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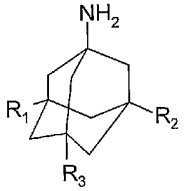
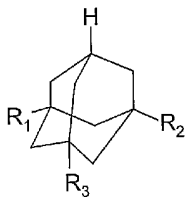
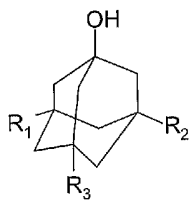
(54) Title: NOVEL PROCESS FOR THE PREPARATION OF AMINOADAMANTANE DERIVATIVES



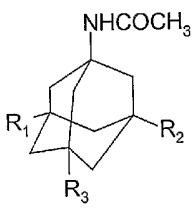
(I)



(IIa)



(IId)



(IIc)

(57) Abstract: A novel process for the preparation of aminoadamantane derivatives, compound of formula (I) (wherein R_1, R_2 are selected from C_{1-4}linear and branched alkyl & R_3 is selected from hydrogen, C_{1-4} linear and branched alkyl) said process comprising a)brominating compound of formula (IIa), hydrolysing and isolating compound of formula (II d). b) converting compound of formula (II d) to compound of formula (II c), and c) deacetylating compound of formula (II c) to yield compound of formula (I).

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

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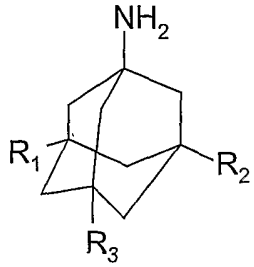
NOVEL PROCESS FOR THE PREPARATION OF AMINOADAMANTANE DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to a novel process for the preparation of aminoadamantane derivatives, compound of formula I, and their pharmaceutically acceptable salts.



Formula I

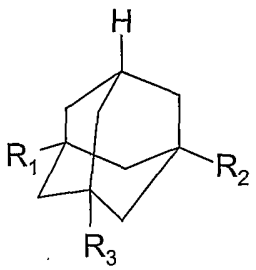
(wherein R_1, R_2 are selected from C_{1-4} linear and branched alkyl & R_3 is selected from hydrogen, C_{1-4} linear and branched alkyl)

Particularly, the present invention relates to a process for the preparation of 1-amino-3,5-dimethyladamantane, compound of formula I, wherein R_1, R_2 are methyl & R_3 is hydrogen, commonly known as memantine (INN Name) used in the treatment of Alzheimer's & Parkinson's disease.

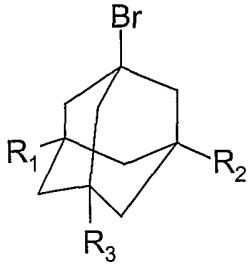
BACKGROUND OF THE INVENTION

United States Patent No 3,391,142 (Assigned to: Eli Lilly and Company, referred to herein as '142) discloses a 4 step process for the preparation of memantine hydrochloride:

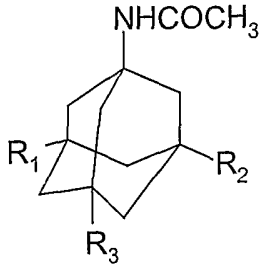
(a) 1,3-dimethyladamantane, compound of formula IIa, wherein R_1, R_2 are methyl & R_3 is hydrogen; is brominated with bromine at reflux to give 1-bromo-3,5-dimethyladamantane, compound of formula IIb, as a liquid;



Formula II a



Formula II b



Formula II c

(wherein R_1, R_2 are selected from C_{1-4} linear and branched alkyl & R_3 is selected from hydrogen, C_{1-4} linear and branched alkyl)

(b)1-bromo-3,5-dimethyladamantane is treated with acetonitrile in concentrated sulphuric acid at ambient temperature overnight to furnish 1-acetamido-3,5-dimethyladamantane, compound of formula IIc; (c) 1-acetamido-3,5-dimethyladamantane is deacetylated in diethyleneglycol with sodium hydroxide at reflux to form compound of formula I, wherein R_1, R_2 are methyl & R_3 is hydrogen, as an oil; and (d) compound of formula I , wherein R_1, R_2 are methyl & R_3 is hydrogen, is converted to the hydrochloride which is precipitated from ether and purified by crystallization from alcohol: ether mixture.

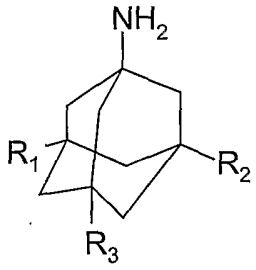
There are several disadvantages of this process. The bromination is carried out at reflux conditions which leads to generation of toxic bromine vapours. Being a tertiary bromide, one would be cautious to store the intermediate, compound of formula IIb, for a longer duration. Diethylene glycol, used as a solvent is toxic and poisonous. When heated to 230^0C with sodium hydroxide it decomposes exothermically to release explosive hydrogen gas and also emits acrid smoke and irritating fumes. Also use of ether in step

(d) constitutes a hazard because of it's highly inflammable nature and tendency to form peroxides. Thus this process is unsafe and environmentally hazardous.

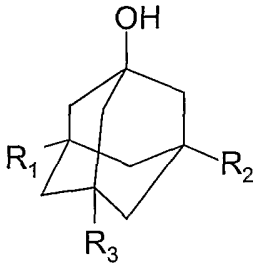
To overcome the disadvantages of prior art process we have developed a safe, environment friendly and commercially scalable process to prepare aminoadamantane derivatives, compound of formula I, via a stable intermediate.

OBJECT OF THE INVENTION

The object of the present invention is to prepare aminoadamantane derivatives, compound of formula I, using a novel process via a stable intermediate, compound of formula IId.



Formula I

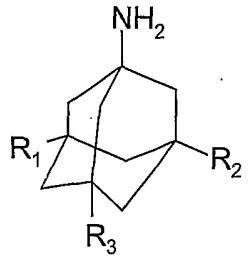


Formula IId

(wherein R_1, R_2, are selected from C_{1-4} linear and branched alkyl & R_3 is selected from hydrogen, C_{1-4} linear and branched alkyl)

SUMMARY OF THE INVENTION

A novel process for the preparation of compound of formula I,

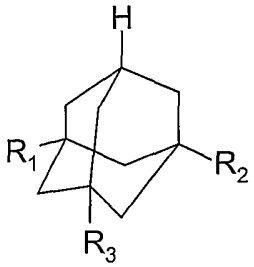


Formula I

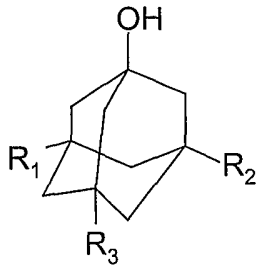
(wherein R_1, R_2 are selected from C_{1-4} linear and branched alkyl & R_3 is selected from hydrogen, C_{1-4} linear and branched alkyl)

said process comprising;

a) brominating compound of formula IIa, hydrolysing and isolating compound of formula IId,



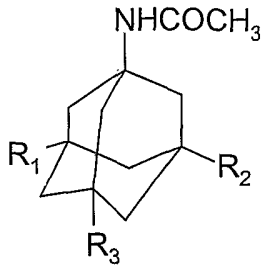
Formula II a



Formula II d

(wherein R_1, R_2, are selected from C_{1-4} linear and branched alkyl & R_3 is selected from hydrogen, C_{1-4} linear and branched alkyl)

b) converting compound of formula IId to compound of formula IIc, and

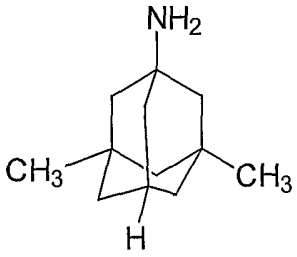


formula IIc

(wherein R_1, R_2, are selected from C_{1-4} linear and branched alkyl & R_3 is selected from hydrogen, C_{1-4} linear and branched alkyl)

c) deacetylating compound of formula IIc to yield compound of formula I.

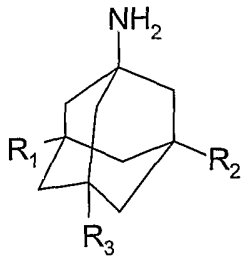
More particularly, compound of formula I, wherein R_1, R_2 are methyl & R_3 is hydrogen, commonly known as memantine



Formula I

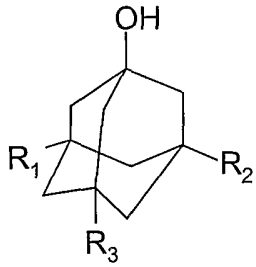
DETAILED DESCRIPTION OF THE INVENTION

The present invention describes a novel process for preparing compound of formula I.



(wherein R_1, R_2, are selected from C_{1-4} linear and branched alkyl & R_3 is selected from hydrogen, C_{1-4} linear and branched alkyl)

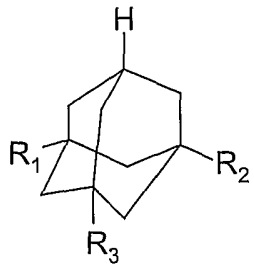
According to one embodiment of the process of the present invention, compound of formula I maybe obtained via hydroxyadamantane derivative, compound of formula IId.



Formula IId

(wherein R_1, R_2 and R_3 are as defined above)

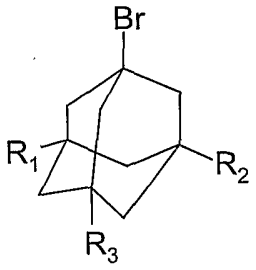
As a first step to introduce a functionality in compound of formula IIa, we resorted to using bromine as described in '142.



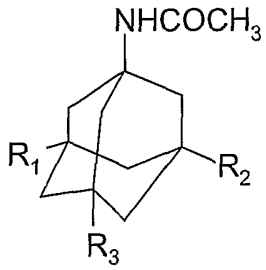
Formula II a

(wherein R_1, R_2 are selected from C_{1-4} linear and branched alkyl & R_3 is selected from hydrogen, C_{1-4} linear and branched alkyl)

To our surprise the reaction occured at ambient conditions with bromine liquid to give bromoadamantane, compound of formula IIb, making the process safe. However, the stability of the bromo compound on storage was a matter of concern. Hence, it was of particular interest for us to isolate an intermediate, which is stable, can be stored and can participate in the next reaction to furnish the desired acetamido intermediate, compound of formula IIc.



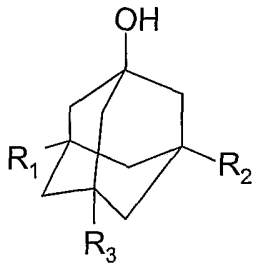
Formula IIb



Formula IIc

(wherein R_1, R_2 are selected from C_{1-4} linear and branched alkyl & R_3 is selected from hydrogen, C_{1-4} linear and branched alkyl)

In our attempt to use a storage stable intermediate we prepared compound of formula IId, the hydroxyadamantane derivative which on reaction with acetonitrile in presence of sulphuric acid yields acetamido derivatives (Ritter reaction) which on deacetylation gives compound of formula I. Accordingly the compound of formula IId can thus be converted to desired compound of formula I.



Formula IId

(wherein R_1, R_2 are selected from C_{1-4} linear and branched alkyl & R_3 is selected from hydrogen, C_{1-4} linear and branched alkyl)

We found that following the process of our invention, bromination of compound of formula IIa with bromine liquid under ambient conditions afforded directly the alcohol derivative, compound of formula IId, as a solid instead of bromoadamantane, compound of formula IIb. The alcohol derivative, compound of formula IId was confirmed by spectral analysis (^{13}C, Mass, elemental analysis). Analytical Data for compounds of formula IIa and IId is depicted in table I.

SUBSTITUTE SHEET (RULE 26)

For instance, compound of formula IId may be prepared by treating compound of formula IIa with 2-3 volumes of bromine at room temperature for 5-20 hours. The reaction mixture is poured in ice followed by washing with reducing agent and stirring for 1-5 hours at room temperature. The reaction mixture is extracted with an organic solvent like methylene dichloride followed by washing with aqueous alkaline carbonate solution and aqueous wash. The organic layer is distilled out to give compound of formula IId.

According to another embodiment of the process of the present invention compound of formula IId may be prepared by brominating , hydrolyzing and isolating compound of formula IIa wherein bromination is carried out under ambient conditions preferably 25 to 40°C. The alcohol derivative, compound of formula IId is stable, of reproducible quality as compared to bromoadamantane and can be prepared in highly pure form. The alcohol derivative, compound of formula IId, participated in Ritter reaction as expected.

According to yet another embodiment of the process of the present invention compound of formula IId is reacted with acetonitrile to give compound of formula IIc in the presence of acid like sulphuric acid.

The reaction proceeds smoothly at 40 – 70^0C, within 1 – 8 hours to yield acetamido derivative, compound of formula IIc, when compared to '142 wherein the reaction of 1-bromo-3,5-dimethyladamantane with acetonitrile and concentrated sulphuric acid is performed at ambient temperature overnight. Further, the process of the present invention avoids use of benzene, a carcinogenic solvent, reported for extraction.

The deacetylation of acetamido derivative, compound of formula IIc, to give compound of formula I maybe carried out by hydrolyzing the compound of formula IIc in presence of acidic or basic catalyst. Also the solvent selected for deacetylation reactions should be suitable as a medium and also assist in hydrolysis.

The acidic catalyst for deacetylation may be selected from hydrochloric acid , sulphuric acid and the like.

The basic catalyst for deacetylation may be selected from inorganic base(s) such as an alkoxide, wherein the alkyl residue is C1 to C6 linear, branched or cyclic alkyl and the counter ion is an alkali or alkaline earth metal, alkali or alkaline earth metal oxide, hydroxide, carbonate or bicarbonate preferably sodium hydroxide, potassium hydroxide, potassium tertiary butoxide and the like; an organic base(s) such as amine base selected from aliphatic or aromatic amines, cyclic or acyclic amines, for example isoquinolines, quinolines, dialkylarylamines, pyridine, substituted pyridines preferably alkanolamine bases like ethanolamine and the like; and mixtures of inorganic base(s) with organic base.(s)

The deacetylation of acetamido derivative, compound of formula IIc, may be carried in a solvent selected from acyclic and cyclic polyether to yield aminoadamantane, compound of formula I. The acyclic or cyclic polyether used in the present invention may be selected from the group comprising 1,2-dimethoxyethane, 1,4-dimethoxybutane,

poly(alkylene glycol)s such as poly(ethylene glycol)s (PEGs), 1,4-dioxane, crown ethers, mono alkylated or dialkylated poly(alkylene glycol)s wherein the alkyl group is selected from C_1 to C_6 linear or branched alkyl, diethylene glycol dimethyl ether (diglyme), triethylene glycol dimethyl ether, triethylene glycol diethyl ether, tetraethylene glycol dimethyl ether (tetraglyme) & the like and mixtures thereof. The poly(alkylene glycol)s and monoalkylated or dialkylated poly(alkylene glycol)s being mixtures are defined by an average molecular weight and do not have specific boiling point, for e.g. PEG 200, PEG 400, poly(ethylene glycol) dimethyl ether 250 and the like.

In the process of the present invention the deacetylation reaction of acetamido derivative, compound of formula IIc, is carried out by basic hydrolysis in 3 to 10 parts by volume of acyclic or cyclic polyether solvent to give compound of formula I.

For instance, the deacetylation reaction of acetamido derivative, compound of formula IIc, is carried out by heating one gram of compound of formula IIc with sodium hydroxide in 5-8 volumes of PEG 400 at 80-150^{0}C temperature for 6 to 12 hours to give compound of formula I.

The compound of formula I may be converted to it pharmaceutically acceptable salts by addition of appropriate acid.

The pharmaceutically acceptable salts may be selected from mineral acid salts such as hydrochloride, hydrobromide, sulfate and the like; organic acid salts such as oxalate, citrate, succinate, maleate, fumarate, malate, tartrate, and the like; and sulfonates such as

methanesulfonate, benzenesulfonate, toluenesulfonate and the like; preferably hydrochloride.

The hydrochloride salt formation of compound of formula 1 may be carried out with hydrochloric acid dissolved in alcoholic solvent like methanol, ethanol, isopropanol, n-propanol, n-butanol, t-butanol, isobutanol or by passing HCl gas at a temperature ranging from about -10 to 100°C to get hydrochloride salt of aminoadamantane. The crystallisation to obtain pure product is carried out in environment friendly organic solvents like polar protic, aprotic and non polar solvents selected from methanol, isopropyl alcohol, ethyl acetate, acetonitrile, acetone, toluene and the mixtures thereof.

The invention is further illustrated but not restricted by the description in the following examples.

Examples

Example 1

Preparation of compound of formula II d (wherein R_1, R_2 are CH_3 & R_3 is H)

500 ml of bromine liquid is added to 200 gm of 1,3 dimethyladamantane and stirred at room temperature for 12 hours and the reaction mixture is poured in 4.0 kg ice cold water The reaction mixture is decolorized with 950 gm sodium metabisulphite and stirred for 1.5 hours at room temperature. Extract with 2.0 lit MDC and the MDC layer is washed with 1.0 lit 10% sodium bicarbonate solution and subsequently with 2.0 lit water, MDC layer is dried over sodium sulphate, distilled and degassed with vacuum. The obtained material is leached with 300 ml of n-hexane at room temperature for 0.5 hours and further cooled to 0-5^{0}C and maintained for 1 hour. Filter and wash with 50 ml chilled n-hexane and dry at 40-45^{0}C.

Table 1

Analytical Data for -Bromo and -hydroxy compounds (^{13}C, Mass, elemental)

S.no	Analysis details	-Bromo compound		-Hydroxy compound	
1	^{13}C	Peak at 66.4 ppm		Peak at 70.2 ppm	
2	Mass	163.2 (M-Br)		181.1(M+1)	
3	Elemental	Found	Calculated	Found	Calculated
	Carbon :	59.25	59.21	80.19	79.87
	Hydrogen :	8.07	7.81	11.51	11.09

Example 2

Preparation of compound of formula IIc (wherein R_1, R_2 are CH_3 & R_3 is H)

46 gm of 1-Hydroxy–3,5-dimethyladamantane, compound of formula II d is added to a mixture of 184 ml acetonitrile and 386 ml sulphuric acid and heated to 45-50^{0}C and maintained for 8 hours. The reaction mass is quenched in 1380 gm of ice water and extracted with 920 ml of MDC, MDC layer is washed with 230 ml of 10% sodium bicarbonate solution and subsequently with 460 ml of water, distilled and degassed with vacuum. The obtained solid is leached with 138 ml of n-hexane at room temperature for 0.5hours and further cooled to 0-5^{0}C and maintained for 1 hour. Filter and wash with chilled hexane and dry at 50-55^{0}C.

Example 3

Preparation of hydrochloride salt of compound of formula I (wherein R_1, R_2 are CH_3 & R_3 is H)

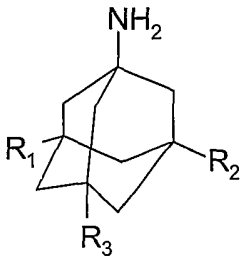
40 gm of 1-acetamido–3,5-dimethyl adamantine, compound of formula IIc, is added to 200 ml of PEG 400 and 57.8 gm of sodium hydroxide is added and heated to 135-140^{0}C, maintained for 10 hours, cooled to 80-85^{0}C and 1.6 lit of water is added. Extracted with 800 ml of toluene and washed the toluene layer with 4.0 lit of water and toluene layer is distilled and degassed with vacuum to obtain memantine free base.

160 ml of methanol is added to the above obtained memantine free base and stirred, added slowly methanolic hydrochloride to adjust the pH to ~2.0 and charcoalised with

2.0 gm activated charcoal, methanol distilled & degassed with vacuum at below 50^0C. 160 ml acetone added to the degassed mass and stirred for 15 min at 50^0C and gradually cooled to 0-5^0C and stirred at 0-5^0C for 30 min. Filter and wash with 40 ml chilled acetone. Dry the material at 50-55^0C.

WE claim:

1) A novel process for the preparation of compound of formula I,

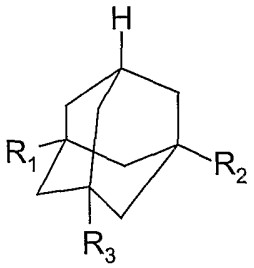


Formula I

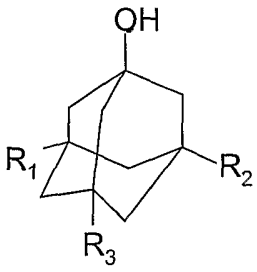
(wherein R_1, R_2 are selected from C_{1-4} linear and branched alkyl & R_3 is selected from hydrogen, C_{1-4} linear and branched alkyl)

said process comprising;

a) brominating compound of formula IIa, hydrolysing and isolating compound of formula IId,



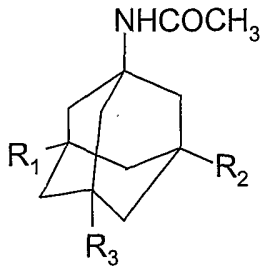
Formula II a



Formula II d

(wherein R_1, R_2, are selected from C_{1-4} linear and branched alkyl & R_3 is selected from hydrogen, C_{1-4} linear and branched alkyl)

b) converting compound of formula IId to compound of formula IIc, and



formula IIc

(wherein R_1, R_2, are selected from C_{1-4} linear and branched alkyl & R_3 is selected from hydrogen, C_{1-4} linear and branched alkyl)

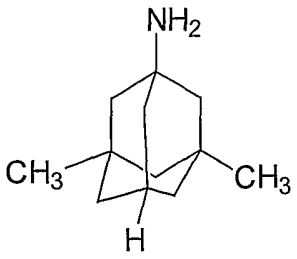
c) deacetylating compound of formula IIc to yield compound of formula I.

2) A novel process as claimed in claim 1 step (a) wherein bromination is carried out at ambient temperature.

3) A novel process as claimed in claim 1 step (b) wherein conversion of IId is carried out with acetonitrile in presence of acid.

4) A novel process as claimed in claim 1 wherein step (c) is carried out in solvent selected from acyclic or cyclic polyether.

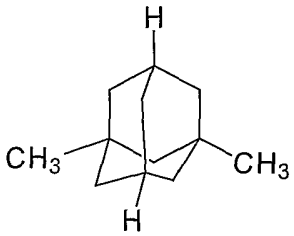
5) A process for the preparation of compound of formula I,



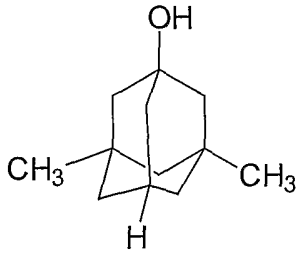
Formula I

said process comprising

a) brominating compound of formula IIa, hydrolysing and isolating compound of formula IId,

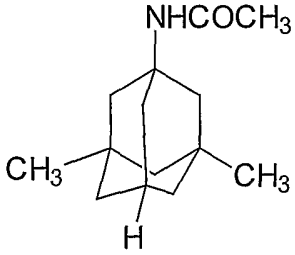


Formula II a



Formula II d

b) converting compound of formula IId to compound of formula IIc, and



formula IIc

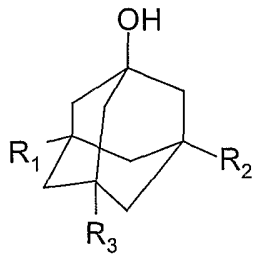
c) deacetylating compound of formula IIc to yield compound of formula I.

6) A process as claimed in claim 5 step (a) wherein bromination is carried out at ambient temperature.

7) A process as claimed in claim 5 step (b) wherein conversion of IId is carried out with acetonitrile in presence of acid.

8) A novel process as claimed in claim 5 wherein step (c) is carried out in solvent selected from acyclic or cyclic polyether.

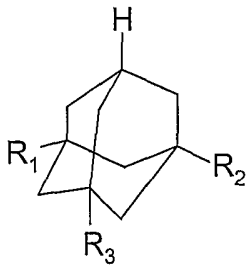
9) A process for the preparation of compound of formula II d,



Formula II d

(wherein R_1, R_2 are selected from C_{1-4} linear and branched alkyl & R_3 is selected from hydrogen, C_{1-4} linear and branched alkyl)

said process comprising brominating compound of formula IIa, hydrolysing and isolating compound of formula IId.



Formula IIa

10. A process as claimed in claim 9 wherein bromination is carried out at ambient temperature.

11) A process for the preparation of compound of formula I as claimed in claims 1 to 10 substantially as herein described and illustrated by examples 1to 3