962,461

PATENT SPECIFICATION

NO DRAWINGS

962,461

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International Classification:—C 07 c, d

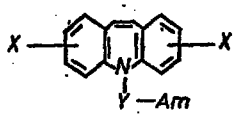
COMPLETE SPECIFICATION

Substituted 5H-Dibenz[b,f] Azepines and processes for their production

We, J. R. GEIGY A.G., a body corporate organised according to the laws of Switzerland, of 215, Schwarzwaldallee, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to substituted 5H-dibenz[b,f]azepines having valuable pharmacological properties, as well as processes for the production thereof.

Specification No. 828,495 describes and claims N-substituted iminostilbenes of the general formula



Ia.

wherein

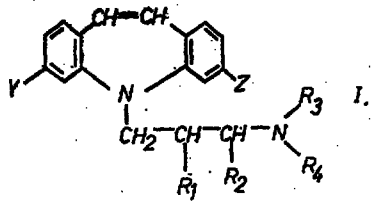
X represents a hydrogen or a halogen atom or a methyl group,

Y represents an alkylene radical having 2—6 carbon atoms, and 2—4 bridging members between N and Am, and

Am represents a dialkylamino radical, each alkyl group of which contains 1 to 4 carbon atoms, wherein both alkyl radicals may be joined to form a saturated N-heretocyclic ring.

Specification No. 828,495 also discloses and claims various processes for the production of compounds of the general formula Ia as defined above.

It has been found that certain 5H-dibenzo[b.f]azepines not disclosed in specification No. 828,495 and having the general formula



I.

wherein

Y represents a hydrogen or a halogen atom,

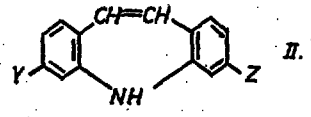
Z represents a hydrogen or a halogen atom,

one of the symbols R_1 and R_2 represents the methyl group and the other hydrogen, and

R_3 and R_4 represent alkenyl radicals each having from 2 to 4 carbon atoms or alkyl radicals each having from 1 to 4 carbon atoms or R_3 and R_4 may jointly represent an alkylene chain having from 2 to 8 carbon atoms and forming with the nitrogen atom to which they are attached a heterocyclic radical other than the hexamethyleneimino radical,

have valuable pharmacological properties, in particluar spasmolytic, anti-allergic, sedative, anticonvulsive and anti-emetic activity.

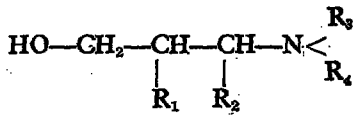
The compounds of the above defined general formula I may be produced by reacting an iminostilbene of the general formula



II.

wherein Y and Z have the meanings given

above, in the presence of an acid-binding agent, with a reactive ester of a basic alcohol of the general formula



III

wherein R_1, R_2, R_3 and R_4 have the meanings given above.

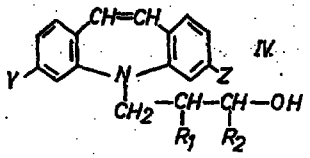
Particularly suitable condensing agents are sodium amide, lithium amide, potassium amide, sodium or potassium, butyl lithium, phenyl lithium, sodium hydride or lithium hydride. The reaction can be performed in the presence or absence of an inert organic solvent, of which examples are benzene, toluene and xylene.

In addition to iminostilbene itself, suitable starting materials of the general formula II are, for example, 3,7-dichloro-iminostilbene, and 3,7-dibromo-iminostilbene as well as the mono-substituted compounds 3-chloro-iminostilbene and 3-bromoiminostilbene. They may be produced, for example, by treating 3,5-diacetyl-iminodibenzyl with hydrazoic acid according to the Schmidt hydrazoic acid reaction (Organic Reactions 1946, *3*, 307) followed by partially hydrolysing the acetamido compound to form 3-amino-5-acetyl-iminodibenzyl, diazotising this, reacting the diazonium halides with cuprous halides according to Sandmeyer and brominating the 3-halogen-5-acetyl-iminodibenzyls obtained in the 10-position with N-bromo-succinimide, splitting off hydrogen halide and hydrolysing, for example with caustic alkalies in the cold, to form 3-halogen-iminostilbenes.

As reactive esters of basic alcohols of the general formula III, in particular the halides, aryl sulphonic acid esters and methane sulphonic acid esters are used. Examples thereof are γ-dimethylamino-n-butyl chloride, γ-diethylamino-n-butyl chloride, γ-di-n-butylamino-n-butyl chloride, γ-pyrrolidino-n-butyl chloride, γ-piperidino-n-butyl chloride and the corresponding bromides and toluene-*p*-sulphonic acid esters, as well as γ-di-methylamino-β-methylpropyl chloride, γ-diethylamino-β-methylpropyl chloride, γ-pyrrolidino-β-methylpropyl chloride and γ-piperidino-β-methylpropyl chloride. The first group of reactive esters of basic alcohols is obtained, for example, starting from 1,3-butylene glycol by reacting it with acetyl chloride to form 3-chloro-n-butyl acetate, reacting the latter with a suitable secondary amine and converting the 3-tertiary amino-n-butanol obtained into its chloride, bromide or toluene sulphonic acid ester.

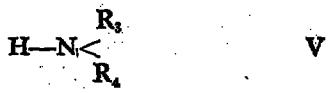
The N-substituted β-methylpropyl chlorides can be obtained for example, by adding hydrogen bromide in the presence of dibenzoylperoxide to β-methallyl chloride and reacting the γ-bromo-β-methylpropyl chloride obtained with suitable secondary amines.

A modified process for the production of compounds of the general formula I consists in reacting a reactive ester of a hydroxy compound of the general formula



IV

wherein R_1, R_2, Y and Z have the meanings given above, e.g. a halide, an aryl sulphonic acid ester or methane sulphonic acid ester, with a secondary amine of the general formula

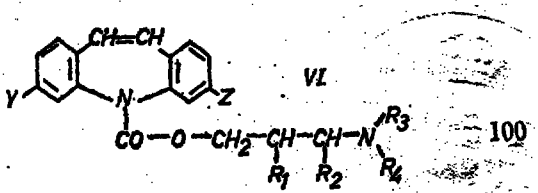


V

wherein R_3 and R_4 have the meanings given above. The reaction can be performed, for example, at a moderately raised temperature of, e.g. 80—120°, in an inert solvent such as, e.g. a low molecular weight alkanol or alkanone, an excess of the amine being reacted being advantageously used as acid-binding agent. Depending on the boiling point of the amine used and of the solvent as well as on the reaction temperature necessary, the reaction is sometimes to be performed in a closed vessel. Reactive esters of hydroxy compounds of the general formula IV are obtained, for example, by reacting alkali metal compounds of optionally substituted iminostilbene of the general formula II with 1-bromo-3-chlorobutane, 1,3-dichlorobutane or γ-bromo-β-methylpropyl chloride or with halogen butyl aryl sulphonic acid esters or halogen butyl methane sulphonic acid esters.

Secondary amines of the general formula V are dimethylamine, diethylamine, di-n-butylamine, pyrrolidine, piperidine.

Compounds of the general formula I are obtained according to a further process by heating a compound of the general formula

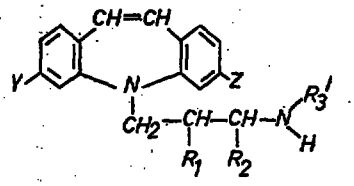


VI

wherein Y, Z, R_1, R_2 R_3 and R_4 have the

meanings given above, until one molecular proportion of carbon dioxide has been split off. The compounds of the general formula VI are obtained in their turn, for example, by reacting phosgene with compounds of the general formula II and reacting the possibly substituted 5-chlorocarbonyl-iminostilbenes obtained with basic alcohols of the general formula III.

A fourth process for the production of compounds of the general formula I consists in treating a compound of the general formula



VII.

wherein R_3^1 represents an alkyl radical having from 1 to 4 carbon atoms or hydrogen and Y, Z, R_1 and R_2 have the meanings given above, with an alkylating agent capable of introducing an alkyl group having from 1 to 4 carbon atoms. Starting materials of the general formula VII are obtained, for example, if analogously to the second process for the production of compounds of the general formula I, ammonia or a low molecular monoalkylamine is reacted instead of a secondary amine with a reactive ester of a hydroxy compound of the general formula IV. As low molecular alkylating agents, for example, dimethyl sulphate, diethyl sulphate, methyl iodide, ethyl iodide, ethyl bromide, n-propyl bromide, n-butyl bromide and toluene-*p*-sulphonic acid methyl ester are used in the presence of acid binding agents such as, e.g. sodium or potassium carbonate, and an inert organic solvent, and also, for example, formaldehyde is used in the presence of formic acid.

The compounds of the general formula I form salts with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane disulphonic acid, acetic acid, citric acid, malic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, benzoic acid, phthalic acid and 8-chlorotheophyllin. Some of these salts are water-soluble.

The following examples further illustrate the production of the new compounds according to the invention. Where not otherwise stated, parts are given as parts by weight and their relationship to parts by volume is as that of grammes to cubic centimetres. The temperatures are in degrees Centigrade.

EXAMPLE 1.

18.3 Parts of iminostilbene are dissolved in 490 parts of anhydrous benzene and a solution consisting of 18.6 parts of γ-diethylamino-n-butyl chloride in 150 parts by volume of anhydrous benzene is added.

A suspension of 4 parts of sodium amide in toluene is added dropwise at 55° while stirring well and the whole is then refluxed for 15 hours. Water is then added to the reaction mixture and the basic portions are removed from the benzene phase by extracting three times with diluted hydrochloric acid. The combined extracts are made alkaline and extracted with ether, and the ethereal solution is dried over potassium carbonate and concentrated. The residue is distilled in a high vacuum whereupon the 5-(γ-diethylamino-n-butyl)-iminostilbene passes over at 185—190° under 0.5 mm. pressure.

The hydrochloride prepared with alcoholic hydrochloric acid and recrystallised from acetone melts at 193—195°.

On using γ-pyrrolidyl-n-butyl chloride ($B.P._{13}$ 82—87°), 5-(γ-pyrrolidyl-n-butyl)-iminostilbene ($B.P._{0.35}$ 206—208°), and on using γ-dimethylamino-n-butyl chloride, 5-(γ-dimethylamino-n-butyl)-iminostilbene ($B.P._{0.25}$ 172—176°) are obtained in an analogous manner.

EXAMPLE 2.

12 Parts of iminostilbene are dissolved in 350 parts by volume of anhydrous benzene and 9.5 parts of γ-pyrrolidyl-β-methylpropyl chloride ($B.P._{16}$ 95°) in 15 parts by volume of anhydrous benzene are added.

A suspension of 2.75 parts of sodium amide in toluene is added at 60° while stirring well and the mixture is stirred for 5 hours at 60°. The whole is then refluxed for 13 hours, whereupon water is added to the reaction mixture and the basic portions are removed from the benzene by extracting three times with diluted hydrochloric acid. The combined extracts are made alkaline and extracted with ether and the ethereal solution is dried over potassium carbonate and concentrated. The residue is distilled in a high vacuum whereupon the 5-(γ-pyrrolidyl-β-methylpropyl)-iminostilbene passes over at 165° under 0.06 mm. pressure.

The hydrochloride prepared with alcoholic hydrochloric acid and recrystallised from acetone melts at 108—115°.

On using γ-diethylamino-β-methylpropyl chloride ($B.P._{17}$ 53°), the 5-(γ-diethylamino-β-methylpropyl)-iminosilbene ($B.P._{0.03}$ 164.5°) is obtained in an analogous manner.

On using 3,7-dichloro-iminostilbene and γ-piperidino-n-butyl chloride, 5-(γ-piperidino-n-butyl)-3,7-dichloro-iminostilbene is obtained in an analogous manner, and on using γ-dimethylamino-β-methylpropyl

chloride, 5 - (γ - dimethylamino - β-methylpropyl)-3,7-dichloro-iminostilbene is obtained.

EXAMPLE 3.

9.65 Parts of iminostilbene are dissolved in 300 parts by volume of anhydrous toluene and 7.5 parts of γ-dimethylamino-β-methylpropyl chloride in 50 parts by volume of anhydrous toluene are added.

A suspension of 2 parts of sodium amide in toluene is added dropwise at 60° while stirring well, and the mixture is then refluxed for 12 hours. Water is then added to the reaction mixture and the basic portions are removed from the separated toluene phase by extracting three times with diluted hydrochloric acid. The combined hydrochloric acid extracts are made alkaline and extracted with ether, and the ethereal solution is dried over potassium carbonate and concentrated. The residue is distilled in a high vacuum whereupon 5-(γ-dimethylamino-β-methylpropyl)-iminostilbene passes over at 158—161° under 0.025 torr. The base crystallises from acetone in the form of yellow microcrystals which melt at 77—78°.

The hydrochloride prepared with alcoholic hydrochloric acid and recrystallised from acetone melts at 202—203°. The crystals were in the form of yellow prisms.

On using 3-chloro-iminostilbene or 3-bromo-iminostilbene, and γ-dimethylamino-β-methylpropyl chloride, 5-(γ-dimethylamino-β-methylpropyl-3-chloro-iminostilbene or 5-(γ - dimethylamino - β - methylpropyl - 3-bromo-iminostilbene respectively are obtained in an analogous manner.

EXAMPLE 4.

9.6 Parts of iminostilbene are dissolved in 270 parts by volume of anhydrous toluene. A suspension of 2.5 parts of sodium amide in toluene is added dropwise at 60—70° while stirring strongly whereupon the reaction mixture is refluxed for 13 hours.

The solution of 8.5 parts of γ-methylethylamino-β-methylpropyl chloride in 100 parts by volume of anhydrous toluene is added dropwise while stirring strongly at 60° and the whole is then refluxed for 16 hours. Water is then added to the reaction mixture, the basic portions are removed from the toluene phase by extracting three times with dilute hydrochloric acid. The combined extracts are made alkaline and extracted with ether, the ethereal solution is dried over potassium carbonate and concentrated. The residue is distilled in a high vacuum whereupon 5 - (γ - methylethylamino - β - methylpropyl)-iminostilbene ($B.P._{0.03}$ 165—169°) is obtained.

EXAMPLE 5.

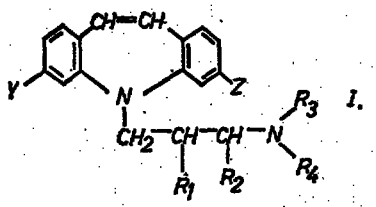
9.6 Parts of iminostilbene and 1.95 parts of sodium amide are refluxed in 100 parts by volume of toluene until evolution of ammonia ceases. A solution of 10 parts of γ-diallylamino-n-butyl chloride in 50 parts by volume of toluene is then added and the whole is refluxed for 14 hours under nitrogen. Water is added to the cooled charge and the phases are separated. The toluene phase is washed with water, dried over potassium carbonate and evaporated. The residue is distilled in a high vacuum to give 5-(γ-diallylamino-n-butyl)iminostilbene.

EXAMPLE 6.

9.6 Parts of iminostilbene and 1.95 parts of sodium amide are refluxed in 100 parts by volume of toluene until evolution of ammonia ceases. A solution of 10 parts of γ-diallylamino-β-methyl-propyl chloride in 50 parts by volume of toluene is then added and the whole is refluxed for 14 hours under nitrogen. Water is added to the cooled charge and the phases are separated. The toluene phase is washed with water, dried over potassium carbonate and evaporated. The residue is distilled in a high vacuum to give 5 - (γ - diallylamino - β - methyl - propyl)-iminostilbene.

WHAT WE CLAIM IS:—

1. Heterocyclic compounds of the general formula



I.

wherein

Y represents a hydrogen or a halogen atom,
Z represents a hydrogen or a halogen atom,
one of the symbols R_1 and R_2 represents the methyl group and the other represents hydrogen, and
R_3 and R_4 represent alkenyl radicals each having from 2 to 4 carbon atoms or alkyl radicals each having from 1 to 4 carbon atoms or R_3 and R_4 may jointly represent an alkylene chain having from 2 to 8 carbon atoms and forming with the nitrogen atom to which they are attached a heterocyclic radical other than the hexamethyleneimino radical.

2. Heterocyclic compounds as claimed in claim 1 in which R_3 and R_4 represent alkyl radicals having from 1 to 4 carbon atoms or R_3 and R_4 may jointly represent an alkylene chain having from 2 to 8 carbon atoms and forming with the nitrogen atom to which they are attached a heterocyclic radical other than the hexamethyleneimino radical.

3. A process for producing heterocyclic

chloride, 5 - (γ - dimethylamino - β-methylpropyl)-3,7-dichloro-iminostilbene is obtained.

EXAMPLE 3.

9.65 Parts of iminostilbene are dissolved in 300 parts by volume of anhydrous toluene and 7.5 parts of γ-dimethylamino-β-methylpropyl chloride in 50 parts by volume of anhydrous toluene are added.

A suspension of 2 parts of sodium amide in toluene is added dropwise at 60° while stirring well, and the mixture is then refluxed for 12 hours. Water is then added to the reaction mixture and the basic portions are removed from the separated toluene phase by extracting three times with diluted hydrochloric acid. The combined hydrochloric acid extracts are made alkaline and extracted with ether, and the ethereal solution is dried over potassium carbonate and concentrated. The residue is distilled in a high vacuum whereupon 5-(γ-dimethylamino-β-methylpropyl)-iminostilbene passes over at 158—161° under 0.025 torr. The base crystallises from acetone in the form of yellow microcrystals which melt at 77—78°.

The hydrochloride prepared with alcoholic hydrochloric acid and recrystallised from acetone melts at 202—203°. The crystals were in the form of yellow prisms.

On using 3-chloro-iminostilbene or 3-bromo-iminostilbene, and γ-dimethylamino-β-methylpropyl chloride, 5-(γ-dimethylamino-β-methylpropyl-3-chloro-iminostilbene or 5-(γ - dimethylamino - β - methylpropyl - 3-bromo-iminostilbene respectively are obtained in an analogous manner.

EXAMPLE 4.

9.6 Parts of iminostilbene are dissolved in 270 parts by volume of anhydrous toluene. A suspension of 2.5 parts of sodium amide in toluene is added dropwise at 60—70° while stirring strongly whereupon the reaction mixture is refluxed for 13 hours.

The solution of 8.5 parts of γ-methylethylamino-β-methylpropyl chloride in 100 parts by volume of anhydrous toluene is added dropwise while stirring strongly at 60° and the whole is then refluxed for 16 hours. Water is then added to the reaction mixture, the basic portions are removed from the toluene phase by extracting three times with dilute hydrochloric acid. The combined extracts are made alkaline and extracted with ether, the ethereal solution is dried over potassium carbonate and concentrated. The residue is distilled in a high vacuum whereupon 5 - (γ - methylethylamino - β - methylpropyl)-iminostilbene ($B.P._{0.03}$ 165—169°) is obtained.

EXAMPLE 5.

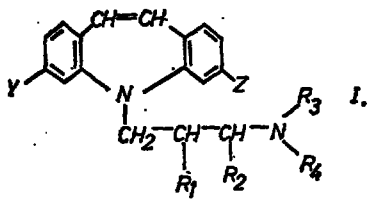
9.6 Parts of iminostilbene and 1.95 parts of sodium amide are refluxed in 100 parts by volume of toluene until evolution of ammonia ceases. A solution of 10 parts of γ-diallylamino-n-butyl chloride in 50 parts by volume of toluene is then added and the whole is refluxed for 14 hours under nitrogen. Water is added to the cooled charge and the phases are separated. The toluene phase is washed with water, dried over potassium carbonate and evaporated. The residue is distilled in a high vacuum to give 5-(γ-diallylamino-n-butyl)iminostilbene.

EXAMPLE 6.

9.6 Parts of iminostilbene and 1.95 parts of sodium amide are refluxed in 100 parts by volume of toluene until evolution of ammonia ceases. A solution of 10 parts of γ-diallylamino-β-methyl-propyl chloride in 50 parts by volume of toluene is then added and the whole is refluxed for 14 hours under nitrogen. Water is added to the cooled charge and the phases are separated. The toluene phase is washed with water, dried over potassium carbonate and evaporated. The residue is distilled in a high vacuum to give 5 - (γ - diallylamino - β - methyl - propyl)-iminostilbene.

WHAT WE CLAIM IS:—

1. Heterocyclic compounds of the general formula



I.

wherein

Y represents a hydrogen or a halogen atom,

Z represents a hydrogen or a halogen atom,

one of the symbols R_1 and R_2 represents the methyl group and the other represents hydrogen, and

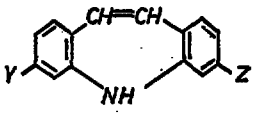
R_3 and R_4 represent alkenyl radicals each having from 2 to 4 carbon atoms or alkyl radicals each having from 1 to 4 carbon atoms or R_3 and R_4 may jointly represent an alkylene chain having from 2 to 8 carbon atoms and forming with the nitrogen atom to which they are attached a heterocyclic radical other than the hexamethyleneimino radical.

2. Heterocyclic compounds as claimed in claim 1 in which R_3 and R_4 represent alkyl radicals having from 1 to 4 carbon atoms or R_3 and R_4 may jointly represent an alkylene chain having from 2 to 8 carbon atoms and forming with the nitrogen atom to which they are attached a heterocyclic radical other than the hexamethyleneimino radical.

3. A process for producing heterocyclic

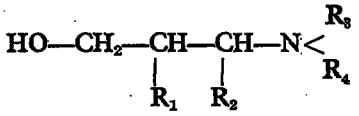
* C L M S *

compounds claimed in claim 1 which comprises reacting, in the presence of an acid-binding agent, an iminostilbene of the general formula



II.

with a reactive ester of a basic alcohol of the general formula

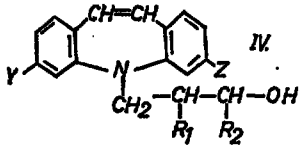


III

wherein R_1, R_2, R_3, R_4, Y and Z have the meanings defined in claim 1.

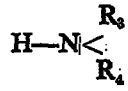
4. A process as claimed in claim 3 in which R_3 and R_4 have the meanings defined in claim 2.

5. A process for producing heterocyclic compounds as claimed in claim 1 which comprises reacting a reactive ester of a hydroxy compound of the general formula



IV.

with a secondary amine of the general formula

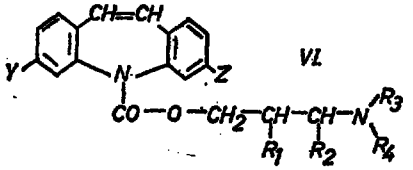


V

wherein Y, Z, R_1, R_2, R_3 and R_4 have the meanings given in claim 1.

6. A process as claimed in claim 5 in which R_3 and R_4 have the meaning defined in claim 2.

7. A process for producing heterocyclic compounds as claimed in claim 1 which comprises heating a compound of the general formula

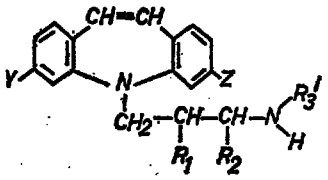


VI.

wherein Y, Z, R_1, R_2, R_3 and R_4 have the meanings given in claim 1, until one molecular proportion of carbon dioxide is split off.

8. A process as claimed in claim 7 in which R_3 and R_4 have the meaning defined in claim 2.

9. A process for producing heterocyclic compounds as claimed in claim 1 which comprises treating a compound of the general formula



VII.

wherein R_3^1 represents a low alkyl radical or hydrogen, and Y, Z, R_1 and R_2 have the meanings given in claim 1, with an alkylating agent capable of introducing an alkyl group having from 1 to 4 carbon atoms.

10. A process as claimed in claim 7 in which R_3 and R_4 have the meaning defined in claim 2.

11. N - (γ - dimethylamino - β - methylpropyl)-iminostilbene.

12. N-heterocyclic compounds as claimed in claim 2 as herein described in Example 1.

13. N-heterocyclic compounds as claimed in claim 2 as herein described in Example 2.

14. N-heterocyclic compounds as claimed in claim 2 as herein described in Example 3.

15. N-heterocyclic compounds as claimed in claim 1 as hereinbefore described in any one of Examples 4 to 6.

16. Process for the production of N-heterocyclic compounds claimed in claim 2 substantially as hereinbefore described in Example 1.

17. Process for the production of N-heterocyclic compounds claimed in claim 2 substantially as hereinbefore described in Example 2.

18. Process for the production of N-heterocyclic compounds claimed in claim 2 substantially as hereinbefore described in Example 3.

19. Process for the production of N-heterocyclic compounds claimed in claim 1 substantially as hereinbefore described in any one of Examples 4 to 6.

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Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to patent No. 914,717.

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