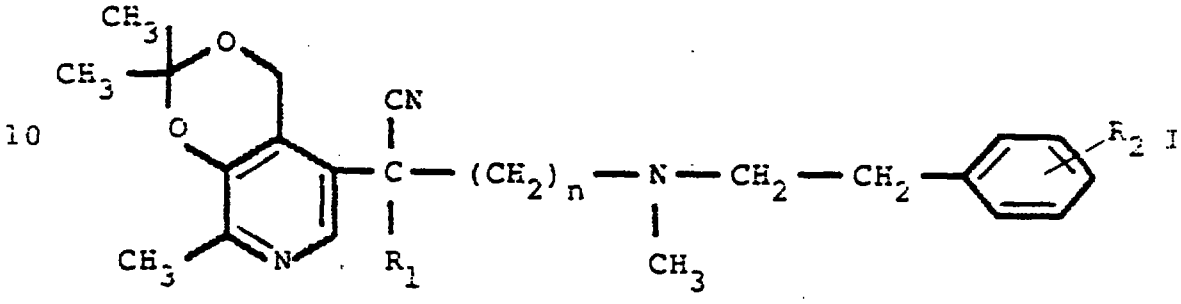
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DIOXINOPYRIDINE DERIVATIVES

The invention relates to 4H-dioxino[4,5-c]pyridine derivatives, to a process for their preparation and to therapeutic compositions in which they are used as active ingredients.

The invention provides 5-(1-cyano-1-alkyl-N--methyl-N-methoxyphenethyl- ω-aminoalkyl)-2,2,8--trimethyl-4H-dioxino[4,5-c]pyridine derivatives having the general formula I

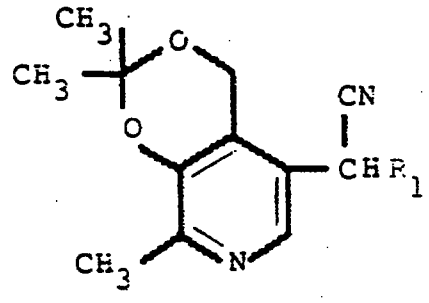


I

wherein n is an integer of from 2 to 5, R_1 represents a straight or branched chain alkyl group having from 1 to 5 carbon atoms and R_2 represents two or three methoxy groups, and further provides therapeutically acceptable salts of these compounds.

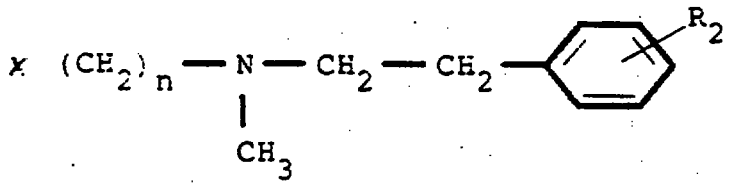
These compounds and their therapeutically acceptable salts are interesting as active ingredients for use in therapeutic compositions active as calcium antagonists. A toxicologic investigation has shown favourable LD_{50} values on rats and mice per os and ip. Accordingly the invention further provides a therapeutic composition comprising a dioxinopyridine derivative I as herein defined or a therapeutically acceptable salt of such a compound in admixture with a therapeutically acceptable diluent or carrier.

The derivatives according to the invention may be readily prepared by reacting a 5-(1-cyano-alkyl)-2,2,8--trimethyl-4H-dioxino[4,5-c]pyridine derivative having the general formula II



II

wherein R_1 is as above defined with an N-methyl-N--methoxyphenethyl-ω aminoalkyl chloride having the general formula III



III

wherein n and R_2 are as above defined and X represents a halogen atom in the presence of sodium hydride in an organic solvent. This process is within the scope of the invention.

The dioxinopyridine derivative II, the ω-aminoalkyl halide III and the sodium hydride are preferably reacted in stoichiometric proportions. The ω-aminoalkyl halide is preferably an ω -aminoalkyl chloride. The organic solvent is suitably dimethylsulphoxide, and the reaction temperature may be from 15°C to 65°C.

The dioxinopyridine derivatives II may be obtained from 5-hydroxymethyl-2,2,8-trimethyl-4H-dioxino[4,5-c]-pyridine described in British Patent Specification No. 1286161. This is treated with thionyl chloride to give the 5-chloromethyl derivative, which is condensed with potassium cyanide to give the 5-cyanomethyl derivative. This is then alkylated with R_1Br or R_1Cl by a process analagous to that of the invention for obtaining I from II and III.

The following Examples illustrate the invention.

Example 1

5-[1-cyano-1,N-dimethyl-N-(3,4-dimethoxyphenethyl)-3--aminopropyl]-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

n = 2 R_1 = methyl $R_2 = (OCH_3)_2$

In a one litre reactor fitted with cooling, warming and stirring means, were placed (after nitrogen cleaning of the apparatus) 4.9 g (0.1 mol) of 50% sodium hydride in oil and 100 ml of dimethylsulphoxide. The mixture was stirred and there was slowly added, dropwise, a solution of 23.2 g (0.1 mol) of 5-(1-cyano-ethyl)-2,2,8-trimethyl-4H-dioxino[4,5-c]-

pyridine dissolved in 150 ml of dimethylsulphoxide.

The reaction mixture darkened and the temperature increased to 30°C. Stirring was maintained for 30 minutes and there was slowly added 25.8 g (0.1 mol) of N-methyl-N-(3,4-dimethoxyphenethyl)-2--aminoethyl chloride dissolved in 100 ml of dimethylsulphoxide.

The reaction mixture was warmed to 50°C, stirred for 4 hours, poured onto icy water and extracted with dichloromethane. The organic phase was then washed with water, separated, dried, treated with carbon black, filtered and concentrated to dryness. The residue was treated with oxalic acid in 100 ml of acetone, giving a yellow precipitate which was separated, washed and recrystallized from methyl ethyl ketone. Yield 38.6 g (71 %) of a yellow crystalline product melting at 164°C (Tottoli), elemental analysis of which showed an excellent correspondence with the formula $C_{26}H_{35}N_3O_4 \cdot C_2H_2O_4$.

Example 2

5-{1-cyano-1-[N-methyl-N-(3,4,5-trimethoxyphenethyl)--3-aminoethyl]-butyl}-2,2,8-trimethyl-4H-dioxino[4,5--c]pyridine.

n = 2 R_1 = n-propyl R_2 = $(OCH_3)_3$

The method of Example 1 was repeated but starting with 5-(1-cyano-butyl)-2,2,8-trimethyl-4H-dioxino[4,5-c]-pyridine and N-methyl-N-(3,4,5-trimethoxyphenethyl)-2--aminoethyl chloride. The reaction temperature was 40 °C and treatment was with hydrochloric acid. There was thus obtained 32.5 g (59 %) of a pale yellow powder melting at 204°C (Tottoli), elemental analysis of which

showed a good correspondence with the formula $C_{29}H_{41}N_3O_5 \cdot HCl$.

Example 3

5-[1-cyano-1,N-dimethyl-N-(3,4-dimethoxyphenethyl)-4-aminobutyl]-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

n = 3 R_1 = methyl R_2 = $(OCH_3)_2$

The method of Example 1 was repeated with the same dioxinopyridine derivative but with N-methyl-N-(3,4-dimethoxyphenethyl)-3-aminopropyl chloride. The reaction temperature was 55°C and the acidic treatment was omitted. There was thus obtained 29.5 g (63 %) of a white product melting at 176-178°C (Tottoli), elemental analysis of which showed an excellent correspondence with the formula $C_{27}H_{37}N_3O_4$.

Example 4

5-[1-cyano-1-ethyl-N-methyl-N-(3,4-dimethoxyphenethyl)-4-aminobutyl]-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

n = 3 R_1 = ethyl R_2 = $(OCH_3)_2$

The method of Example 3 was repeated with the same ω-aminoalkyl chloride but with 5-(1-cyano-propyl)-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine. The reaction temperature was 50°C. There was thus obtained 25.2 g (52 %) of a white powder melting at 197-200°C (Tottoli), elemental analysis of which showed a good correspondence with the formula $C_{28}H_{39}N_3O_4$.

Example 5

5-[1-cyano-1-isopropyl-N-methyl-N-(3,4-dimethoxyphenethyl)--4-aminobutyl]-2,2, 8-trimethyl-4H-dioxino[4,5-c]pyridine.

n = 3 R_1 = isopropyl R_2 = $(OCH_3)_2$

The method of Example 3 was repeated but with 5-(1-cyano-2-methyl-propyl)-2,2,8-trimethyl-4H-dioxino-[4,5-c] pyridine and the same ω-aminoalkyl chloride. The reaction temperature was 40°C and acidic treatment with oxalic acid was included. There was thus obtained 405 g (69%) of a white crystalline powder melting at 185-186°C (Tottoli), elemental analysis of which showed an excellent correspondence with the formula $C_{29}H_{41}N_3O_4 \cdot C_2H_2O_4$.

Example 6

5-[1-cyano-1-isopropyl-N-methyl-N-(3,4,5-trimethoxyphenethyl)--4-aminobutyl]-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

n = 3 R_1 = isopropyl R_2 = $(OCH_3)_3$

The method of Example 5 was repeated with the same pyridine derivative but with N-methyl-N-(3,4,5--trimethoxyphenethyl)-3-aminopropyl chloride. The reaction temperature was 45°C. There was thus obtained 45 g (73 %) of a white crystalline powder melting at 170-173°C (Tottoli), elemental analysis of which showed an excellent correspondence with the formula $C_{30}H_{43}N_3O_5 \cdot C_2H_2O_4$.

Example 7

5-{ 1-cyano-1-[N-methyl-N-(3,4,5-trimethoxyphenethyl)-3--aminopropyl]-pentyl } -2,2,8-trimethyl-4H-dioxino[4,5-c]-pyridine.

n = 3 R_1 = n-butyl R_2 = $(OCH_3)_3$

The method of Example 6 was repeated but with

5-(1-cyano-pentyl)-2,2,8-trimethyl-4H-dioxino[4,5-c]-pyridine, and the same ω-aminoalkyl chloride. The reaction temperature was 60°C. There was thus obtained 35.7 g (57 %) of a white crystalline product melting at 144÷146°C (Tottoli), elemental analysis of which showed a good correspondence with the formula $C_{31}H_{45}N_3O_5 \cdot C_2H_2O_4$.

Example 8

5-[1-cyano-1,N-dimethyl-N-(3,4-dimethoxyphenethyl)-5--aminopentyl]-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

n = 4 R_1 = methyl R_2 = $(OCH_3)_2$

The method of Example 3 was repeated with the same dioxinopyridine derivative but with N-methyl-N-(3,4--dimethoxyphenethyl)-4-aminobutyl chloride. The reaction temperature was 65°C. Yield was 30.8 g (64 %) of a white product melting at 154-155°C (Tottoli), elemental analysis of which showed a good correspondence with the formula $C_{28}H_{39}N_3O_4$.

Example 9

5-{ 1-cyano-1-[N-methyl-N-(3,4-dimethoxyphenethyl)-4--aminobutyl]-hexyl } -2,2,8-trimethyl-4H-dioxino[4,5-c]-pyridine.

n = 4 R_1 = n-pentyl R_2 = $(OCH_3)_2$

The method of Example 8 was repeated but with 5-(1-cyano-hexyl)-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine and the same ω-aminoalkyl chloride. The reaction temperature was 45°C and acidic treatment with hydrochloric acid was included. There was thus obtained 29.7 g (52 %) of a white powder melting at 167-169°C (Tottoli), elemental analysis of which showed a good

correspondence with the formula $C_{32}H_{47}N_3O_4 \cdot HCl$.

Example 10

5-[1-cyano-1-ethyl-N-methyl-N-(3,4-dimethoxyphenethyl)--6-aminohexyl]-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

n = 5 R_1 = ethyl R_2 = $(OCH_3)_2$

The method of Example 4 was repeated with the same dioxinopyridine derivative but with N-methyl-N-(3,4--dimethoxyphenethyl)-5-aminopentyl chloride. The reaction temperature was 35°C. Yield was 23.2 g (46%) of a pale yellow product melting at 193-197°C (Tottoli), elemental analysis of which showed a good correspondence with the formula $C_{30}H_{43}N_3O_4$.

Example 11

5-[1-cyano-1-isopropyl-N-methyl-N-(3,4-dimethoxyphenethyl)--6-aminohexyl]-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

n = 5 R_1 = isopropyl R_2 = $(OCH_3)_2$

The method of Example 10 was repeated but with 5-(1-cyano-2-methyl-propyl)-2,2,8-trimethyl-4H--dioxino [4,5-c]pyridine and the same ω -aminoalkyl chloride. The reaction temperature was 30°C and acidic treatment with oxalic acid was included. There was thus obtained 39.6 g (65 %) of a white crystalline product melting at 144°C (Tottoli), elemental analysis of which showed a very good correspondence with the formula $C_{31}H_{45}N_3O_4 \cdot C_2H_2O_4$.

Example 12

5-[1-cyano-1-butyl-N-methyl-N-(3,4,5-trimethoxyphenethyl)--6-aminohexyl]-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

n = 5 R_1 = n-butyl R_2 = $(OCH_3)_3$

The method of Example 7 was repeated with the same

dioxinopyridine derivative but with N-methyl-N-(3,4,5--trimethoxyphenethyl)-5-aminopentyl chloride. The reaction temperature was 40°C. There was thus obtained 38.1 g (58 %) of a white crystalline product melting at 131°C (Tottoli), elemental analysis of which showed a very good correspondence with the formula $C_{33}H_{49}N_3O_5 \cdot C_2H_2O_4$.

TOXICITY

The LD_{50} of the compounds of the invention, determined on mice per os, is at least 450 mg/kg. For purposes of comparison, the reference compound Verapamil (DCI) has an LD_{50} of 150 mg/kg. Cardiotoxicity on anaesthetized dogs starts at 3 mg/kg iv whereas Verapamil is cardiotoxic at 1 mg/kg.

PHARMACOLOGY

The interest of the compounds of the invention has been evidenced by various tests.

A) Isolated rabbit aorta strips treated by various contracturing agents.

This experiment was conducted along the lines of the methods described by FURCHGOTT R.F. and BHADRAKOM S., J. Pharmac. Exp. Therapeut., 1953, 108, 129-143; VAN ROSSUM J. M., Arch Int. Pharmacodyn. Ther., 1963, 143, 299-330; and ARUNLAKSHANA, O. and SCHILD, H.O., 1959, Brit. J. Pharmac. 14, 48-58, using noradrenaline (NE), serotonine (5-HT), histamine (HIST), KCl and angiotensine II as agonists.

The compounds of the invention were compared to Verapamil on these agonists and showed a similar range of action, with significant and generally comparable values of PA_2 (for NE, 5-HT and HIST) or of IC_{50}

(for KCl or angiotensine); however, they appear 5 to 10 times more active on 5-HT (average value for the compounds of the invention 1.1×10^{-8} compared with 7×10^{-8} for Verapamil). These compounds are competitive antagonists of the 5-HT receptor.

B) Experimental ulcer induced by dimaprit.

15 batches each of 5 male Sprague Dawley rats (150-200 g) were treated as follows:

Batches 1 - 12: The rats of each of these batches received 25 mg/kg per os of one of the compounds of the invention, suspended in 1 ml of physiologic serum.

Batches 13 and 14: The rats of these batches received 1 ml of physiologic serum.

Batch 15: The rats of this batch received 25 mg/kg of ramitidine, as reference compound, suspended in 1 ml of physiologic serum.

30 minutes after this administration, all batches, except batch 13, received, ip, 175 mg/kg of dimaprit (1-dimethylamino-3-amidino-propane).

Four hours after this treatment, the animals were killed and the ulcers counted. Batch 13 was a blank control and batch 14 the ulceration control. Results were given in percentage of protection compared with ulceration control. Protection by ramitidine was 39%, whereas protection for the compounds of the invention was from 39 to 46.5%.

PRESENTATION-POSOLOGY

For oral use, the compounds of the invention may be presented in 50 mg dosage units associated with an

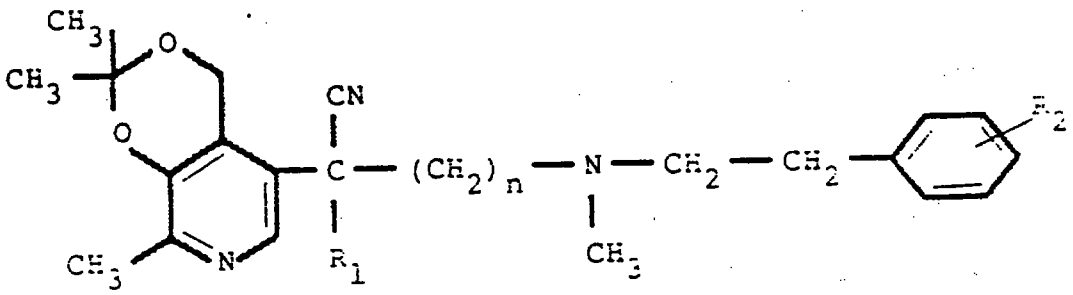
appropriate diluent or carrier, in tablet, gelatine capsules or in suspension - Posology is of 1 or 2 units per diem.

For iv route, phials contain 10 mg of active compound and posology is 1 or 2 phials per diem.

Indications are angor, vasospasms and headaches.

CLAIMS

1. A dioxinopyridine derivative having the general formula I



I

wherein n is an integer of from 2 to 5, R_1 represents a straight or branched chain alkyl group having from 1 to 5 carbon atoms and R_2 represents two or three methoxy groups; or a therapeutically acceptable salt of such a compound.

2. 5-[1-cyano-1,N-dimethyl-N-(3,4-dimethoxyphenethyl)-3-aminopropyl]-
-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

3. 5-{1-cyano-1-[N-methyl-N-(3,4,5-trimethoxyphenethyl)-3-aminoethyl]-butyl}-
-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

4. 5-[1-cyano-1,N-dimethyl-N-(3,4-dimethoxyphenethyl)-4-aminobutyl]-
-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

5. 5-[1-cyano-1-ethyl-N-methyl-N-(3,4-dimethoxyphenethyl)-4-aminobutyl]-
-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

6. 5-[1-cyano-1-isopropyl-N-methyl-N-(3,4-dimethoxyphenethyl)-4-aminobutyl]-
-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

7. 5-[1-cyano-1-isopropyl-N-methyl-N-(3,4,5-trimethoxyphenethyl)-4-aminobutyl]-
-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

8. 5-{1-cyano-1-[N-methyl-N-(3,4,5-trimethoxyphenethyl)-3-aminopropyl]-pentyl}-
-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

9. 5-[1-cyano-1,N-dimethyl-N-(3,4-dimethoxyphenethyl)-5-aminopentyl]-
-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

10. 5-{1-cyano-1-[N-methyl-N-(3,4-dimethoxyphenethyl)-4-aminobutyl]-hexyl}-
-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

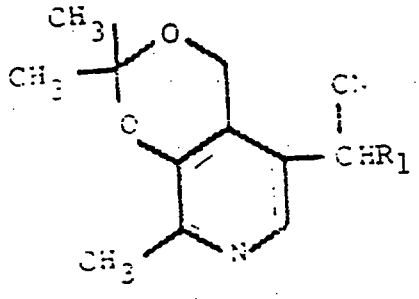
11. 5-[1-cyano-1-ethyl-N-methyl-N-(3,4-dimethoxyphenethyl)-6-aminohexyl]-
-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

12. 5-[1-cyano-1-isopropyl-N-methyl-N-(3,4-dimethoxyphenethyl)-6-aminohexyl]-
-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

13. 5-[1-cyano-1-butyl-N-methyl-N-(3,4,5-trimethoxyphenethyl)-6-aminohexyl]-
-2,2,8-trimethyl-4H-dioxino[4,5-c]pyridine.

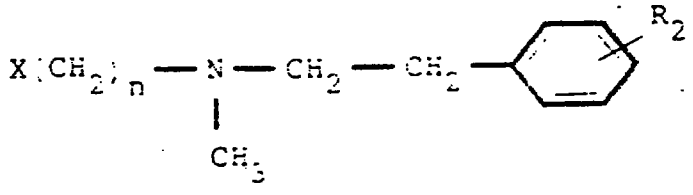
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14. A process for the preparation of a dioxino pyridine derivative according to claim 1, the process comprising reacting a dioxinopyridine derivative having the general formula II



II

wherein R_1 is as defined in claim I with an ω-aminoalkyl halide having the general formula III



wherein n and R_2 are as defined in claim 1 and X represents a halogen atom in the presence of sodium hydride in an organic solvent.

15. A process according to claim 14 in which the dioxinopyridine derivative II, the ω-aminoalkyl halide III and the sodium hydride are reacted in stoichiometric proportions.

16. A process according to claim 14 or claim 15 in which the ω-aminoalkyl halide III is an ω-aminoalkyl chloride.

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17. A process according to any of claims 14 to 16 in which the organic solvent is dimethylsulphoxide.

18. A process according to any of claims 14 to 17 in which the reaction is conducted at from 15° to 65°C.

19. A process for the preparation of a dioxinopyridine derivative according to claim 1, the process being substantially as described herein with reference to any of the Examples.

20. A therapeutic composition comprising a dioxinopyridine derivative according to claim 1 or a therapeutically acceptable salt of such a compound in admixture with a therapeutically acceptable diluent or carrier.