PATENT OFFICE

PATENT SPECIFICATION

NO DRAWINGS

1,114,660

1,114,660

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Int. Cl.:—C 07 d 35/10

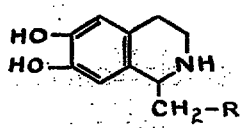
COMPLETE SPECIFICATION

Tetrahydro-Isoquinolines

We, TANABE SEIYAKU CO., LTD., a corporation of Japan, of No. 21, 3-chome, Doshomachi, Higashi-ku, Osaka, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is performed, to be particularly described in and by the following statement:—

This invention relates to derivatives of 1 - benzyl - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline and acid addition salts thereof and also to a process for preparing these derivatives.

In accordance with the present invention there is provided a tetrahydro-isoquinoline having the general formula:



in which R is a dimethoxyphenyl, trimethoxyphenyl or dimethoxy - monohydroxy - phenyl group and acid addition salts thereof.

We have found that the said compounds are useful as bronchodilator or cardiotonic agents. Thus, 1 - (3, 4, 5 - trimethoxy - benzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrochloride shows excellent preventitive and depressive effects for the paroxysms of asthma when compared with: 1 - (3, 4 - dihydroxyphenyl) - 2 - isopropylamino - ethanol sulphate, commonly known as isoproterenol sulphate, which has been considered to be the most effective bronchodilator. The same tetrahydro-isoquinoline is respectively about 4, 5 and 10 times more effective as a bronchodilator than isoproterenol sulphate when guinea pigs were caused to inhale a 5% histamine spray or a 5% acetylcholine spray after they had had the compounds administered to them by subcutaneous injection, oral administration or inhalation. The paroxysms of adult man suffering from asthma were arrested within one minute after inhalation of an aerosol solution containing 0.6% of the same compound and the effect lasted for 3 hours.

The duration of the arresting effect of the compound was more than twice that obtained with isoproterenol sulphate.

1 - (3, 4 - dimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydroisoquinoline hydrochloride and 1 - (3, 5 - dimethoxy - benzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrochloride have a similar duration of bronchodilator action, although their effectiveness is a little less than that of isoproterenol sulphate.

The cardiotonic action of the compounds of this invention is also of long duration. Thus, 1 - (3, 4, 5 - trimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrochloride and 1 - (3, 5 - dimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrochloride showed cardiotonic activity of more than five times the duration of that encountered with isoproterenol sulphate in pharmacological tests using dogs, although their effectiveness is less than that of isoproterenol sulphate.

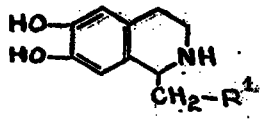
Auriculoventricular block and cardiac arrest in adult man encountered in cardiosurgery were overcome within several seconds by intravenously injecting 0.2—0.5 ml. of a solution containing 1 mg./ml. of 1 - (3, 4, 5 - trimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydroisoquinoline hydrochloride accompanied by subsequent cardiac massage. 1 - (2, 3, 4 - trimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrochloride also has a good car-

[*Price 4s. 6d.*]

diotonic action, although its bronchodilator action is exceptionally weak when compared with the 3, 4, 5 - trimethoxy derivative.

Moreover, the compounds of this invention have a remarkably low toxicity. The LD_{50} value of the compounds when injected subcutaneously into mice were calculated to be more than 1,600 mg./kg., while the LD_{50} of isoproterenol sulphate was calculated to be about 500 mg./kg. in the same test.

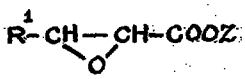
According to a feature of the invention a process for preparing an acid addition salt of a tetrahydro-isoquinoline having the general formula:



in which R^1 is a dimethoxyphenyl or trimethoxyphenyl group, comprises reacting 3, 4 - dihydroxyphenethylamine with an aldehyde having the general formula:

$$R^1—CH_2—CHO$$

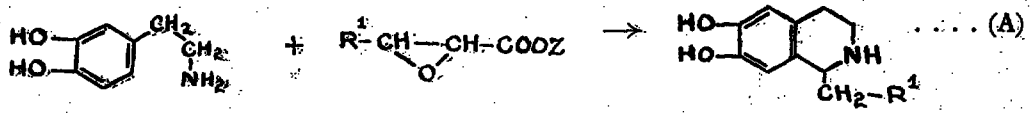
or with the corresponding glycidic acid derivative having the general formula:



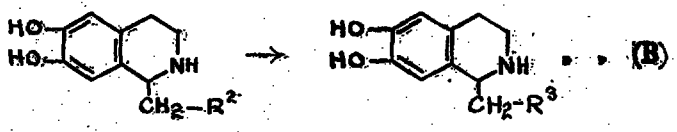
in which R^1 is as above defined and Z is an alkyl group or an alkali metal under acid condition.

According to a further feature of the invention a 1 - (trimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline prepared by such process may undergo partial hydrolysis of the methoxy groups to produce the corresponding di - methoxy - monohydroxy benzyl derivative.

These reactions may be represented as follows:



. . . . (A)



. . (B)

in which R^1 is a dimethoxyphenyl or trimethoxyphenyl group, R^2 is a trimethoxyphenyl group, R^3 is a dimethoxy - mono - hydroxyphenyl group and Z is an alkyl group or an alkali metal.

The condensation reaction (A) may be carried out by admixing 3, 4 - dihydroxy - phenethylamine, preferably in the form of an acid addition salt thereof with an alkyl ester or an alkali metal salt of appropriately substituted phenyl-glycidic acid under acid conditions, preferably at a temperature from 20° to 28° C. The pH of the reaction mixture may be adjusted with a conventional acid, for example, hydrochloric acid or acetic acid. It is preferable to react both reactants in equimolar ratios and to employ water, water miscible organic solvent, for example methanol, ethanol, propanol or the mixtures thereof as the reaction solvent.

Under these acidic reaction conditions, the glycidic acid compound is converted into the corresponding aldehyde having the general formula:

$$R^1—CH_2—CHO$$

in which R^1 is as hereinbefore defined and it is the aldehyde which reacts with the 3, 4 - dihydroxy - phenethylamine. Therefore, the above condensation reaction can be also carried out by employing the aldehyde itself instead of the corresponding glycidic acid.

The tetrahydro - isoquinolines of the present invention which can be prepared by the above process include 1 - (3, 4 - dimethoxy - benzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline, 1 - (3, 5 - di - methoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline, 1 - (2, 3, 4 - trimethoxybenzyl) - 6, 7, - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline and 1 - (3, 4, 5 - trimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline.

A 1 - (dimethoxy - mono - hydroxy - benzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline can be prepared by partially hydrolysing a 1 - (trimethoxy - benzyl) - 6, 7, - dihydroxyl - 1, 2, 3, 4 -

tetrahydro - isoquinoline with a mineral acid under moderate conditions. When hydrochloric acid is used as the hydrolysing agent, the partial hydrolysis can be preferably carried out by heating at a temperature of from 90° to 120° C. for several hours at normal atmospheric pressure. If concentrated hydrobromic acid is chosen as the hydrolysing agent, the partial hydrolysis should be carried out at a temperature lower than 100° C. When sulphuric acid is used it is preferable to carry out the hydrolysis at 30°—40° C. More harsh conditions result in the hydrolysis of all methoxy groups.

The invention will now be more particularly described by reference to the following Examples.

EXAMPLE 1

4.7 g. of sodium 3 - (3, 4, 5 - trimethoxyphenyl) - glycidate and 2.8 g. of 3, 4 - ~~di—hydrophenethylamine~~ hydrochloride were dissolved in 250 ml. of water. 7 ml. of 10% hydrochloric acid and 7 ml. of acetic acid were added to the solution and the solution was allowed to stand for 120 hours at 37° C. After filtering off the resultant precipitate, the filtrate was decoloured with activated carbon and was evaporated to remove water. The resultant crystals were separated and recrystallized twice from ethanol, whereby 0.25 g. of 1 - (3, 4, 5 - trimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrochloride decomposing at 224.5—226° C. was obtained.

Analysis calculated for $C_{19}H_{24}O_5NCl$:
C, 59.76; H, 6.34; N, 3.67; Cl, 9.28.
Found:
C, 59.72; H, 6.33; N, 3.96; Cl, 9.20.

EXAMPLE 2

A solution of 5.7 g. of sodium 3 - (3, 5 - dimethoxyphenyl) - glycidate in 270 ml. of water was added to a solution of 4 g. of 3, 4 - dihydroxyphenethylamine hydrochloride in 60 ml. of water. The mixture was adjusted to pH 2.6—2.8 by adding 2.3 ml. of 10% hydrochloric acid and 2.3 ml. of acetic acid, stirred for 96 hours at room temperature and concentrated under reduced pressure. The resultant crystals were collected by filtration whereby 2.5 g. of 1 - (3, 5 - dimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrochloride were obtained. The crystals were recrystallized from a methanol-ether mixture to give colourless prisms decomposing at 247.5—249° C.

Analysis calculated for $C_{18}H_{22}NO_4Cl$:
C, 61.55; H, 6.31; N, 3.99; Cl, 10.09.
Found:
C, 61.34; H, 6.36; N, 3.89; Cl, 10.10.

EXAMPLE 3

4.3 g. of sodium 3 - (3, 4 - dimethoxyphenyl) - glycidate and 2.8 g. of 3, 4 - dihydroxy - phenethylamine hydrochloride were treated as described in Example 1, whereby 0.30 g. of 1 - (3, 4 - dimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrochloride was obtained. M.p.t. 275 °C. (decomp.)

Analysis calculated for $C_{18}H_{22}NO_4Cl$:
C, 61.55; H, 6.31; N, 3.99; Cl, 10.09.
Found:
C, 60.91; H, 6.15; N, 4.06; Cl, 10.22.

EXAMPLE 4

A solution of 10.6 g. of sodium 3 - (2, 3, 4 - trimethoxyphenyl) - glycidate in 90 ml. of water was added to a solution of 6.3 g. of 3, 4 - dihydroxyphenethylamine hydrochloride in 400 ml. of water. The mixture was stirred at 30°—32° C. for 46 hours after adjusting pH to 3.8—4.0 with hydrochloric acid and acetic acid and was stirred for additional 24 hours after adjusting pH to 3.0—3.4 with the same acids. The precipitated resinous substance was filtered off and the filtrate was evaporated under reduced pressure to remove water. The residue was extracted with ethanol and ether was added to the ethanol solution. The vessel containing the solution was scratched and 3.7 g of 1 - (2, 3, 4 - ~~tri—methoxy—benzyl~~) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydroisoquinoline hydrochloride was crystallized out. Colourless prisms of the compound decomposing at 199.5—201° C. were obtained after recrystallization from methanol-acetone-ether mixture.

Analysis calculated for $C_{19}H_{24}O_5NCl$:
C, 59.76; H, 6.34; N, 3.67; Cl, 9.28.
Found:
C, 59.76; H, 6.06; N, 3.73; Cl, 9.19.

EXAMPLE 5

2.25 g of 3, 4 - dihydroxyphenethylamine hydrochloride and 2.5 g. of 3, 4, 5 - trimethoxyphenyl - acetaldehyde were dissolved in a mixture of 15 ml. of methanol and 50 ml. of water. The solution was adjusted to pH 2.0—2.2 with hydrochloric acid and stirred at 25—30° C for 21 hours. Then the reaction mixture was evaporated to remove methanol, extracted with ether to remove the water-insoluble substances and evaporated to remove water. Thus, 2.7 g of 1 - (3, 4, 5 - trimethoxybenzyl)6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrochloride were obtained as crystals. M.p.t. 224.5—226° C. (decomp.) after recrystallization.

Analysis calculated for $C_{19}H_{24}O_5NCl$:
C, 59.76; H, 6.34; N, 3.67; Cl, 9.28.
Found:
C, 59.74; H, 6.11; N, 3.50; Cl, 9.09.

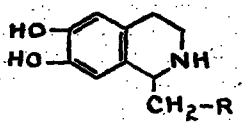
EXAMPLE 6

One gramme of 1 - (3, 4, 5 - trimethoxy - benzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrochloride was added to 35 ml. of concentrated hydrochloric acid and the mixture was refluxed for 4 hours. After cooling, the resultant crystals were collected by filtration, whereby 0.8 g. of 1 - (3, 5 - dimethoxy - 4 - hydroxy - benzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - iso - quinoline hydrochloride melting at 245—247° C. (decomp.) was obtained. After recrystallization of the crystals from diluted hydrochloric acid, a colourless powder melting at 248.5—249° C. (decomp.) was obtained.

Analysis calculated for $C_{18}H_{22}NO_5Cl$:
C, 58.77; H, 6.03; Cl, 9.64.
Found:
C, 58.97; H, 5.69; Cl, 9.61.

WHAT WE CLAIM IS:—

1. A tetrahydro - isoquinoline having the general formula:



in which R is a dimethoxyphenyl, trimethoxyphenyl or dimethoxy - monohydroxyphenyl group, and acid addition salts thereof.

2. 1 - (3, 4 - dimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - iso - quinoline hydrohalide.

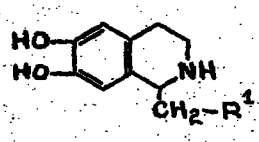
3. 1 - (3, 5 - dimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - iso - quinoline hydrohalide.

4. 1 - (3, 4, 5 - trimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - iso - quinoline hydrohalide.

5. 1 - (2, 3, 4 - trimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - iso - quinoline hydrohalide.

6. 1 - (3, 5 - dimethoxy - 4 - hydroxy - benzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrohalide.

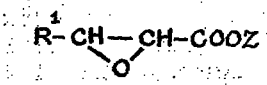
7. A process for preparing an acid addition salt of a tetrahydro - isoquinoline having the general formula:



in which R^1 is a dimethoxyphenyl or trimethoxyphenyl group, which comprises reacting 3, 4 - dihydroxyphenethylamine with an aldehyde having the general formula:

$$R^1—CH_2—CHO$$

or with the corresponding glycidic acid derivative having the general formula:



in which R^1 is as defined above and Z is an alkyl group or an alkali metal under acid condition.

8. A process as claimed in claim 7 in which the reactants are employed in equimolar proportions.

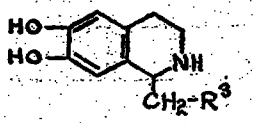
9. A process as claimed in either claim 7 or claim 8 in which the alkali metal is sodium.

10. A process as claimed in any of claims 7 to 9 in which 3, 4 - dihydroxyphenethyl - amine is employed as a hydrohalide addition salt thereof.

11. A process as claimed in any of claims 7 to 10 in which the reaction is carried out in the presence of water or of a water-miscible organic solvent.

12. A process as claimed in any of claims 7 to 11 in which the reaction is carried out at a temperature of from 20° to 80° C.

13. A process for preparing a tetrahydro-isoquinoline having the general formula:



in which R^3 is a dimethoxymonohydroxyphenyl group which comprises preparing a 1 - (trimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline by the process of any of claims 7 to 12 and thereafter effecting partial hydrolysis of the methoxy groups.

14. A process as claimed in claim 13 in which the partial hydrolysis is carried out at a temperature of from 90° to 120° C employing hydrochloric acid.

15. A process as claimed in claim 13 in which the partial hydrolysis is carried out at a temperature of below 100° C employing concentrated hydrobromic acid.

16. A process as claimed in claim 13 in which the partial hydrolysis is carried out at 30° to 40° C employing sulphuric acid.

17. A process for the preparation of a tetrahydro - isoquinoline substantially as hereinbefore described with reference to any of the Examples.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

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Alan Ironmonger

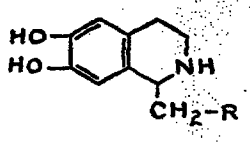
EXAMPLE 6

One gramme of 1 - (3, 4, 5 - trimethoxy - benzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrochloride was added to 35 ml. of concentrated hydrochloric acid and the mixture was refluxed for 4 hours. After cooling, the resultant crystals were collected by filtration, whereby 0.8 g. of 1 - (3, 5 - dimethoxy - 4 - hydroxy - benzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrochloride melting at 245—247° C. (decomp.) was obtained. After recrystallization of the crystals from diluted hydrochloric acid, a colourless powder melting at 248.5—249° C. (decomp.) was obtained.

Analysis calculated for $C_{18}H_{22}NO_5Cl$:
C, 58.77; H, 6.03; Cl, 9.64.
Found:
C, 58.97; H, 5.69; Cl, 9.61.

WHAT WE CLAIM IS:—

1. A tetrahydro - isoquinoline having the general formula:



in which R is a dimethoxyphenyl, trimethoxyphenyl or dimethoxy - monohydroxyphenyl group, and acid addition salts thereof.

2. 1 - (3, 4 - dimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrohalide.

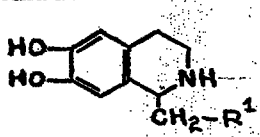
3. 1 - (3, 5 - dimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrohalide.

4. 1 - (3, 4, 5 - trimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrohalide.

5. 1 - (2, 3, 4 - trimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrohalide.

6. 1 - (3, 5 - dimethoxy - 4 - hydroxy - benzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline hydrohalide.

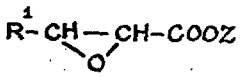
7. A process for preparing an acid addition salt of a tetrahydro - isoquinoline having the general formula:



in which R^1 is a dimethoxyphenyl or trimethoxyphenyl group, which comprises reacting 3, 4 - dihydroxyphenethylamine with an aldehyde having the general formula:

$R^1—CH_2—CHO$

or with the corresponding glycidic acid derivative having the general formula:



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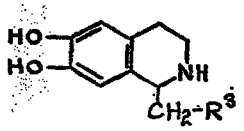

in which R^3 is a dimethoxymonohydroxyphenyl group which comprises preparing a 1 - (trimethoxybenzyl) - 6, 7 - dihydroxy - 1, 2, 3, 4 - tetrahydro - isoquinoline by the process of any of claims 7 to 12 and thereafter effecting partial hydrolysis of the methoxy groups.

14. A process as claimed in claim 13 in which the partial hydrolysis is carried out at a temperature of from 90° to 120° C employing hydrochloric acid.

15. A process as claimed in claim 13 in which the partial hydrolysis is carried out at a temperature of below 100° C employing concentrated hydrobromic acid.

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