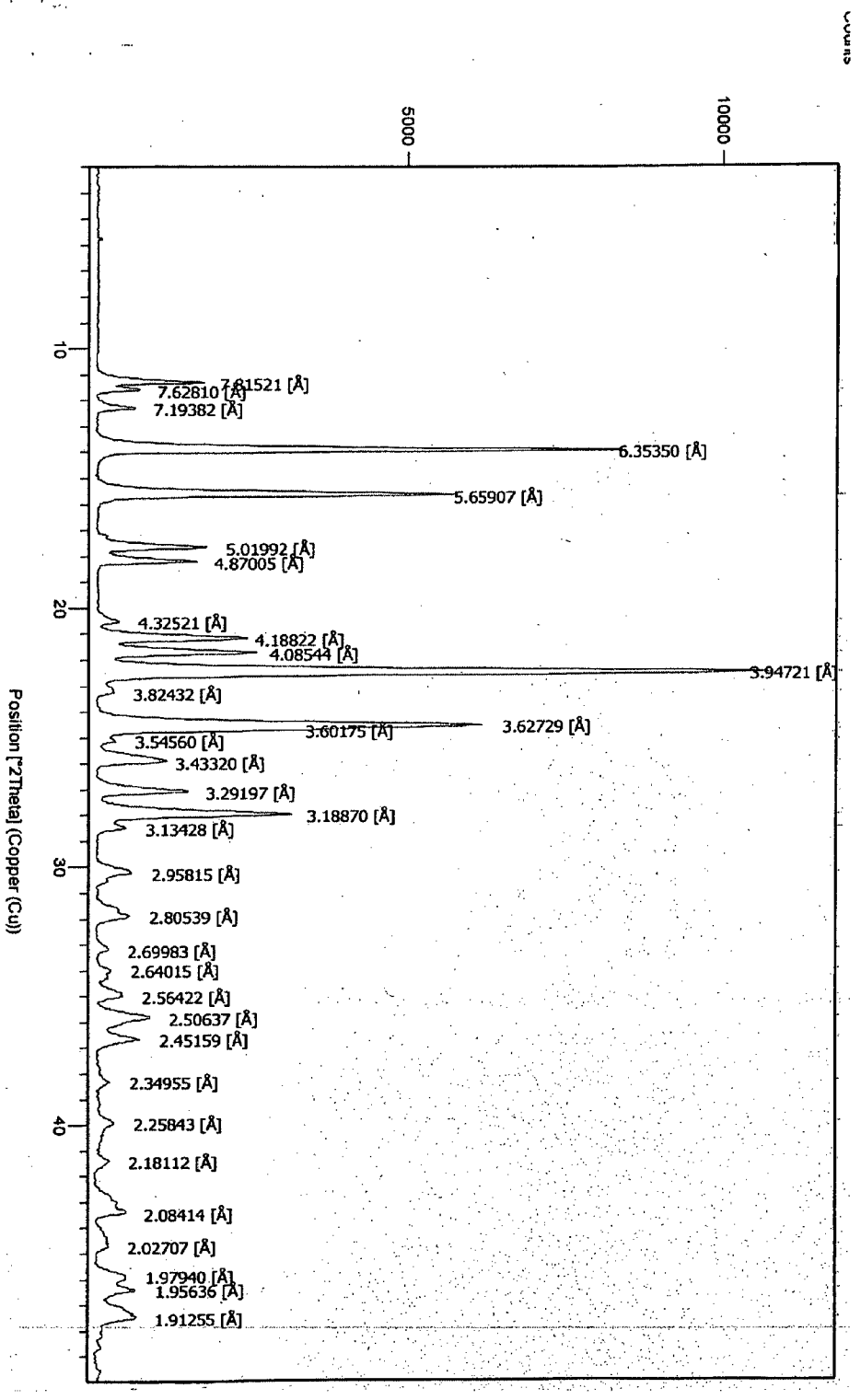


Figure 2: X-Ray diffractogram of Praziquantel of formula I