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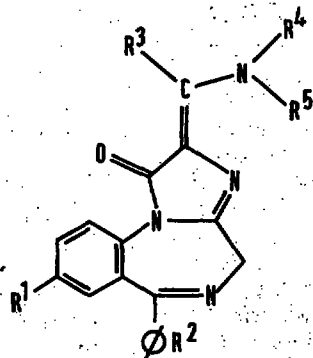


(54) 1,2-DIHYDRO-4H-IMIDAZO[1,2-a][1,4]BENZODIAZEPIN-1-ONES, PROCESSES FOR THEIR PREPARATION, AND COMPOSITIONS INCORPORATING THEM

(71) We, ROUSSEL LABORATORIES LIMITED, a British Company, of North End Road, Wembley, Middlesex, 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:—

This invention relates to imidazolobenzodiazepines, processes for their preparation, and compositions incorporating them. More particularly, the invention concerns certain pharmaceutically-active 1,2-dihydro-6-phenyl-4H-imidazo-[1,2-a][1,4]benzodiazepin-1-ones that may be of use in human or veterinary medicine.

In one aspect, therefore, this invention provides the 1,2-dihydro-6-phenyl-4H-imidazo-[1,2-a][1,4]benzodiazepin-1-ones of the general formula:



wherein:

R¹ represents a hydrogen atom, a halogen atom, a nitro radical or a trifluoromethyl radical;

R², which may be at any position in the phenyl (Ø) ring, represents a hydrogen atom or a halogen atom;

R³ represents a hydrogen atom or a methyl radical; and

R⁴ and R⁵, which may be the same or different, either each represents a hydrogen atom, an alkyl radical containing from 1 to 5 carbon atoms, a hydroxyalkyl radical containing from 1 to 5 carbon atoms, an aminoalkyl or alkylaminoalkyl radical (the alkyl moieties each containing from 1 to 5 carbon atoms), an aryl radical, or a cycloalkyl radical, or R⁴ and R⁵ together with the nitrogen atom represent a saturated, substituted or unsubstituted, heterocycle optionally containing another hetero atom; and acid addition salts thereof.

Where R¹ represents a halogen atom, it may conveniently be a fluorine, chlorine or bromine atom, but is preferably a chlorine atom.

Where R² represents a halogen atom, it too may conveniently be a fluorine, chlorine or bromine atom, but is preferably a fluorine or chlorine atom. Furthermore, the halogen atom R² is preferably in the *ortho*-position.

R³ is most preferably a hydrogen atom.

Where either of R⁴ and R⁵ represents an alkyl radical, it may conveniently be a methyl, ethyl, *n*-propyl, *isopropyl*, *n*-butyl, *t*-butyl or pentyl radical, but is preferably a methyl, ethyl, *n*-propyl, *n*-butyl or *t*-butyl radical.

Where either of R⁴ and R⁵ represents a hydroxyalkyl radical, the alkyl moiety may conveniently be a methyl, ethyl, propyl, butyl or pentyl radical, but is preferably an ethyl radical.

Where either of R⁴ and R⁵ represents an

aminoalkyl or alkylaminoalkyl radical (which latter term includes both monoalkyl- and dialkylaminoalkyl), each of the alkyl moieties may conveniently be a methyl, ethyl, propyl or butyl radical, but is preferably a methyl or ethyl radical. Preferably R^4 and/or R^5 represent an aminomethyl, aminoethyl, dimethylaminoethyl or diethylaminoethyl radical, but may also represent an aminopropyl, aminobutyl, methylaminomethyl, methylaminoethyl or dimethylaminopropyl radical.

When either of R^4 and R^5 represents an aryl radical this may be mono- or di-nuclear—thus, for example, phenyl or naphthyl. The phenyl radical is preferred.

Where either of R^4 and R^5 represents a cycloalkyl radical, it is conveniently one containing from 3 to 8 carbon atoms, and is preferably a cyclohexyl radical.

R^4 and R^5 may be the same—they each may be, for example, a methyl group—or different, and when they are different one of them is preferably hydrogen.

Where R^4 and R^5 , together with the conjoining nitrogen atom, form a heterocyclic grouping, this grouping is saturated, may be substituted or unsubstituted, and may optionally contain a second heteroatom. Typical examples of unsubstituted heterocyclic groupings are pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl and piperazinyl. Preferred substituents for such heterocyclic groupings are alkyl radicals containing from 1 to 5 carbon atoms, such as methyl, ethyl and *n*-propyl; hydroxyalkyl radicals containing from 1 to 5 carbon atoms, such as hydroxyethyl; dialkylphosphinylalkyl radicals, each alkyl moiety of which contains from 1 to 5 carbon atoms, such as methyl; cycloalkylalkyl radicals containing from 3 to 6 carbon atoms in the cycloalkyl moiety and from 1 to 5 carbon atoms in the alkyl moiety, such as cyclopropylmethyl; alkenyl radicals containing from 2 to 5 carbon atoms, such as allyl; aryl radicals, such as phenyl; and nitrogen heterocyclic radicals, such as 1-phenyl-4-oxo-5-imidazolyl. Typical examples of substituted heterocyclic groupings are the 4-alkyl-piperazin-1-yls and especially 4-methyl-, 4-ethyl- and 4-propyl-piperazin-1-yl; the 4-hydroxyalkyl-piperazin-1-yls and especially 4- β -hydroxyethyl-piperazin-1-yl; the 4-dialkylphosphinylalkyl-piperazin-1-yls and especially 4-dimethylphosphinylmethyl-piperazin-1-yl; the 4-cycloalkylalkyl-piperazin-1-yls and especially 4-cyclopropylmethyl-piperazin-1-yl, 4-alkenyl-piperazin-1-yls and especially 4-allyl-piperazin-1-yl; 4-phenyl-piperazin-1-yl; and 4-(1'-phenyl-4'-oxo-5'-imidazolyl)-piperidin-1-yl.

Within the broad area encompassed by general formula I, the following smaller groups of compounds, and their acid addition salts, are preferred:

a) the imidazolobenzodiazepines of general formula I wherein either R^4 and R^5 , which may be the same or different, each represents a hydrogen atom, an alkyl radical containing from 1 to 5 carbon atoms, a hydroxyethyl radical, a dimethyl- or diethylaminoethyl radical, a phenyl radical, or a cyclohexyl radical, or R^4 and R^5 together with the nitrogen atom form a pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazin-1-yl, 4-alkyl-piperazin-1-yl, 4-hydroxyalkyl-piperazin-1-yl, 4-phenyl-piperazin-1-yl or 4-(1'-phenyl-4'-oxo-5'-imidazolyl)-piperidin-1-yl radical;

b) the imidazolobenzodiazepines of general formula I wherein R^1 represents a chlorine atom or a nitro radical, R^2 represents a hydrogen atom, a chlorine atom or a fluorine atom, R^3 represents a hydrogen atom, and either R^4 and R^5 , which may be the same or different, each represents a hydrogen atom, a straight alkyl radical containing from 1 to 5 carbon atoms, a hydroxyethyl radical, a phenyl radical, or a cyclohexyl radical, or R^4 and R^5 together with the nitrogen atom form a piperidinyl, morpholinyl, piperazin-1-yl, 4-alkyl-piperazin-1-yl or 4- β -hydroxyethyl-piperazin-1-yl radical;

c) the imidazolobenzodiazepines of general formula I wherein R^1 represents a chlorine atom or a nitro radical, R^2 represents a hydrogen, chlorine or fluorine atom, R^3 represents a hydrogen atom, and either R^4 represents a hydrogen atom and R^5 represents a methyl, ethyl, propyl or butyl radical, or R^4 and R^5 together with the nitrogen atom form a piperazin-1-yl, 4-methyl-piperazin-1-yl, 4-ethyl-piperazin-1-yl, 4-propyl-piperazin-1-yl or 4- β -hydroxyethyl-piperazin-1-yl radical;

d) the imidazolobenzodiazepines of general formula I wherein R^1 represents a chlorine atom or a nitro radical, R^2 represents a hydrogen, chlorine or fluorine atom, R^3 represents a hydrogen atom, and R^4 and R^5 together with the nitrogen atom form a 4-methyl-piperazin-1-yl, 4-ethyl-piperazin-1-yl or 4-*n*-propyl-piperazin-1-yl radical;

e) the imidazolobenzodiazepines of general formula I wherein R^1 represents a hydrogen atom, a chlorine atom or a nitro radical, R^2 represents a hydrogen atom, a chlorine atom or a fluorine atom, R^3 represents a hydrogen atom and R^4 and R^5 together with the nitrogen atom form a 4-dialkylphosphinylalkyl-piperazin-1-yl radical; and

f) the imidazolobenzodiazepines of general formula I wherein R^1 represents a hydrogen atom, a chlorine atom or a nitro radical, R^2 represents a hydrogen atom or a chlorine atom, R^3 represents a hydrogen atom and R^4 and R^5 together with the nitrogen atom form a 4-dimethylphosphinylmethyl-piperazin-1-yl radical.

The imidazolobenzodiazepines I may be in the form of acid addition salts, and these may be salts with mineral or organic acids. Typical mineral acids are hydrochloric, hydrobromic, hydroiodic, nitric, sulphuric and phosphoric acids, while typical organic acids are acetic, formic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic, aspartic, alkanesulphonic and arylsulphonic acids. Preferred acid addition salts are the tartrates and alkanesulphonates, and the methanesulphonates are especially preferred.

There are further preferred groups of compounds of the invention in the form of acid addition salts. These are as follows:—

g) acid addition salts of the imidazolobenzodiazepines of general formula I wherein R¹ represents a hydrogen atom, a chlorine atom or a nitro radical, R² represents a hydrogen atom, a chlorine atom or a fluorine atom, R³ represents a hydrogen atom and R⁴ and R⁵ together with the nitrogen atom form a 4-alkyl-piperazin-1-yl radical; and

h) the tartrates and alkanesulphonates (particularly methanesulphonates) of the imidazolobenzodiazepines of general formula I wherein R¹ represents a chlorine atom or a nitro radical, R² represents a hydrogen atom or a chlorine atom, R³ represents a hydrogen atom and R⁴ and R⁵ together with the nitrogen atom form a 4-methyl-piperazin-1-yl or a 4-ethyl-piperazin-1-yl radical.

Specifically preferred imidazolobenzodiazepines of general formula I and their salts are:

8 - chloro - 1,2 - dihydro - 2 - (4 - methyl-piperazin - 1 - yl)methylene - 6 - phenyl-4H - imidazo[1,2 - a][1,4]benzodiazepin - 1-one;

8 - chloro - 1,2 - dihydro - 2 - (4 - methyl-piperazin - 1 - yl)methylene - 6 - phenyl-4H - imidazo[1,2 - a][1,4]benzodiazepin - 1-one tartrate;

8 - chloro - 1,2 - dihydro - 2 - (4 - β -hydroxyethyl - piperazin - 1 - yl)methylene-6 - phenyl - 4H - imidazo[1,2 - a][1,4]-benzodiazepin-1-one;

8 - chloro - 1,2 - dihydro - 2 - (4 - methyl-piperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one;

8 - chloro - 1,2 - dihydro - 2 - (4 - methyl-piperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one tartrate;

8 - nitro - 1,2 - dihydro - 2 - (4 - methyl-piperazin - 1 - yl)methylene - 6 - phenyl-4H - imidazo[1,2 - a][1,4]benzodiazepin - 1-one;

8 - chloro - 1,2 - dihydro - 2 - (n - butyl-amino)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one;

8 - chloro - 1,2 - dihydro - 2 - (4 - methyl-piperazin - 1 - yl)methylene - 6 - (o - fluoro-

phenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one; 65

8 - chloro - 1,2 - dihydro - 2 - (n - propyl-amino)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one;

8 - nitro - 1,2 - dihydro - 2 - (4 - methyl-piperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one; 70

8 - nitro - 1,2 - dihydro - 2 - (4 - methyl-piperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one methanesulphonate; 75

8 - nitro - 1,2 - dihydro - 2 - (4 - methyl-piperazin - 1 - yl)methylene - 6 - (o - fluoro-phenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one; 80

8 - chloro - 1,2 - dihydro - 2 - (4 - ethyl-piperazin - 1 - yl)methylene - 6 - phenyl-4H - imidazo[1,2 - a][1,4]benzodiazepin - 1-one; 85

8 - chloro - 1,2 - dihydro - 2 - (4 - n-propyl - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one;

8 - chloro - 1,2 - dihydro - 2 - (4 - ethyl-piperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one; 90

8 - chloro - 1,2 - dihydro - 2 - (4 - ethyl-piperazin - 1 - yl)methylene - 6 - (o - fluoro-phenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one; 95

8 - nitro - 1,2 - dihydro - 2 - (4 - ethyl-piperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one; 100

8 - nitro - 1,2 - dihydro - 2 - (4 - ethyl-piperazin - 1 - yl)methylene - 6 - (o - fluoro-phenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one; 105

8 - chloro - 1,2 - dihydro - 2 - (ethyl-amino)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one;

8 - chloro - 1,2 - dihydro - 2 - (4 - dimethylphosphinylmethyl - piperazin - 1 - yl)-methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one; 110

8 - chloro - 1,2 - dihydro - 2 - (4 - dimethylphosphinylmethyl - piperazin - 1 - yl)-methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one; 115

1,2 - dihydro - 2 - (4 - dimethylphosphinylmethyl - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one; and 120

8 - nitro - 1,2 - dihydro - 2 - (4 - dimethylphosphinylmethyl - piperazin - 1 - yl)-methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one.

Of these specifically preferred compounds, 8 - nitro - 1,2 - dihydro - 2 - (4 - methyl-piperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzo- 125

diazepin-1-one methanesulphonate has shown a particularly remarkable pharmacological activity.

5 The imidazolobenzodiazepines of general formula I may conveniently be prepared by a process starting from corresponding compounds unsubstituted at the 2-position, and these in their turn can be prepared from corresponding 2-alkoxycarbonyl- or 2-carboxy-
10 methylamino-benzodiazepines. These processes, which form another aspect of this invention, are set out in the Reaction Scheme shown in the accompanying drawings, and will now be described. In this description, the
15 Roman numerals refer to the general formulae in the Reaction Scheme, and each substituent group symbol is, unless stated otherwise, as first defined.

20 This invention provides processes for the preparation of compounds of general formula I wherein R^3 represents a hydrogen atom and R^4 and R^5 each represent a methyl radical, in which an 8 - R^1 - 1,2 - dihydro - 6 - (R^2 - phenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one V is reacted with a dimethyl-
25 formamide acetal VI (wherein "alk" represents an alkyl radical containing from 1 to 5 carbon atoms) to give the desired 8 - R^1 - 1,2 - dihydro - 2 - (dimethylamino)methylene - 6 - (R^2 - phenyl) - 4H - imidazo[1,2 - a][1,4]-
30 benzodiazepin-1-one Ia.

35 The reaction with the acetal VI is conveniently carried out in an anhydrous organic solvent—for example, an arene such as benzene—and in the presence of a base, which is preferably a nitrogenous base such as an amine, for instance triethylamine.

40 This invention also provides processes for the preparation of compounds of general formula I wherein R^3 , R^4 and R^5 each represent a methyl radical, in which an 8 - R^1 - 1,2 - dihydro - 6 - (R^2 - phenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one V is reacted with an N-dimethyl-acetamide VII to
45 give the desired 8 - R^1 - 1,2 - dihydro - 2 - (1'-dimethylamino)ethylidene - 6 - (R^2 - phenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one Ib.

50 The reaction with the acetamide VII is conveniently carried out in an anhydrous organic solvent—for example, a chlorinated alkane such as methylene chloride—at a temperature below room temperature (and preferably lower than 10° C), and in the presence of a condensation promotor—for example, a halo-
55 genated derivative such as phosphorus oxychloride.

60 The imidazolobenzodiazepin starting material V may conveniently be prepared by subjecting either a 2-carboxymethylamino- or 2 - alkoxycarbonylmethylamino - 7 - R^1 - 5 - (R^2 - phenyl) - 3H - 1,4 - benzodiazepin IV (wherein R represents a hydrogen atom or an alkyl radical) respectively to the action of a

dehydrating agent or to pyrolysis to give the desired product.

The dehydrating agent reacted with the acid IV is conveniently a carbodiimide, such as dicyclohexylcarbodiimide, and the reaction is advantageously performed in a chlorinated
70 alkane such as methylene chloride. The pyrolysis of the ester IV is conveniently carried out in a high boiling point solvent such as an arene like toluene.

75 The benzodiazepine starting material IV which it itself a new compound when R is other than an ethyl group, may conveniently be prepared by reacting 7 - R^1 - 1,3 - dihydro - 5 - (R^2 - phenyl) - 2H - 1,4 - benzodiazepine-2-thione II with glycine (aminoacetic acid) or an alkyl ester thereof III to give the
80 desired product.

85 The reaction is advantageously carried out in an organic solvent, preferably an alcohol such as ethanol, and at a high temperature, which is conveniently the boiling temperature of the reaction mixture.

90 The invention further provides processes for the preparation of compounds of general formula I wherein R^4 and R^5 do not both represent methyl radicals, in which 2-(dimethylamino)methylene - imidazolobenzodiazepin-1-one. Ia or 2-(1'-dimethylamino)-ethylidene - imidazolobenzodiazepin - 1 - one Ib is transaminated by reaction with an amine
95 VIII (wherein R^4 and R^5 are as defined hereinbefore, except that they do not both represent a methyl radical) to give the desired 8 - R^1 - 1,2 - dihydro - 2 - (substituted amino)methylene- or 8 - R^1 - 1,2 - dihydro - 2 - (1' - substituted amino)ethylidene - 6 - (R^2 - phenyl) - 1H,4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one Ic or Id, wherein
100 R^4 and R^5 are as just desired.

105 Naturally, the compound Ia or Ib is preferably prepared by a process as described and claimed herein.

110 The reaction with the amine VIII is conveniently carried out in an anhydrous organic solvent—for example, an arene such as toluene—and at a high temperature; which is preferably the boiling temperature of the reaction mixture. It will be understood that when it is desired to form a compound I wherein R^4 and R^5 are both hydrogen the
115 compound VIII used in the transamination will be ammonia itself.

120 The formed imidazolobenzodiazepines Ic, or Id may if desired, be further reacted to convert them into different compounds of general formula Ic or Id. In particular, compounds wherein R^4 and R^5 together with the nitrogen atom represent a heterocycle may be further reacted so as to introduce substituents onto the heterocyclic ring.
125

When it is desired to prepare a compound Ic or Id wherein R_4 and R_5 form with the conjoined nitrogen atom a R_6 -piperazin-1-yl

radical, wherein R_4 represents a cycloalkyl-alkyl radical, an alkenyl radical or a 4-dialkyl-phosphinylalkyl radical, one may first prepare a compound Ic or Id, wherein R_4 and R_5 form a piperazin-1-yl radical with the conjoined nitrogen atom, and then react this compound with a halo- R_6 compound to form the desired product.

When it is desired to prepare a compound Ic or Id wherein R^4 and R^5 form, together with the conjoined nitrogen atom, a 4-dialkyl-phosphinylalkyl-piperazin-1-yl radical, one may first prepare a compound Ic or Id, wherein R^4 and R^5 form, with the nitrogen atom, a piperazin-1-yl radical with the conjoined nitrogen atom, and then react this compound with a haloalkyl-dialkylphosphine oxide to form the desired product.

The preferred haloalkyl-dialkylphosphine oxides for use in such a conversion are the chloroalkyl-dialkylphosphine oxides, and the reaction is preferably carried out in an organic solvent—for example, an arene such as toluene.

The formed compounds Ia, Ib, Ic and Id may be salified by normal methods. In another aspect this invention provides processes for the preparation of acid addition salts of compounds of general formula I, in which an imidazolobenzodiazepine I is reacted, in substantially stoichiometric proportions, with a mineral or organic acid to form the desired acid addition salt.

The salification reaction is conveniently effected in an organic solvent or a mixture of organic solvents, such as one or more alkanols—for example, methanol or ethanol—and/or one or more alkyl halides—for example, methylene chloride.

This invention extends, of course, to imidazolobenzodiazepin-1-ones Ia, Ib, Ic or Id, and acid addition salts thereof, whenever prepared by a process as described and claimed herein.

The imidazolobenzodiazepin-1-ones of the invention possess very interesting pharmacological properties. They are endowed especially with remarkable sedative, hypnotic, anxiolytic, tranquillising, anticonvulsive and myorelaxant properties which may make them of use as medicaments in the treatment of states of agitation or irritability, of aggression, of insomnia, of certain psychosomatic syndromes, of certain character and behavioural disorders, and of certain spasms or muscular contractions.

However, before any of the compounds of this invention may be used in medicine, they should preferably be formed into pharmaceutical compositions by association with suitable pharmaceutical vehicles.

The term "pharmaceutical" is used herein to exclude any possibility that the nature of the vehicle, considered of course, in relation to the route by which the composition is intended to be administered, could be harmful rather than

beneficial. The choice of a suitable mode of presentation, together with an appropriate vehicle, is believed to be within the competence of those accustomed to the preparation of pharmaceutical formulations.

Accordingly, in yet another aspect this invention provides pharmaceutical compositions containing one or more imidazolobenzodiazepin-1-ones I, or pharmaceutically-acceptable acid addition salts thereof, in association with a suitable pharmaceutical vehicle.

Preferred pharmaceutical compositions of the invention are those which contain, as active material, one or more compounds selected from the following:—

a) the imidazolobenzodiazepines of general formula I falling within the preferred groups a) to f) set out hereinbefore, and their acid addition salts;

b) 8-chloro-1,2-dihydro-2-(4-methyl-piperazin-1-yl)methylene-6-phenyl-4H-imidazo[1,2-a][1,4]benzodiazepin-1-one and its tartrate, 8-chloro-1,2-dihydro-2-(4-methyl-piperazin-1-yl)methylene-6-(o-chlorophenyl)-4H-imidazo[1,2-a][1,4]benzodiazepin-1-one, 8-chloro-1,2-dihydro-2-(4-methyl-piperazin-1-yl)methylene-6-(o-fluorophenyl)-4H-imidazo[1,2-a][1,4]benzodiazepin-1-one, 8-nitro-1,2-dihydro-2-(4-methyl-piperazin-1-yl)methylene-6-(o-chlorophenyl)-4H-imidazo[1,2-a][1,4]benzodiazepin-1-one and its methone sulphonate, 8-nitro-1,2-dihydro-2-(4-methyl-piperazin-1-yl)methylene-6-(o-fluorophenyl)-4H-imidazo[1,2-a][1,4]benzodiazepin-1-one and 8-chloro-1,2-dihydro-2-(4-dimethylphosphinylmethyl-piperazin-1-yl)methylene-6-phenyl-4H-imidazo[1,2-a][1,4]benzodiazepin-1-one; and

c) 8-nitro-1,2-dihydro-2-(4-methyl-piperazin-1-yl)methylene-6-(o-chlorophenyl)-4H-imidazo[1,2-a][1,4]benzodiazepin-1-one.

The compositions of this invention may be administered orally, transcutaneously or rectally, and in respect of these modes the "pharmaceutical vehicle" is preferably:—

a) the ingestible excipient of a tablet, such as a coated or sublingual tablet, or of a pill; the ingestible container of a capsule or cachet; the ingestible pulverulent solid carrier of a powder; or the ingestible liquid medium of a syrup, solution, suspension or elixir;

b) a sterile injectable liquid solution or suspension medium; or

c) a base material of low melting point capable of releasing the active ingredient to perform its pharmacological function, which base material when appropriately shaped forms a suppository.

The vehicle may, as appropriate, be a solid (such as talc, gum arabic, lactose, starch, an animal or vegetable fat, magnesium stearate, or cocoa butter), or it may be an aqueous or non-aqueous liquid (such as an animal or vegetable oil, a paraffin derivative, or a glycol). It may if desired incorporate wetting, dispersing or emulsifying agents, and preserving agents.

Whilst the modes of presentation just listed represent those most likely to be employed, they do not necessarily exhaust the possibilities.

The compositions of this invention may preferably be administered in the form of tablets, of injectable solutions or suspensions dispensed in single-dose ampoules or multi-dose phials, and of suppositories.

Whilst the dosages of the pharmacologically-active ingredient will, to a certain degree, depend upon the route by which the compositions are to be administered, nevertheless, by way of general indication, it may be said the useful dose ranges from 1 mg to 50 mg active ingredient per day for an adult, a unit dose containing from 0.5 mg to 20 mg active ingredient.

The following Examples, Formulations and Test Results are now given, though only by way of illustration, to show details of various aspects of the invention.

EXAMPLES.

Example 1.

8-chloro-1,2-dihydro-2-(dimethylamino)-methylene-6-phenyl-4H-imidazo-[1,2-a]-[1,4]benzodiazepin-1-one (Ia)

Stage A: 2 - carboxymethylamino - 7-chloro - 5 - phenyl - 3H - 1,4-benzodiazepine (IV)

7 - Chloro - 1,3 - dihydro - 5 - phenyl-2H - 1,4 - benzodiazepine - 2 - thione II (3.5 g), glycine III (5.5 g) and sodium carbonate (5.5 g) were suspended in ethanol (100 ml) and water (30 ml), and were stirred and refluxed for 1 hour. The suspension was then poured into water to give a clear solution, and this was acidified to pH 4 with 2N HCl, and extracted with CHCl₃. Some solid precipitated from the extracts, and was filtered off.

The organic layer was dried over MgSO₄ and evaporated to give a gum that crystallized on trituration with methanol. This solid, and the solid filtered off above, was crystallized from a large amount of ethanol to give 2-carboxymethylamino - 7 - chloro - 5 - phenyl-3H - 1,4 - benzodiazepine, 3.1 g (77%). m.p. = 215°—220° C.

Stage B: 8 - chloro - 1,2 - dihydro - 6-phenyl - 4H - imidazo[1,2 - a]-[1,4]benzodiazepin - 1 - one (V)
2 - Carboxymethylamino - 7 - chloro-5 - phenyl - 3H - 1,4 - benzodiazepine IV (2.5 g) was suspended in dry CH₂Cl₂

(120 ml), and stirred, and dicyclohexylcarbodiimide (2.1 g) was added. The suspension was stirred at room temperature for 3 hours, then filtered, and the filtrate was evaporated to give 8 - chloro - 1,2 - dihydro - 6 - phenyl-4H - imidazo[1,2 - a][1,4]benzodiazepin - 1-one V in the form of a colourless oil, which was used as it is in the following stage.

Stage C: 8 - chloro - 1,2 - dihydro - 2-(dimethylaminomethylene - 6 - phenyl - 4H - imidazo[1,2 - a]-[1,4]benzodiazepin - 1 - one (Ia)

The 8 - chloro - 1,2 - dihydro - 6 - phenyl-4H - imidazo[1,2 - a][1,4]benzodiazepin - 1-one V obtained in stage B above was dissolved in dry benzene, and dimethylformamide diethyl acetal VI (1.5 g) and triethylamine (1 ml) was added. The solution was stirred at room temperature for 1.5 hours, then evaporated to give a brown-yellow residue. Recrystallization from ethylacetate/methanol gave pale yellow rods of 8 - chloro - 1,2 - dihydro - 2 - (dimethylamino)methylene - 6-phenyl - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one Ia, 2.7 g (97%). m.p. = 264° - 5° C.

Analysis: C₂₀H₁₇Cl N₄ O = 364.9

Calculated:

C% 65.85 H% 4.66 N% 15.37 Cl% 9.74

Found:

65.87 4.67 15.37 9.74

I.R. Spectra (KBr disc):

C=O at 1690 cm⁻¹; C=N at 1621 cm⁻¹.

Examples 2 to 6.

Using a similar method to that used in Example 1, the following compounds IV, V and Ia were prepared:

Example

2. Compound IV: 2 - carboxymethylamino - 7 - nitro - 5 - phenyl - 3H - 1,4 - benzodiazepine.

Compound V: 8 - nitro - 1,2 - dihydro - 6 - phenyl - 4H - imidazo-[1,2 - a][1,4]benzodiazepin - 1-one.

Compound Ia: 8 - nitro - 1,2 - dihydro - 2 - (dimethylamino)-methylene - 6 - phenyl - 4H-imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.

3. Compound IV: 2 - carboxymethylamino - 7 - chloro - 5 - o - chlorophenyl - 3H - 1,4 - benzodiazepine.

Compound V: 8 - chloro - 1,2 - dihydro - 6 - o - chlorophenyl - 4H-imidazo[1,2 - a][1,4]benzodiazepine - 1 - one.

Compound Ia: 8 - chloro - 1,2 - dihydro - 2 - (dimethylamino)methylene - 6 - o - chlorophenyl - 4H-imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.

4. Compound IV: 2 - carboxymethyl-amino - 7 - nitro - 5 - *o* - chlorophenyl - 3H - 1,4 - benzodiazepine. 25
Compound V: 8 - nitro - 1,2 - dihydro - 6 - *o* - chlorophenyl - 4H-imidazo[1,2 - *a*][1,4]benzodiazepin - 1 - one. 30
Compound Ia: 8 - nitro - 1,2 - dihydro - 2 - (dimethylamino)methylene - 6 - *o* - chlorophenyl - 4H-imidazo[1,2 - *a*][1,4]benzodiazepin - 1 - one. 35
5. Compound IV: 2 - carboxymethyl-amino - 7 - chloro - 5 - *o* - fluorophenyl - 3H - 1,4 - benzodiazepine. 40
Compound V: 8 - chloro - 1,2 - dihydro - 6 - *o* - fluorophenyl - 4H-imidazo[1,2 - *a*][1,4]benzodiazepin - 1 - one.
Compound Ia: 8 - chloro - 1,2 - dihydro - 2 - (dimethylamino)methylene - 6 - *o* - fluorophenyl - 4H-

In each case the compound III was glycine, the compound VI was dimethylformamide diethyl acetal, the compound V was used without further purification, and the crystallization solvent for the compound Ia was methanol. The data for these compounds (excluding the compounds V) is summarized in Table I below.

TABLE 1

Example	Compound IV			R ¹	R ²	Compound Ia	
	Yield %	M.p. °C	Crystallisation solvent			Yield %	M.p. °C
2	66	154-5	MeOH	NO ₂	H	43	227-8
3	75	136-9	MeOH-Et ₂ O	Cl	<i>o</i> -Cl	53	288-90
4	83	158-61	Et ₂ O	NO ₂	<i>o</i> -Cl	78	253-5
5	69	gum	—	Cl	<i>o</i> -F	63	257-60
6	44	—	Et ₂ O	NO ₂	<i>o</i> -F	80	228-31

- 45 Example 7.
8-chloro-2-[1' - (dimethylamino)ethylidene]-1,2-dihydro-6-phenyl-4H-imidazo-1,2-*a*][1,4]benzodiazepin-1-one (Ib)
50 8 - Chloro - 1,2 - dihydro - 6 - phenyl - 4H - imidazo[1,2 - *a*][1,4]benzodiazepin - 1 - one V, prepared as described in Stage B of Example 1, was dissolved in dry methylene chloride (200 ml) with dimethylacetamide VII (2.0 g). The solution was cooled to 0° C, and phosphorus oxychloride (3.7 g) was added dropwise over 5 minutes with good stirring. The solution was then stirred at room temperature over 20 hours, and poured into saturated NaHCO₃ solution (500 ml). The mixture was stirred until the evolution of CO₂ ceased, the organic layer was removed, and the aqueous layer was extracted with methylene chloride (2 × 100 ml). The com-

bined organic extracts were washed with saturated NaHCO₃ solution, and water, dried over MgSO₄, and evaporated to give a yellow solid. Recrystallization of this solid from chloroform/diethyl ether gave 8 - chloro - 2 - [1' - (dimethylamino)ethylidene] - 1,2 - dihydro - 6 - phenyl - 4H - imidazo[1,2 - *a*][1,4]benzodiazepin - 1 - one Ib, 2.3 g (40%). m.p. = 251-2° C.

Analysis: C₂₁H₁₈Cl N₂ O = 378.9

Calculated:

C% 66.58 H% 5.02 N% 14.79 Cl% 9.38

Found:

66.32 4.91 14.77 9.02

I.R. Spectra (KBr disc):

C = O at 1653 cm⁻¹; C = N at 1610 cm⁻¹

Example 8.

8-chloro-1,2-dihydro-2-(4-methylpiperazin-1-yl)methylene-6-phenyl-4H-imidazo[1,2-a][1,4]benzodiazepin-1-one (Ic), and its tartrate

- 5 A) 8 - Chloro - 1,2 - dihydro - 2 - (dimethylamino)methylene - 6 - phenyl - 4H-imidazo[1,2 - a][1,4]benzodiazepin - 1 - one Ia (obtained as in Stage C of Example 1) 10 (2.3 g) and N-methyl-piperazine (4.0 g) were stirred under reflux in dry toluene (50 ml) for 24 hours. On cooling, crystals separated out, and were filtered off. Evaporation of the solvent gave a pale yellow solid, 15 and this was treated with methanol, and filtered. The two sets of solids were combined and recrystallized from methanol/ethyl acetate to give 8 - chloro - 1,2 - dihydro-2 - ((4 - methylpiperazin - 1 - yl)methylene-6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one Ic 2.3 g (87%). 20 m.p. = 255°/6° C.

Analysis: $C_{23}H_{22}ClN_5O = 419.9$

Calculated:

- 25 C% 65.80 H% 5.24 N% 16.69 Cl% 8.46

Found:

65.64 5.27 16.63 8.56

I.R. Spectra (KBr disc):

C = O at 1705 cm^{-1} ; C = N at 1635 cm^{-1}

- 30 B) The tartrate salt of 8 - chloro - 1,2-dihydro - 2 - (4 - methylpiperazin - 1 - yl)-methylene - 6 - phenyl - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one Ic was prepared by adding a stoichiometric amount in 35 methanol of tartaric acid to the 8 - chloro-1,2 - dihydro - 2 - (4 - methyl - piperazin-1 - yl)methylene - 6 - phenyl - 4H - imidazo-[1,2 - a][1,4]benzodiazepine - 1 - one Ic. The formed crude salt was recrystallized from 40 methanol to give the desired product. M.Pt. = 146—150° C.

Analysis: $C_{27}H_{28}ClN_5O_7 = 570.1$

Calculated:

- 45 C% 56.89 H% 4.92 N% 11.29 Cl% 6.23

Found:

56.44 4.93 11.79 5.93

I.R. Spectra (KBr disc):

- 50 OH at 3400 cm^{-1} and 2500 cm^{-1} ; C = O at 1730 $^{-1}$ and 1960 cm^{-1} ; C = N at 1630 cm^{-1} .

Examples 9 to 46.

- 55 In these Examples, except where it is stated otherwise, a method analogous to that used in the preparation of 8 - chloro - 1,2 - dihydro - 2 - (4 - methylpiperazin - 1 - yl)-methylene - 6 - phenyl - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one Ic in Example 8 was used to prepare the following compounds I:

Example

Compound I

9. 8 - Chloro - 1,2 - dihydro - 2 - (4-morpholinyl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a]-[1,4]benzodiazepin - 1 - one.
10. 8 - Chloro - 1,2 - dihydro - 2 - (4- β - hydroxyethyl - piperazin - 1-yl)methylene - 6 - phenyl - 4H-imidazo[1,2 - a][1,4]benzodiazepin - 1 - one. 65
11. 8 - Chloro - 1,2 - dihydro - 2 - (4-phenyl - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo-[1,2 - a][1,4]benzodiazepin - 1 - one. 70
12. 8 - Chloro - 1,2 - dihydro - 2 - (4-methyl - piperazin - 1 - yl)-methylene - 6 - (o - chlorophenyl)-4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one. 75
12B. 8 - Chloro - 1,2 - dihydro - 2 - (4-methyl - piperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H-imidazo[1,2 - a][1,4]benzodiazepin - 1 - one tartrate. 80

Method: analogous to Example 8B

- 85 13. 8 - Nitro - 1,2 - dihydro - 2 - (4-methyl - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo-1,2 - a][1,4]benzodiazepin - 1 - one. 90
14. 8 - Chloro - 1,2 - dihydro - 2 - piperazin - 1 - yl)methylene - 6 - phenyl-4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.
15. 8 - Chloro - 1,2 - dihydro - 2 - (n-butyl - amino)methylene - 6 - phenyl - 4H - imidazo[1,2 - a]-[1,4]benzodiazepin - 1 - one. 95
16. 8 - Chloro - 1,2 - dihydro - 2 - (amino)methylene - 6 - phenyl-4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one. 100

Method:

- 8 - Chloro - 1,2 - dihydro - 2 - (dimethyl-amino)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one Ia (2.1 g) was suspended in dry methanol (100 ml). The suspension was stirred, cooled in a dry-ice/acetone bath, and ammonia gas VIII was bubbled through for 15 minutes. The 110 suspension was then warmed to room temperature, stirred for a further two days and the solvent was evaporated. The solid residue was recrystallized from methanol/ethyl acetate to give 8 - chloro - 1,2 - dihydro - 2 - (amino)-methylene - 6 - phenyl - 4H - imidazo [1,2-a][1,4]benzodiazepin - 1 - one Ic; 1.9 g (98%). m.p. = 265°—7° C. 115

Example	Compound I
17.	8 - Chloro - 1,2 - dihydro - 2 - (1-piperidinyl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.
18.	8 - Chloro - 1,2 - dihydro - 2 - (4-thiomorpholinyl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.
19.	8 - Chloro - 1,2 - dihydro - 2 - diethylaminoethylamino)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.
20.	8 - Chloro - 1,2 - dihydro - 2 - (N-methyl - N - (dimethylamino)ethylamino)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.
21.	8 - Chloro - 1,2 - dihydro - 2 - (methylamino)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.
22.	8 - Chloro - 1,2 - dihydro - 2 - (cyclohexylamino)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.
23.	8 - Chloro - 1,2 - dihydro - 2 - (4-methyl - piperazin - 1 - yl)methylene - 6 - (o - fluorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.
24.	8 - Chloro - 1,2 - dihydro - 2 - [4-(1' - phenyl - 4' - oxo - 5' - imidazolyl)piperidin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.
25.	8 - Chloro - 1,2 - dihydro - 2 - (phenylamino)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.
26.	8 - Chloro - 1,2 - dihydro - 2 - [1-4 - methyl - piperazin - 1 - yl)ethylidene] - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]dibenzodiazepin - 1 - one.

Method:

8 - Chloro - 2 - [1 - (dimethylamino)ethylidene] - 1,2 - dihydro - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one Ib (Example 7) (2.3 g) and N-methyl-piperazine VIII (15 ml) were stirred at 120° C under nitrogen for 9 hours. The cooled solution was poured into water, NaCl was added to complete precipitation, and the brown precipitate was filtered off, dissolved in CHCl₃, washed with water, dried over MgSO₄, and evaporated to give a dark red oil. The oil crystallized on triturating with diethylether/methanol, and was recrystallized from ethyl acetate to give 8 - chloro - 2 - [1 - (4-methylpiperazin - 1 - yl)ethylidene] - 1,2-dihydro - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one Id, 1.0 g (38%). m.p. = 193°—5° C.

Example	Compound I	
27.	8 - Chloro - 1,2 - dihydro - 2 - (t-butylamino)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.	65
28.	8 - Chloro - 1,2 - dihydro - 2 - (hydroxyethylamino)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.	70
29.	8 - Chloro - 1,2 - dihydro - 2 - (n-propylamino)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.	75
30.	8 - Nitro - 1,2 - dihydro - 2 - (4-methyl - piperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.	80
31.	8 - Nitro - 1,2 - dihydro - 2 - (4-methyl - piperazin - 1 - yl)methylene - 6 - (o - fluorophenyl) - 4H - imidazo[1,2 - a][1,2]benzodiazepin - 1 - one.	85
32.	8 - Chloro - 1,2 - dihydro - 2 - (4-ethyl - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.	90
32B.	8 - Chloro - 1,2 - dihydro - 2 - (4-ethyl - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one tartrate.	95
Method: analogous to Example 8B		
33.	8 - Chloro 1,2 - dihydro - 2 - (4-n - propyl - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.	100
34.	8 - Chloro - 1,2 - dihydro - 2 - [4-(n - butyl) - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazol][1,2 - a][1,4]benzodiazepin - 1 - one.	105
35.	8 - Chloro - 1,2 - dihydro - 2 - [4-(isopropyl) - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.	110

Method:

8 - Chloro - 1,2 - dihydro - 2 - (piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one (the compound of Example 14, obtained as in Example 8) (1.5 g.), isopropyl iodide (2.5 g.) and sodium carbonate (3.0 g.) were stirred at 80° C in acetonitrile (25 ml) and methylene chloride (5 ml.) for 18 hours. The cooled solution was poured into water and extracted with chloroform. The extracts were washed with water, dried over MgSO₄, and evaporated to give a pale yellow solid. Recrystallisation of this solid from ethyl acetate gave 8 - chloro - 1,2 - dihydro - 2 - (4 - isopropyl-

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piperazin - 1 - yl)methylene - 6 - phenyl-4H - imidazo[1,2 - a][1,4]benzodiazepin-1-one 1c, 1.2 g. (73%). M.pt. = 146°-8° C.

Example

Compound I

- 5 36. 8 - Chloro - 1,2 - dihydro - 2 - (4-allyl - piperazin - 1 - yl)methylene-6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.

Method: analogous to Example 35.

- 10 37. 8 - Chloro - 1,2 - dihydro - 2 - (4-cyclopropylmethyl - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.

Method: analogous to Example 35.

- 15 38. 8 - Chloro - 1,2 - dihydro - 2 - (4-ethyl - piperazin - 1 - yl)methylene-6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.

- 20 39. 8 - Chloro - 1,2 - dihydro - 2 - (4-ethyl - piperazin - 1 - yl)methylene-6 - (o - fluorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.

- 25 40. 8 - Nitro - 1,2 - dihydro - 2 - (4-ethyl - piperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.

- 30 41. 8 - Nitro - 1,2 - dihydro - 2 - (4-ethyl - piperazin - 1 - yl)methylene-6 - (o - fluorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.

- 35 42. 8 - Chloro - 1,2 - dihydro - 2 - (ethylamino)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.

- 40 43. 8 - Chloro - 1,2 - dihydro - 2 - (4-dimethylphosphinylmethyl - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one.

Method:

8 - Chloro - 1,2 - dihydro - 2 - (piperazin-1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one (the compound of Example 14, obtained as in Example 8) (2.5 g.), chloromethyldimethylphosphine oxide (1.5 g.) and sodium carbonate (5.0 g.) were stirred under reflux in toluene (80 ml) for 3 days. The cooled suspension was distributed between chloroform and water, and the chloroform extract was separated, dried over MgSO₄, and evaporated to give a pale yellow oil which crystallized with methanol. The solid (unrequired by-product) was filtered off, and the filtrate was evaporated to give a pale orange oil. This oil was dissolved in chloroform and chromatographed on Kieselgel. 60. Elution with chloroform/methanol (5%) gave a pale yellow solid, which on recrystallization from methylene chloride/diethyl ether gave 8 - chloro - 1,2 - dihydro - 2 - (4 - dimethylphosphinylmethylpiperazin - 1 - yl)methylene - 6 - phenyl-4H - imidazo[1,2 - a][1,4]benzodiazepin-1 - one. 1c (1.25 g.) (41%). M.Pt. = 261°-2° C.

Example

Compound I

44. 8 - Chloro - 1,2 - dihydro - 2 - (4-n - propyl - piperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one. 75
- 45 8 - Chloro - 1,2 - dihydro - 2 - (ethylamino)methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one. 80
46. 8 - Chloro - 1,2 - dihydro - 2 - (n - propylamino)methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one. 85

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TABLE 2

Examples	Formula Ib/Ic					Analyses Found/Calculated				Infrared Spectra cm ⁻¹ (KBr Disc)			
	R ¹	R ²	-N(R ³)(R ⁵)	Melting point (°C)	Molecular Formula	M.Wt.	%C	%H	%N	%Cl	NH, OH	C-O	C-N
9	Cl	H	morpholinyl	223-4	C ₂₂ H ₁₉ ClN ₄ O ₂	406.9	64.89 64.95	4.68 4.68	13.79 13.78	8.87 8.73	-	1695	1630
10	Cl	H	4-β-hydroxyethyl-piperazin-1-yl	177-9	C ₂₄ H ₂₄ ClN ₅ O ₂	450.0	63.91 64.07	5.41 5.34	15.59 15.57	8.15 7.90	3380 (OH)	1690	1630
11	Cl	H	4-phenylpiperazin-1-yl	206-8	C ₂₈ H ₂₄ ClN ₅ O	482.0	69.68 69.77	5.10 4.98	14.39 14.54	7.48 7.37	-	1695	1630
12	Cl	Cl	4-methylpiperazin-1-yl	247-8	C ₂₃ H ₂₁ Cl ₂ N ₅ O	455.4	60.91 60.80	4.72 4.66	15.35 15.41	15.46 15.61	-	1695	1625
12B	Cl	Cl	"	155-160	C ₂₇ H ₂₇ Cl ₂ N ₅ O ₇	604.5	- 53.66	- 4.50	- 11.59	- 11.73	-	-	-
13	NO ₂	H	"	284-6	C ₂₃ H ₂₂ N ₆ O ₃	430.5	63.80 64.18	5.17 5.12	19.54 19.54	- -	-	1692	1635
14	Cl	H	piperazin-1-yl	233-5	C ₂₂ H ₂₀ ClN ₅ O	405.9	65.05 65.10	5.03 4.93	17.25 17.26	9.09 8.75	3300 (NH)	1695	1625
15	Cl	H	N-butylamino	165-7	C ₂₂ H ₂₁ ClN ₄ O	392.9	66.96 67.25	5.46 5.35	14.13 14.27	9.24 9.04	3200 (NH)	1690	1638
16	Cl	H	amino	265-7	C ₁₆ H ₁₃ ClN ₄ O	336.8	64.22 64.19	3.92 3.86	16.68 16.64	10.53 10.54	3320 3180(NH)	1690 1665	1640 1625
17	Cl	H	1-piperidinyl	249-50	C ₂₃ H ₂₁ ClN ₄ O	404.9	68.08 68.24	5.29 5.23	14.13 13.84	8.77 8.73	-	1690	1625

TABLE 2 (Continued)

Examples	Formula Ib/c					Analyses Found/Calculated				Infrared Spectra cm^{-1} (KBr Disc)			
	R ¹	R ²	-N(R ³)(R ⁵)	Melting point (°C)	Molecular Formula	M.Wt.	%C	%H	%N	%Cl	NH, OH	C=O	C=N
18	Cl	H	4-thiomorpholinyl	255-8	$\text{C}_{22}\text{H}_{19}\text{ClN}_4\text{OS}$	422.9	62.02 62.49	4.62 4.53	13.05 13.25	— 8.36	—	1700	1630
19	Cl	H	diethylamino-ethylamino	113-6	$\text{C}_{24}\text{H}_{28}\text{ClN}_5\text{O}$	436.0	66.38 66.13	6.28 5.97	16.26 16.07	8.04 8.15	3210 (NH)	1690 —	1640 1630
20	Cl	H	N-methyl-N-(dimethylamino)ethylamino	152-5	$\text{C}_{23}\text{H}_{28}\text{ClN}_5\text{O}$	422.0	65.33 65.49	5.71 5.37	16.27 16.60	8.50 8.38	—	1690	1630
21	Cl	H	methylamino	233-5	$\text{C}_{19}\text{H}_{19}\text{ClN}_4\text{O}$	350.9	64.86 65.07	4.46 4.31	15.74 15.98	10.20 10.08	3300 (NH)	1690	1620
22	Cl	H	cyclohexylamino	143-5	$\text{C}_{24}\text{H}_{23}\text{ClN}_4\text{O}$	419.0	68.39 68.82	5.78 5.49	13.53 13.39	8.18 8.48	3420 (NH)	1695	1635
23	Cl	F	4-methylpiperazin-1-yl	249-51	$\text{C}_{23}\text{H}_{21}\text{ClFN}_6\text{O}$	438.0	62.44 63.08	4.91 4.83	15.68 15.59	8.57 8.09	—	1700	1630
24	Cl	H	4-(1'-phenyl-4-oxo-5'-imidazolyl)-piperidin-1-yl	289-91	$\text{C}_{31}\text{H}_{27}\text{ClN}_6\text{O}_2$	551.1	— 67.57	— 4.94	— 15.25	— 6.43	3400 (NH)	1715 1680	1620
25	Cl	H	phenylamino	249-51	$\text{C}_{24}\text{H}_{17}\text{ClN}_4\text{O}$	412.9	69.61 68.82	4.19 4.15	13.40 13.57	8.97 8.59	3400 (NH)	1690 1678	1650
26	Cl	H	4-methylpiperazin-1-yl	193-5	$\text{C}_{24}\text{H}_{24}\text{ClN}_5\text{O}$	434.0	66.32 66.43	5.50 5.54	15.98 16.14	8.11 8.38	—	1660	1615

TABLE 2 (Continued)

Examples	Formula Ib/Ic					Analyses Found/Calculated				Infrared Spectra cm ⁻¹ (KBr Disc)			
	R ¹	R ²	-N(R ³)(R ⁴)	Melting point (°C)	Molecular Formula	M. Wt.	%C	%H	%N	%Cl	NH, OH	C=O	C-N
27	Cl	H	<i>t</i> -butylamino	230-2	C ₂₂ H ₂₁ ClN ₂ O	392.9	67.26	5.39	14.26	9.02	3320 (NH)	1690	1640
28	Cl	H	hydroxyethyl amino	223-5	C ₂₀ H ₁₇ ClN ₂ O ₂	380.9	62.98 63.08	4.72 4.50	14.65 14.71	9.58 9.31	3280 (NH)	1700	1630
29	Cl	H	<i>n</i> -propylamino	153-5	C ₂₁ H ₁₉ ClN ₂ O	378.9	66.48 66.58	5.09 5.02	14.64 14.79	9.43 9.38	3230 (NH)	1700	1630
30	NO ₂	Cl	4-methylpiperazin-1-yl	214-5	C ₂₃ H ₂₂ ClN ₂ O ₃	465.0	59.31 59.43	4.68 4.55	18.00 18.08	7.85 7.63	—	1690	1630
31	NO ₂	F	„	303-6	C ₂₃ H ₂₁ FN ₂ O ₃	448.5	61.43 61.60	4.83 4.72	18.82 18.74	—	—	1690	1630
32	Cl	H	4-ethylpiperazin-1-yl	183-4	C ₂₄ H ₂₄ ClN ₂ O	434.0	66.43	5.57	16.14	8.17	—	1695	1630
32B	Cl	H	„	143-7	C ₂₈ H ₃₀ ClN ₂ O ₇	584.1	56.55 57.57	5.16 5.13	11.44 11.99	6.15 6.08	3400 2500	1710 1690	1630
33	Cl	H	4- <i>n</i> -propylpiperazin-1-yl	148-52	C ₂₄ H ₂₈ ClN ₂ O	448.0	67.03	5.85	15.63	7.91	—	1695	1630

25

TABLE 2 (Continued)

Examples							Analyses Found/Calculated					Infrared Spectra cm ⁻¹ (KBr disc)			
	R ¹	R ²	-N(R ³)(R ⁵)	Melting Point (°C)	Molecular Formula	M.Wt.	%C	%H	%N	%Cl	NH, OH	C=O	C-N		
34	Cl	H	4-(n-butyl)-piperazin-1-yl	186-7	C ₂₈ H ₃₈ ClN ₃ O	462.0	67.46 67.61	6.16 6.07	15.10 15.17	7.73 7.69	-	1697	1630		
35	Cl	H	4-(isopropyl)-piperazin-1-yl	146-8	C ₂₅ H ₃₆ ClN ₃ O	448.0	66.71 67.05	5.94 5.89	15.90 15.62	7.92 8.14	-	1698	1630		
36	Cl	H	4-allylpiperazin-1-yl	187-8	C ₂₅ H ₃₄ ClN ₃ O	446.0	67.02 67.33	5.41 5.39	15.62 15.71	8.00 7.97	-	1695	1635		
37	Cl	H	4-(cyclopropylmethyl)piperazin-1-yl	202-4	C ₂₈ H ₃₈ ClN ₃ O	460.0	67.87 67.90	5.73 5.66	15.18 15.24	7.80 7.73	-	1695	1630		
38	Cl	Cl	4-ethyl-piperazin-1-yl	243-5	C ₂₄ H ₂₈ Cl ₂ N ₃ O	469.4	61.75 61.54	5.11 4.95	14.35 14.95	15.03 15.14	-	1695	1632		
39	Cl	F	4-ethyl-piperazin-1-yl	235-7	C ₂₄ H ₂₈ ClFN ₃ O	452.0	63.04 63.19	5.17 5.13	15.19 15.50	7.96 7.84	-	1697	1637		
40	NO ₂	Cl	4-ethyl-piperazin-1-yl	265-7	C ₂₄ H ₂₈ ClN ₃ O ₂	480.0	60.25 60.19	4.90 4.81	17.45 17.56	7.86 7.42	-	1697	1640		
41	NO ₂	F	4-ethyl-piperazin-1-yl	262-4	C ₂₄ H ₂₈ FN ₃ O ₂	462.5	62.28 62.33	5.15 5.01	17.95 18.17	-	-	1693	1630		
42	Cl	H	Ethylamino	234-6	C ₂₀ H ₁₇ ClN ₃ O	364.8	65.36 65.85	4.72 4.66	15.03 15.37	9.56 9.74	3250 (NH)	1690	1640		
43	Cl	H	4-(dimethylphosphinylmethyl)-piperazin-1-yl	261-2	C ₂₈ H ₃₇ ClN ₃ PO ₂	496.1	- 60.54	- 5.45	- 7.16	- 14.13	-	1692	1630		

TABLE 2 (Continued)

Example	R ¹	R ²	-N(R ³)(R ³)	Melting Point (°C)	Molecular Formula	M.W.	Analyses Found/Calculated				Infrared Spectra cm ⁻¹ (KBr disc)		
							%C	%H	%N	%Cl	NH,OH	C-O	C-N
44	Cl	Cl	4-(n-propyl)-piperazin-1-yl	247-9	C ₂₃ H ₃₅ Cl ₂ N ₅ O	483.5	62.31 62.24	5.28 5.22	14.67 14.52	14.67 14.70	-	1696	1632
45	Cl	Cl	Ethylamino	235-7	C ₂₀ H ₁₆ Cl ₂ N ₄ O	399.3	60.21 60.16	4.05 4.04	13.90 14.03	17.95 17.76	3280 (NH)	1700	1646
46	Cl	Cl	n-propylamino	227-9	C ₂₁ H ₁₈ Cl ₂ N ₄ O	413.4	61.02 61.03	4.37 4.39	13.36 13.56	17.32 17.16	3240 (NH)	1695	1640

Example 47.

8-chloro-1,2-dihydro-2-(4-dimethylphosphinylmethyl-piperazin-1-yl)methylene-6-(o-chlorophenyl)-4H-imidazo[1,2-a]-[1,4]benzodiazepin-1-one

5

8 - Chloro - 1,2 - dihydro - 2 - (piperazin-1-yl)methylene - 6 - (o - chlorophenyl)-4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one Ic (obtained by a method analogous to that described in Example 8) (850 mg), chloromethyl-dimethylphosphine oxide (1.0 g), sodium iodide (1.0 g) and sodium carbonate (2.0 g) were stirred under reflux in dry toluene (50 ml) for 24 hours. The cooled solution was partitioned between chloroform and water, the chloroform extract separated, dried over magnesium sulphate, and evaporated to give a gummy solid. This was chromatographed on silica eluting with chloroform to give a solid which on crystallisation from methanol/ethyl acetate/ether gave 8 - chloro-

10

1,2 - dihydro - 2 - (4 - dimethylphosphinylmethyl - piperazin - 1 - yl)methylene - 6 - (o - chlorophenyl)-4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one Ic, m.p. = 231-4° C.

25

I.R. Spectra (KBr disc):

C = O at 1700 cm⁻¹; C = N at 1630 cm⁻¹

Example 48.

30

1,2-dihydro-2-(4-dimethylphosphinylmethylpiperazin-1-yl)methylene-6-phenyl-4H-imidazo[1,2-a][1,4]benzodiazepin-1-one

35

This compound was prepared, by a method analogous to that used in Example 47, from 1,2 - dihydro - 2 - (piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one Ic — which in turn was prepared by a method analogous to that described in Example 8.

40

- The formed 1,2 - dihydro - 2 - (4 - dimethylphosphinylmethylpiperazin - 1 - yl)-methylene - 6 - phenyl - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one Ic melted at 245—7° C.

I.R. Spectra (KBr disc)

C = O at 1695 cm⁻¹; C = N at 1630 cm⁻¹

Example 49.

- 8-nitro-1,2-dihydro-2-(4-dimethylphosphinylmethylpiperazin-1-yl)methylene-6-(o-chlorophenyl)-4H-imidazo[1,2-a][1,4]benzodiazepin-1-one

- This compound was prepared, by a method analogous to that used in Example 47, from 8 - nitro - 1,2 - dihydro 2 - (piperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H-imidazo[1,2 - a][1,4]benzodiazepin - 1 - one Ic — which in turn was prepared by a method analogous to that described in Example 8.

- The formed 8 - nitro - 1,2 - dihydro - 2 - (4 - dimethylphosphinylmethyl - piperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H 1 imidazo[1,2 - a][1,4]benzodiazepin - 1 - one Ic melted at 245—8° C.

- I.R. Spectra (KBr disc)

C = O at 1700 cm⁻¹; C = N at 1642 cm⁻¹

Example 50.

- 8-nitro-1,2-dihydro-2-(4-methylpiperazin-1-yl)-methylene-6-(o-chlorophenyl)-4H-imidazo[1,2-a][1,4]benzodiazepin-1-one methanesulphonate

- Methanesulphonic acid (1.1 g) was added dropwise to 8 - nitro - 1,2 - dihydro - 2 - (4 - methyl - piperazin - 1 - yl)methylene-6 - ((o - chlorophenyl) - 4H - imidazo [1,2 - a][1,4]benzodiazepin - 1 - one (obtained as in Example 30) (4.6 g) in dry methylene chloride (100 ml) and methanol (5 ml). Dry diethyl ether was added slowly until crystals formed on scratching and the solution was allowed to crystallise, further ether being added to complete the crystallisation. The pale yellow solid was filtered off, washed with diethyl ether and recrystallised from methylene chloride-methanol to give 8 - nitro - 1,2 - dihydro - 2 - (4 - methylpiperazin - 1 - yl)-methylene - 6 - (o - chlorophenyl) - 4H-imidazo[1,2 - a][1,4]benzodiazepin - 1 - one methanesulphonate (5.4 g), m.p. = 205—10° C.

FORMULATIONS

Formulation 1: Tablets

Tablets were prepared having the following constituents per tablet:

- | | | |
|----|---|--------|
| 55 | 8 - chloro - 1,2 - dihydro - 2 - (4 - methylpiperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one | 5 mg |
| 60 | Excipient (q.s. for a tablet) up to | 100 mg |

The excipient was lactose, starch, talc and magnesium stearate.

Formulation 2: Capsules

The ingredients for gelatin capsules were prepared to have the following constituents per capsule:

- | | | |
|--|--------|----|
| 8 - chloro - 1,2 - dihydro - 2 - (4 - methylpiperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one - tartrate | 5 mg | 70 |
| Excipient (q.s. for a gelatin capsule up to | 100 mg | |

The excipient was talc, starch and magnesium stearate.

Formulation 3: Injectable ampoules

Injectable ampoules were prepared containing a solution having the following constituents:

- | | | |
|--|--------|---------|
| 8 - chloro - 1,2 - dihydro - 2 - (4 - methylpiperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one tartrate | 10 mg | 80 |
| aqueous solvent | q.s.v. | 2 ml 85 |

Formulation 4: Tablets

Tablets were prepared having the following constituents per tablet:

- | | | |
|---|--------|----|
| 8 - chloro - 1,2 - dihydro - 2 - (4 - methylpiperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one | 5 mg | 90 |
| Excipient (q.s. for a tablet) up to | 100 mg | |

The excipient was lactose, starch, talc and magnesium stearate.

Formulation 5: Tablets

Tablets were prepared having the following constituents per tablet:

- | | | |
|---|--------|-----|
| 8 - chloro - 1,2 - dihydro - 2 - (4 - methylpiperazin - 1 - yl)methylene - 6 - (o - fluorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one | 5 mg | 100 |
| Excipient (q.s. for a tablet) up to | 100 mg | 105 |

The excipient was lactose, starch, talc and magnesium stearate.

Formulation 6: Tablets

Tablets were prepared having the following constituents per tablet:

- | | | |
|--|--------|-----|
| 8 - nitro - 1,2 - dihydro - 2 - (4 - methylpiperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a][1,4]benzodiazepin - 1 - one | 5 mg | 110 |
| Excipient (q.s. for a tablet) up to | 100 mg | 115 |

The excipient was lactose, starch, talc and magnesium stearate.

Formulation 7: Tablets

Tablets were prepared having the following constituents per tablet:

- 8 - nitro - 1,2 - dihydro - 2 - (4-methyl - piperazin - 1 - yl)-methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a]-[1,4]benzodiazepin - 1 - one methanesulphonate 5 mg
Excipient (q.s. for a tablet) up to 100 mg

The excipient was lactose, starch, talc and magnesium stearate.

15 Formulation 8: Tablets

Tablets were prepared having the following constituents per tablet:

- 8 - chloro - 1,2 - dihydro - 2 - (4-methyl - piperazin - 1 - yl)-methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2 - a]-[1,4]benzodiazepin - 1 - one tartrate 5 mg
Excipient (q.s. for a tablet) up to 100 mg

25 The excipient was lactose, starch, talc and magnesium stearate.

PHARMACOLOGICAL ACTIVITY

1) *Antiaggressive activity in mice (AAM)*

- 30 Groups of 20 randomly selected male mice (25-30 g body weight; Tuck T.O. strain) were given oral doses of either vehicle alone (10 ml per kg distilled water) or vehicle plus test compound. 30 minutes after dosing, pairs of mice were placed under an inverted 1 litre pyrex beaker on a metal grid. The grid was connected to a Palmer square wave stimulator, and the feet of the mice were electrically stimulated with 90 volt pulses of 5 milli-second duration at a frequency of 2 pulses per second for a period of 2 minutes. This procedure provoked fighting in the control mice (a fight being defined as a frontal aggressive attack, usually biting, by either mouse on the other one). The total number of fights in the control group was calculated.

- 45 The ED₅₀ of a test compound is that dose which causes a 50% reduction in the number of fights of the batch of mice given that compound as compared with the control batch. 50 (Tedeschi, R. E. *et al* (1959) J. PHARM. Exptl. Ther. 125:28-34).

The results are shown in Table 3 below.

2) *Anticonvulsant test against maximal electroshock in mice (AEM)*

- 55 Groups of ten mice were injected orally with the test compound in a vehicle at various dose levels (a control group receiving the

vehicle alone). 30 minutes after dosing each group was then shocked via auricular electrodes using electroshock apparatus (Ugo Basile ECT apparatus for small mammals). The shocks had a pulse width of 0.2 milliseconds, and a frequency of 100 Hz, and each shock was given for 0.2 seconds at a current of 55 milliamps. 60 65

The number of mice which underwent tonic extension of their hind limbs was noted. The dose protecting 50% of the mice (TED₅₀), as compared with the control group, was noted, and the results are shown in Table 3 below. 70

3) *Anticonvulsant test against pentylene-tetrazole in mice (ALM)*

Groups of ten mice were injected orally with the test compound in a vehicle at various dose levels, with a control group receiving the vehicle alone. 30 minutes after dosing each mouse received a sub-cutaneous 130 mg/kg pentylenetetrazole challenge (pentylenetetrazole is a central nervous system stimulant), and the mice were then individually housed in observation boxes. The number of mice showing tonic convulsions within 30 minutes of the pentylenetetrazole challenge was noted, and the results for the tonic phase were expressed as a percentage reduction of the control levels. 75 80 85 From a constructed dose response curve, the doses protecting 50% of the mice (TED₅₀) against tonus were estimated, and are shown in Table 3 below.

4) *Anticonvulsant test against strychnine in mice (ASM)*

Groups of ten mice received the test compound and vehicle orally at various dose levels, with a control group receiving the vehicle alone. 30 minutes after dosing, each mouse received a sub-cutaneous 1 mg/kg strychnine challenge (strychnine is a central nervous system stimulant), and the mice were then housed individually in observation boxes. The number of mice exhibiting tonic convulsions within 15 minutes of the strychnine challenge was noted, and the results for the tonic phase expressed as a percentage reduction of the control value. From a constructed dose response line, the doses protecting 50% of the mice (TED₅₀) against tonus were estimated, and are shown in Table 3 below. 90 95 100 105

5) *Potentiation of hexobarbital in mice (PHM)*

A group of ten control mice received an ED₅₀ dose of hexobarbital intraperitoneally (150 mg/kg) (hexobarbital is a sedative and hypnotic), followed by an oral dose of either a vehicle alone or various oral doses of the vehicle and a test compound. The number of mice which exhibited loss of the righting reflex for 30 seconds half-an-hour after dosing was noted, and a dose response curve was constructed; the dose of test compound 115

which caused 50% of the mice in a group to lose the righting reflex was estimated (ED_{50}), and the results are shown in Table 3 below.

5 6) *Potentiation of chlorprothixene in mice (PXM)*

Groups of ten randomly selected male CFLP mice (Carworth Europe), weighing 20–25 g each, were given chlorprothixene (12.5 mg/kg) intraperitoneally (chlorprothixene is a tranquilizer and antipsychotic); this dose consistently caused 10% of mice to lose their righting reflex 30 minutes after dosing. At the same time the test groups of mice were given orally either vehicle alone (distilled water, 10 ml/kg), or a dose of vehicle plus test compound. Each mouse was then placed individually in a small observation chamber, and tested for loss of righting reflex 30 minutes after dosing.

20 The ED_{50} value of a test compound is the dose which causes loss of the righting reflex in 50% of the number of mice in a group which, in the absence of oral treatment, would

not be expected to lose their righting reflex. The results are shown in Table 3 below.

7) *Rotating drum test in mice (RDM)*

Groups of ten mice were injected orally with vehicle plus the test compound at various dose levels, with a control group receiving the vehicle alone. 30 minutes after dosing, each group of mice were placed on a 30 cm diameter rotating drum revolving at 1 revolution/minute. The mice were placed on the drum against its direction of movement, and the number of mice falling off within a 2 minute test period was noted. From the results obtained a dose response line was constructed, and the dose causing 50% of the mice to fall off the drum (ED_{50}) was estimated. The results are shown in Table 3 below.

8) *Mouse Acute Toxicity Test (ATM)*

Acute toxicity tests by oral and intraperitoneal routes were conducted using groups of ten mice at various dose levels. The groups were assessed for mortality at 24 hours, and the results are shown in Table 3 below, given in mg/kg.

38

TABLE 3

The compound of Example	AAM (anti-aggression)	AEM (electro-shock)	ALM (pentylene-tetrazole)	ASM (strychnine)	PHM (hexo-barbital)	PXM (chlorpro-thixene)	RDM (drum)	ATM ip (toxicity)
8A	2.65	4.1	0.8	7.1	4.9	5.4	7.1	>1000
8B	4	4.2	0.8	7.4	2.55	6.8	1.7	—
10	4	12.5	1.85	~50	14	29	—	>1000
12	0.2	2.1	0.165	1.8	0.038	1.6	0.78	>1000
12B	—	—	—	—	—	2.67	—	—
13	2.2	4.2	0.92	6.6	3.6	4.5	8.6	>1000
15	3.35	12.5	1.15	17	0.66	1.8	24	>1000
22	1.4	8.5	2.35	15	8.3	6.2	—	—
23	0.34	0.27	0.115	1.3	0.21	1.35	2.6	>1000
29	0.92	4.0	>1, <2	50	3.9	2.6	2.85	—
30	0.42	0.76	0.028	0.41	1.0	1.1	2.2	—
31	0.26	1.2	0.13	0.46	0.8	1.6	1.5	—
32	0.94	2.2	0.48	5.5	1.1	5.0	1.6	—
32B	0.62	8.3	1.45	30	>50	9.5	7.4	—

(36)

TABLE 3 (Continued)

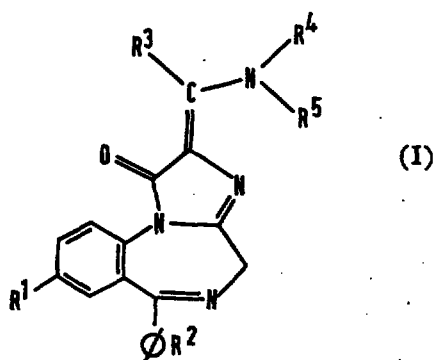
The compound of Example	AAM (anti- aggression)	AEM (electro- shock)	ALM (pentylene- tetrazole)	ASM (strychnine)	PHM (hexo- barbital)	PXM (chlorpro- thixene)	RDM (drum)	ATM ip (toxicity)
33	1.3	2.7	>1, <2	6.4	3.6	3.2	1.1	—
38	0.5	2.2	0.087	2.3	2.5	1.2	0.56	—
39	0.48	1.55	—	1.6	2.8	2.35	0.7	—
40	0.03	—	0.15	—	—	0.99	—	—
41	0.64	—	—	—	0.8	—	—	—
42	1.45	—	—	—	0.72	—	—	—
43	0.84	—	—	—	—	—	—	—
44	0.66	3.5	0.185	1.85	0.064	1.7	0.29	—
45	1.0	18.0	0.39	25	0.27	9.6	11.5	—
46	2.4	>30	1.0	>25	0.06	5.6	8.0	—
50	0.42	0.76	0.03	0.41	1.0	1.1	0.85	—

The results obtained show that the compounds of the invention possess a very important activity on the central nervous system as anticonvulsant, anti-anxiety and hypnotic sedatives, and that they have a very low toxicity.

- 5 The references in the following claims to general formulae are, unless stated otherwise, references to those formulae shown in the Reaction Scheme of the accompanying drawings. The substituent group symbols employed
- 10 are, unless stated otherwise, as first defined.

WHAT WE CLAIM IS:—

1. A 1,2 - dihydro - 6 - phenyl - 4H - imidazo[1,2 - a][1,4]benzodiazepine of the general
- 15 formula:



wherein:

- 20 R¹ represents a hydrogen atom, a halogen atom, a nitro radical or a trifluoromethyl radical;

R², which may be at any position in the phenyl (Ø) ring, represents a hydrogen atom or a halogen atom;

- 25 R³ represents a hydrogen atom or a methyl radical; and

either R⁴ and R⁵, which may be the same or different, each represents a hydrogen atom, an alkyl radical containing from 1 to 5 carbon atoms, a hydroxyalkyl radical containing from 1 to 5 carbon atoms, an aminoalkyl or alkyl-aminoalkyl radical (the alkyl moieties each containing from 1 to 5 carbon atoms), an aryl radical, or a cycloalkyl radical,

- 30 or R⁴ and R⁵ together with the nitrogen atom represent a saturated, substituted or unsubstituted heterocyclic optionally containing another hetero atom;

and acid addition salts thereof.

- 40 2. A compound as claimed in claim 1, wherein R¹ represents a chlorine atom.

3. A compound as claimed either of the preceding claims, wherein R² represents a halogen atom in the *ortho*-position.

- 45 4. A compound as claimed in any of the preceding claims, wherein R² represents a fluorine or chlorine atom.

5. A compound as claimed in any of the preceding claims wherein R³ represents a hydrogen atom.

- 50 6. A compound as claimed in any of the

preceding claims, wherein either of R⁴ and R⁵ represents a methyl, ethyl, *n*-propyl, *n*-butyl or *t*-butyl radical.

7. A compound as claimed in any of claims 1 to 5, wherein, where either of R⁴ and R⁵ represents a hydroxyalkyl radical, the alkyl moiety is an ethyl radical.
- 55

8. A compound as claimed in any of claims 1 to 5, wherein where either of R⁴ and R⁵ represents an aminoalkyl or alkylaminoalkyl radical each of the alkyl moieties is a methyl or ethyl radical.
- 60

9. A compound as claimed in claim 8, wherein either of R⁴ and R⁵ represents an aminomethyl, aminoethyl, dimethylaminoethyl or diethylaminoethyl radical.
- 65

10. A compound as claimed in any of claims 1 to 5, wherein either of R⁴ and R⁵ represents a phenyl radical.

11. A compound as claimed in any of claims 1 to 5, wherein either of R⁴ and R⁵ represents a cycloalkyl radical containing from 3 to 8 carbon atoms.
- 70

12. A compound as claimed in claim 11, wherein either of R⁴ and R⁵ represents a cyclohexyl radical.
- 75

13. A compound as claimed in any of the preceding claims, wherein one of R⁴ and R⁵ represents hydrogen.

14. A compound as claimed in any of claims 1 to 5, wherein, where R⁴ and R⁵, together with the conjoining nitrogen atom, form an unsubstituted heterocyclic grouping, this grouping is a pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazin-1-yl grouping.
- 80

15. A compound as claimed in any of claims 1 to 5, wherein, where R⁴ and R⁵, together with the conjoining nitrogen atom, form a substituted heterocyclic grouping, the substituent is an alkyl radical containing from 1 to 5 carbon atoms, a hydroxyalkyl radical containing from 1 to 5 carbon atoms, an aryl radical or a nitrogen containing heterocyclic radical.
- 85

16. A compound as claimed in any of claims 1 to 5, wherein R⁴ and R⁵, together with the conjoining nitrogen atom, form a substituted heterocyclic grouping which is a 4-methyl-, 4-ethyl or 4-propyl-piperazin-1-yl group, or a 4-β-hydroxyethyl-piperazin-1-yl, 4-dimethylphosphinylmethyl-piperazin-1-yl, 4-cyclopropylmethyl-piperazin-1-yl, 4-allyl-piperazin-1-yl, 4-phenyl-piperazin-1-yl, or 4-(1'-phenyl-4'-oxo-5'-imidazolyl)piperidin-1-yl group.
- 90

17. A compound as claimed in claim 1, wherein either R⁴ and R⁵, which may be the same or different, each represents a hydrogen atom, an alkyl radical containing from 1 to 5 carbon atoms, a hydroxyethyl radical, a dimethyl- or diethylaminoethyl radical, a phenyl radical, or a cyclohexyl radical, or R⁴ and R⁵ together with the nitrogen atom form a pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazin-1-yl, 4-alkyl-piperazin-1-yl, 4-hydroxyalkyl-piperazin-
- 105
- 110
- 115

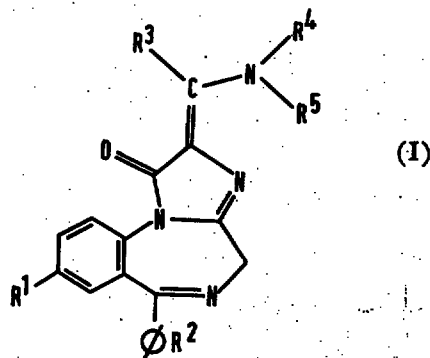


The results obtained show that the compounds of the invention possess a very important activity on the central nervous system as anticonvulsant, anti-anxiety and hypnotic sedatives, and that they have a very low toxicity.

The references in the following claims to general formulae are, unless stated otherwise, references to those formulae shown in the Reaction Scheme of the accompanying drawings. The substituent group symbols employed are, unless stated otherwise, as first defined.

WHAT WE CLAIM IS:—

1. A 1,2 - dihydro - 6 - phenyl - 4H - imidazo[1,2 - *a*][1,4]benzodiazepine of the general formula:



wherein:

R¹ represents a hydrogen atom, a halogen atom, a nitro radical or a trifluoromethyl radical;

R², which may be at any position in the phenyl (Ø) ring, represents a hydrogen atom or a halogen atom;

R³ represents a hydrogen atom or a methyl radical; and

either R⁴ and R⁵, which may be the same or different, each represents a hydrogen atom, an alkyl radical containing from 1 to 5 carbon atoms, a hydroxyalkyl radical containing from 1 to 5 carbon atoms, an aminoalkyl or alkyl-aminoalkyl radical (the alkyl moieties each containing from 1 to 5 carbon atoms), an aryl radical, or a cycloalkyl radical,

or R⁴ and R⁵ together with the nitrogen atom represent a saturated, substituted or unsubstituted heterocyclic optionally containing another hetero atom;

and acid addition salts thereof.

2. A compound as claimed in claim 1, wherein R¹ represents a chlorine atom.

3. A compound as claimed either of the preceding claims, wherein R² represents a halogen atom in the *ortho*-position.

4. A compound as claimed in any of the preceding claims, wherein R² represents a fluorine or chlorine atom.

5. A compound as claimed in any of the preceding claims wherein R³ represents a hydrogen atom.

6. A compound as claimed in any of the

preceding claims, wherein either of R⁴ and R⁵ represents a methyl, ethyl, *n*-propyl, *n*-butyl or *t*-butyl radical.

7. A compound as claimed in any of claims 1 to 5, wherein, where either of R⁴ and R⁵ represents a hydroxyalkyl radical, the alkyl moiety is an ethyl radical.

8. A compound as claimed in any of claims 1 to 5, wherein where either of R⁴ and R⁵ represents an aminoalkyl or alkylaminoalkyl radical each of the alkyl moieties is a methyl or ethyl radical.

9. A compound as claimed in claim 8, wherein either of R⁴ and R⁵ represents an aminomethyl, aminoethyl, dimethylaminoethyl or diethylaminoethyl radical.

10. A compound as claimed in any of claims 1 to 5, wherein either of R⁴ and R⁵ represents a phenyl radical.

11. A compound as claimed in any of claims 1 to 5, wherein either of R⁴ and R⁵ represents a cycloalkyl radical containing from 3 to 8 carbon atoms.

12. A compound as claimed in claim 11, wherein either of R⁴ and R⁵ represents a cyclohexyl radical.

13. A compound as claimed in any of the preceding claims, wherein one of R⁴ and R⁵ represents hydrogen.

14. A compound as claimed in any of claims 1 to 5, wherein, where R⁴ and R⁵, together with the conjoining nitrogen atom, form an unsubstituted heterocyclic grouping, this grouping is a pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazin-1-yl grouping.

15. A compound as claimed in any of claims 1 to 5, wherein, where R⁴ and R⁵, together with the conjoining nitrogen atom, form a substituted heterocyclic grouping, the substituent is an alkyl radical containing from 1 to 5 carbon atoms, a hydroxyalkyl radical containing from 1 to 5 carbon atoms, an aryl radical or a nitrogen containing heterocyclic radical.

16. A compound as claimed in any of claims 1 to 5, wherein R⁴ and R⁵, together with the conjoining nitrogen atom, form a substituted heterocyclic grouping which is a 4-methyl-, 4-ethyl or 4-propyl-piperazin-1-yl group, or a 4-β-hydroxyethyl-piperazin-1-yl, 4-dimethylphosphinylmethyl-piperazin-1-yl, 4-cyclopropylmethyl-piperazin-1-yl, 4-allyl-piperazin-1-yl, 4-phenyl-piperazin-1-yl, or 4-(1'-phenyl-4'-oxo-5'-imidazolyl)piperidin-1-yl group.

17. A compound as claimed in claim 1, wherein either R⁴ and R⁵, which may be the same or different, each represents a hydrogen atom, an alkyl radical containing from 1 to 5 carbon atoms, a hydroxyethyl radical, a dimethyl- or diethylaminoethyl radical, a phenyl radical, or a cyclohexyl radical, or R⁴ and R⁵ together with the nitrogen atom form a pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazin-1-yl, 4-alkyl-piperazin-1-yl, 4-hydroxyalkyl-piperazin-

1 - yl, 4 - phenyl - piperazin - 1 - yl or 4 - (1'phenyl - 4' - oxo - 5' - imidazolyl) piperidin - 1 - yl radical.

18. A compound as claimed in claim 1, wherein R¹ represents a chlorine atom or a nitro radical, R² represents a hydrogen atom, a chlorine atom or a fluorine atom, R³ represents a hydrogen atom, and either R⁴ and R⁵, which may be the same or different, each represent a hydrogen atom, a straight alkyl radical containing from 1 to 5 carbon atoms, a hydroxyethyl radical, a phenyl radical, or a cyclohexyl radical, or R⁴ and R⁵ together with the nitrogen atom form a piperidinyl, morpholinyl, piperazin - 1 - yl, 4 - alkyl - piperazin - 1 - yl or 4 - β - hydroxyethyl - piperazin - 1 - yl radical.

19. A compound as claimed in claim 1, wherein R¹ represents a chlorine atom or a nitro radical, R² represents a hydrogen, chlorine or fluorine atom, R³ represents a hydrogen atom, and either R⁴ represents a hydrogen atom and R⁵ represents a methyl, ethyl, propyl or butyl radical, or R⁴ and R⁵ together with the nitrogen atom form a piperazin - 1 - yl, 4 - methyl - piperazin - 1 - yl, 4 - ethyl - piperazin - 1 - yl, 4 - propyl - piperazin - 1 - yl or 4 - β - hydroxyethyl - piperazin - 1 - yl radical.

20. A compound as claimed in claim 1, wherein R¹ represents a chlorine atom or a nitro radical, R² represents a hydrogen, chlorine or fluorine atom, R³ represents a hydrogen atom, and R⁴ and R⁵ together with the nitrogen atom form a 4 - methyl - piperazin - 1 - yl, 4 - ethyl - piperazin - 1 - yl or 4 - n - propyl - piperazin - 1 - yl radical.

21. A compound as claimed in claim 1, wherein R¹ represents a hydrogen atom, a chlorine atom or a nitro radical, R² represents a hydrogen atom or a chlorine atom, R³ represents a hydrogen atom and R⁴ and R⁵ together with the nitrogen atom form a 4 - dialkylphosphinylalkyl - piperazin - 1 - yl radical.

22. A compound as claimed in claim 1, wherein R¹ represents a hydrogen atom, a chlorine atom or a nitro radical, R² represents a hydrogen atom or a chlorine atom, R³ represents a hydrogen atom and R⁴ and R⁵ together with the nitrogen atom form a 4 - dimethylphosphinylmethyl - piperazin - 1 - yl radical.

23. An acid addition salt as claimed in any of the preceding claims, which is formed with hydrochloric, hydrobromic, hydroiodic, nitric, sulphuric or phosphoric acid, or with acetic, formic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic, aspartic, an alkanesulphonic or an arylsulphonic acid.

24. An acid addition salt, as claimed in claim 23, which is formed with methanesulphonic acid.

25. An acid addition salt as claimed in claim 1, wherein R¹ represents a hydrogen atom, a chlorine atom or a nitro radical, R² represents

a hydrogen atom, a chlorine atom or a fluorine atom, R³ represents a hydrogen atom and R⁴ and R⁵ together with the nitrogen atom form a 4 - alkyl - piperazin - 1 - yl radical.

26. An acid addition salts as claimed in claim 1, which is a tartrate or an alkanesulphonate wherein R¹ represents a chlorine atom or a nitro radical, R² represents a hydrogen atom or a chlorine atom, R³ represents a hydrogen atom and R⁴ and R⁵ together with the nitrogen atom form a 4 - methyl - piperazin - 1 - yl or a 4 - ethyl - piperazin - 1 - yl radical.

27. An acid addition salt as claimed in claim 26 which is a methanesulphonate.

28. 8 - Chloro - 1,2 - dihydro - 2 - (4 - methyl - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2-*a*][1,4]benzodiazepin - 1 - one.

29. 8 - Chloro - 1,2 - dihydro - 2 - (4 - methyl - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2-*a*][1,4]benzodiazepin - 1 - one tartrate.

30. 8 - Nitro - 1,2 - dihydro - 2 - (4 - methyl - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2-*a*][1,4]benzodiazepin - 1 - one.

31. 8 - Chloro - 1,2 - dihydro - 2 - (4 - methyl - piperazin - 1 - yl)methylene - 6 - (*o* - chlorophenyl) - 4H - imidazo[1,2-*a*][1,4]benzodiazepin - 1 - one.

32. 8 - Chloro - 1,2 - dihydro - 2 - (4 - methyl - piperazin - 1 - yl)methylene - 6 - (*o* - fluorophenyl) - 4H - imidazo[1,2-*a*][1,4]benzodiazepin - 1 - one.

33. 8 - Nitro - 1,2 - dihydro - 2 - (4 - methyl - piperazin - 1 - yl)methylene - 6 - (*o* - chlorophenyl) - 4H - imidazo[1,2-*a*][1,4]benzodiazepin - 1 - one.

34. 8 - Nitro - 1,2 - dihydro - 2 - (4 - methyl - piperazin - 1 - yl)methylene - 6 - (*o* - chlorophenyl) - 4H - imidazo[1,2-*a*][1,4]benzodiazepin - 1 - one methanesulphonate.

35. 8 - Chloro - 1,2 - dihydro - 2 - (4 - methyl - piperazin - 1 - yl)methylene - 6 - (*o* - chlorophenyl) - 4H - imidazo[1,2-*a*][1,4]benzodiazepin - 1 - one tartrate.

36. 8 - Nitro - 1,2 - dihydro - 2 - (4 - methyl - piperazin - 1 - yl)methylene - 6 - (*o* - fluorophenyl) - 4H - imidazo[1,2-*a*][1,4]benzodiazepin - 1 - one.

37. 8 - Chloro - 1,2 - dihydro - 2 - (4 - ethyl - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2-*a*][1,4]benzodiazepin - 1 - one.

38. 8 - Chloro - 1,2 - dihydro - 2 - (4 - n - propyl - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2-*a*][1,4]benzodiazepin - 1 - one.

39. 8 - Chloro - 1,2 - dihydro - 2 - (n - butyl - amino)methylene - 6 - phenyl - 4H - imidazo[1,2-*a*][1,4]benzodiazepin - 1 - one.

40. 8 - Chloro - 1,2 - dihydro - 2 - (4 - β - hydroxyethyl - piperazin - 1 - yl)methylene -



- 6 - phenyl - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one.
41. 8 - Chloro - 1,2 - dihydro - 2 - (n-propylamino)methylene - 6 - phenyl - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one. 70
42. 8 - Chloro - 1,2 - dihydro - 2 - (4-ethyl - piperazin - 1 - yl)methylene - 6 - (o-chlorophenyl) - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one.
43. 8 - Chloro - 1,2 - dihydro - 2 - (4-ethyl - piperazin - 1 - yl)methylene - 6 - (o-fluorophenyl) - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one.
44. 8 - Nitro - 1,2 - dihydro - 2 - (4-ethyl - piperazin - 1 - yl)methylene - 6 - (o-chlorophenyl) - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one.
45. 8 - Nitro - 1,2 - dihydro - 2 - (4-ethyl - piperazin - 1 - yl)methylene - 6 - (o-fluorophenyl) - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one.
46. 8 - Chloro - 1,2 - dihydro - 2 - (ethylamino)methylene - 6 - phenyl - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one.
47. 8 - Chloro - 1,2 - dihydro - 2 - (4 - dimethylphosphinylmethyl - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one.
48. 8 - Chloro - 1,2 - dihydro - 2 - (4 - dimethylphosphinylmethyl - piperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one.
49. 1,2 - Dihydro - 2 - (4 - dimethylphosphinylmethyl - piperazin - 1 - yl)methylene - 6 - phenyl - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one.
50. 8 - Nitro - 1,2 - dihydro - 2 - (4 - dimethylphosphinylmethyl - piperazin - 1 - yl)methylene - 6 - (o - chlorophenyl) - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one.
51. A process for the preparation of a compound of general formula I wherein R³ represents a hydrogen atom and R⁴ and R⁵ each represent a methyl radical, in which an 8 - R¹ - 1,2 - dihydro - 6 - (R² - phenyl) - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one V is reacted with a dimethylformamide acetal VI (wherein "alk" represents an alkyl radical containing from 1 to 5 carbon atoms) to give the desired 8 - R¹ - 1,2 - dihydro - 2 - (dimethylamino)methylene - 6 - (R² - phenyl) - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one Ia.
52. A process as claimed in claim 51, in which the reaction with the acetal VI is carried out in an anhydrous organic solvent.
53. A process as claimed in claim 52, in which the solvent is benzene.
54. A process as claimed in any of claims 51 to 53, in which the reaction with the acetal VI is carried out in the presence of a base.
55. A process as claimed in claim 54, in which the base is triethylamine.
56. A process for the preparation of a compound of general formula I wherein R³, R⁴ and R⁵ each represent a methyl radical, in which an 8 - R¹ - 1,2 - dihydro - 6 - (R² - phenyl) - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one V is reacted with an N-dimethyl-acetamide VII to give the desired 8 - R¹ - 1,2 - dihydro - 2 - (1' - dimethylamino)ethylidene - 6 - (R² - phenyl) - 4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one Ib.
57. A process as claimed in claim 56, in which the reaction with the acetamide VII is carried out in an anhydrous organic solvent.
58. A process as claimed in claim 57, in which the solvent is methylene chloride.
59. A process as claimed in any of claims 56 to 58, in which the reaction with the acetamide VII is effected at a temperature below 10°C.
60. A process as claimed in any of claims 56 to 59, in which the reaction with the acetamide VII is effected in the presence of a condensation promotor.
61. A process as claimed in claim 60, in which the condensation promotor is phosphorus oxychloride.
62. A process as claimed in any of claims 51 to 61, in which the imidazolobenzodiazepine starting material V is prepared by reacting a corresponding 2-carboxy methylamino- or 2 - alkoxy - carbonylmethylamino - 7 - R¹ - 5 - (R² - phenyl) - 3H - 1,4 - benzodiazepine IV (wherein R represents a hydrogen atom or an alkyl radical) with a dehydrating agent to give the desired product.
63. A process as claimed in claim 62, in which the dehydrating agent is a carbodiimide.
64. A process as claimed in claim 63, in which the carbodiimide is dicyclohexylcarbodiimide.
65. A process as claimed in any of claims 62 to 64, in which the reaction is performed in methylene chloride.
66. A process as claimed in any of claims 62 to 65, in which the benzodiazepine starting material IV is prepared by reacting a 7 - R¹ - 1,3 - dihydro - 5 - (R² - phenyl) - 2H - 1,4-benzodiazepin - 2 - thione II with glycine or an alkyl ester thereof III to give the desired product.
67. A process as claimed in claim 66, in which the reaction is carried out in an organic solvent.
68. A process as claimed in claim 67, in which the solvent is ethanol.
69. A process as claimed in any of claims 66 to 68, in which the reaction is effected at the boiling temperature of the reaction mixture.
70. A process for the preparation of a compound of general formula I wherein R⁴ and R⁵ are as defined in claim 1 except that they do not both represent a methyl radical, in which a 2 - (dimethylamino)methylene - imidazolobenzodiazepin - 1 - one Ia or a 2 - [1' - dimethylamino)ethylidene - imidazolobenzodiazepin - 1 - one Ib is transaminated, by

- reaction with an amine VIII (wherein R⁴ and R⁵ are as defined in claim 1 except that they do not both represent a methyl radical) to give the desired 8 - R¹ - 1,2 - dihydro - 2 - (substituted amino)methylene- or 8 - R¹ - 1,2-dihydro - 2 - (1' - substituted amino)ethylidene - 6 - (R² - phenyl) - 1H,4H - imidazo[1,2-a][1,4]benzodiazepin - 1 - one Ic or Id, wherein R⁴ and R⁵ are just as desired.
71. A process as claimed in claim 70, in which the reaction with the amine VIII is carried out in an anhydrous organic solvent.
72. A process as claimed in claim 71, in which the solvent is toluene.
73. A process as claimed in any of claims 70 to 72, in which the reaction is effected at the boiling temperature of the reaction mixture.
74. A process as claimed in any of claims 70 to 73, in which the imidazolobenzodiazepine starting material Ia or Ib is prepared by a process as claimed in any of claims 52 to 69.
75. A process for the preparation of a compound Ic or Id wherein R₄ and R₅ form with the conjoined nitrogen atom a R₆ - piperazin-1-yl radical, wherein R₆ represents a cycloalkylalkyl radical, an alkenyl radical or a 4-dialkylphosphinylalkyl radical, in which a compound Ic or Id wherein R₄ and R₅ form a piperazin-1-yl radical with the conjoined nitrogen atom, is reacted with a halo-R₆ compound to form the desired product.
76. A process for the preparation of a compound Ic or Id wherein R⁴ and R⁵ form, together with the conjoined nitrogen atom, a 4-dialkylphosphinylalkylpiperazin-1-yl radical, in which a compound Ic or Id, wherein R⁴ and R⁵ form a piperazin-1-yl radical with the conjoined nitrogen atom, is reacted with a haloalkyldialkylphosphine oxide to form the desired product.
77. A process as claimed in claim 76, in which the haloalkyl-dialkylphosphine oxide used is a chloroalkyldialkylphosphine oxide.
78. A process as claimed in claim 76 or claim 77, in which the reaction is carried out in an organic solvent.
79. A process as claimed in claim 78, in which the organic solvent is toluene.
80. A process as claimed in any of claims 75 to 79, in which the starting material of general formula Ic or Id wherein R⁴ and R⁵ form, with the nitrogen atom, a piperazin-1-yl radical is prepared by a process as claimed in any of claims 70 to 74.
81. A process for the preparation of an acid addition salt of an imidazolobenzodiazepine of general formula I, in which an imidazolobenzodiazepine I is reacted, in substantially stoichiometric proportions, with a mineral or organic acid to form the desired acid addition salt.
82. A process as claimed in claim 81, in which the reaction is effected in an organic solvent or a mixture of organic solvents.
83. A process as claimed in claim 82, in which the reaction is effected in methanol, ethanol or methylene chloride.
84. A process as claimed in any of claims 81 to 83, in which the imidazolobenzodiazepine I is prepared by a process as claimed in any of claims 51 to 80.
85. A process as claimed in any of claims 51 to 84 and substantially as described hereinbefore, with reference to the Examples.
86. An imidazolobenzodiazepin-1-one I, or an acid addition salt thereof, whenever prepared by a process as claimed in any of claims 51 to 85.
87. A pharmaceutical composition containing one or more imidazolobenzodiazepin-1-one I, or a pharmaceutically-acceptable acid addition salt thereof, as claimed in any of claims 1 to 50 and 86, in association with a suitable pharmaceutical vehicle.
88. A pharmaceutical composition containing one or more imidazolobenzodiazepin-1-one I, or a pharmaceutically-acceptable acid addition salt thereof, as claimed in any of claims 17 to 22, in association with a suitable pharmaceutical vehicle.
89. A pharmaceutical composition containing one or more imidazolobenzodiazepin-1-one I, or a pharmaceutically-acceptable acid addition salt thereof, as claimed in any of claims 28, 29, 31 to 34, 36 and 47, in association with a suitable pharmaceutical vehicle.
90. A pharmaceutical composition containing 8-nitro-1,2-dihydro-2-(4-methylpiperazin-1-yl)methylene-6-(o-chlorophenyl)-4H-imidazo[1,2-a][1,4]benzodiazepin-1-one methanesulphonate, in association with a suitable pharmaceutical vehicle.
91. A composition as claimed in any of claims 87 to 90, wherein the pharmaceutical vehicle is:—
- a) the ingestible excipient of a tablet, or pill; the ingestible container of a capsule or cachet; the ingestible pulverulent solid carrier of a powder; or the ingestible liquid medium of a syrup, solution, suspension or elixir;
 - b) a sterile injectable liquid solution or suspension medium; or
 - c) a base material of low melting point capable of releasing the active ingredient to perform its pharmacological function, which base material when appropriately shaped forms a suppository.
92. A composition as claimed in claim 91, wherein the vehicle is talc, gum arabic, lactose, starch, an animal or vegetable fat, magnesium stearate, or cocoa butter, or water, an animal or vegetable oil, a paraffin derivative, or a glycol.
93. A composition as claimed in any of claims 87 to 92, which is in unit dose form and contains from 0.5 to 20 mg active ingredient.



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94. A composition as claimed in any of claims 87 to 93, and substantially as described hereinbefore, with reference to the Formulations.

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