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PATENT SPECIFICATION (11) 1 579 365

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(19)



(54) NOVEL PIPERAZINE AND PIPERIDINE DERIVATIVES

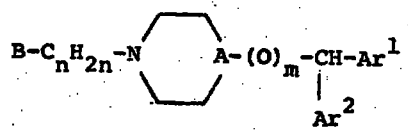
(71) We, JANSSEN PHARMACEUTICA N.V., a Belgian Body Corporate, of Turnhoutsebaan 30, Beerse, Belgium, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to piperazine and piperidine derivatives.

A number of 1-[(heterocyclyl)alkyl]piperazines and a number of 1-substituted 4-(diarylmethyl)piperazine and 4-(diarlymethoxy)piperadine derivatives having pharmacological properties are described in the prior art. Such compounds are described in the following references: United States Patents Nos. 3,362,956, 3,742,854, 3,369,022, 2,882,271 and 3,956,328 and C.A., *64*, 3499e (1966).

The compounds of this invention differ from the prior art compounds essentially by the nature of the B—C_nH_{2n}— group, present in the 1-position of the piperazine or piperadine group, and/or by the nature of the diarylmethyl or diarylmethoxy group present in the 4-position of said piperazine or piperidine group.

Accordingly, the present invention provides piperazine and piperidine derivatives which may structurally be represented by the formula:



(I)

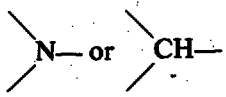
and the pharmaceutically acceptable acid addition salts thereof, wherein:

Ar^1 and Ar^2 are each independently a pyridinyl phenyl or substituted phenyl group, the substituted phenyl group having 1 or 2 substituents which are each

independently a halogen atom, a lower alkyl, lower alkyloxy, trifluoromethyl or nitro group;

m is 0 or 1;

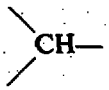
A is a



group, provided that when A is



then *m* is 0 and when A is

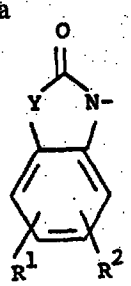


then *m* is 1;

n is an integer of from 2 to 6 inclusive, provided that when c_nH_{2n} represents a branched alkylene chain, then at least 2 carbon atoms are present in the linear portion of the chain linking B with the piperidine or piperazine nitrogen atom; and

B is:

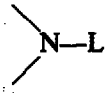
a) a group having the formula



wherein:

R^1 and R^2 are each independently a hydrogen or halogen atom, or a lower alkyl or trifluoromethyl group; and

Y is an oxygen or sulfur atom or a possibly substituted nitrogen atom of the formula



wherein L is a hydrogen atom or a lower alkyl, lower alkylcarbonyl, lower alkyloxy-carbonyl-lower alkyl, carboxy-lower alkyl, phenyl, phenylmethyl, lower alkylaminocarbonyl, hydroxymethyl or lower alkenyl group; or

b) a group having the formula



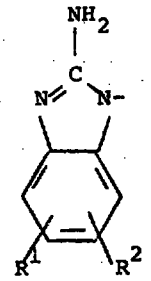
wherein:

R^1 and R^2 are as above defined; and

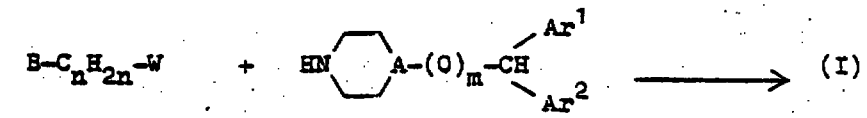
M is a hydrogen atom or a lower alkyl, phenyl, phenylmethyl, mercapto, lower alkylthio, amino, lower alkylcarbonylamino, lower alkyloxycarbonylamino or cycloalkyl group having from 3 to 6 carbon atoms.

By the term "lower alkyl" as used herein is meant straight and branched chain alkyl groups having from 1 to 6 carbon atoms such as, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, butyl, pentyl and hexyl; by the term "lower alkenyl" as used herein is meant straight and branched chain alkenyl groups having from 2 to 6 carbon atoms such as, ethenyl, 1-methylethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 1-methyl-2-butenyl, 2-pentenyl and 2-hexenyl; by the term "cycloalkyl" as used herein is meant cyclic hydrocarbon groups having from 3 to 6 carbon atoms such as, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; the expression "C_nH_{2n}" refers to straight and branched chain alkylene chains having from 2 to 6 carbon atoms and having at least 2 carbon atoms in the linear portion of the chain linking the B-group with the piperidine or piperazine nitrogen, such as, 1,2-ethanediyl, 1,3-propanediyl, 2-methyl-1,3-propanediyl, 1,4-butanediyl, 2-methyl-1,4-butanediyl, 1,5-pentanediyl and 1,6-hexanediyl; and by the term "halogen" is meant halogens of atomic weight less than 127, i.e. fluorine, chlorine, bromine and iodine.

The compounds of formula (I), except those wherein B is a 2-amino-1H-benzimidazol-1-yl group, may conveniently be prepared by reacting an appropriate reactive ester of formula (II) wherein *n* is as previously defined, B is as previously defined except a 2-amino-1H-benzimidazol-1-yl group of the formula:



wherein R^1 and R^2 are as previously defined, and W is an appropriate reactive ester function derived from the corresponding alcohol such as, halogen, methanesulfonyl or 4-methylbenzenesulfonyl, with an appropriate piperidine or piperazine derivative of formula (III) wherein A, *m*, Ar_1 and Ar^2 are as previously defined:

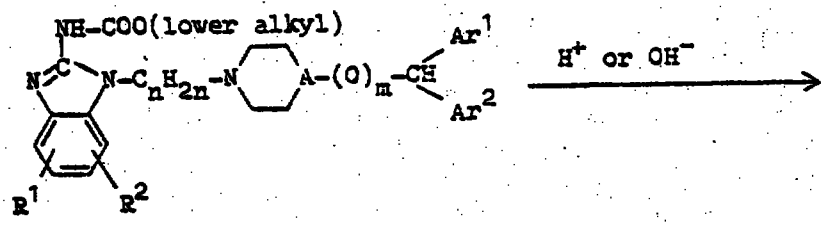


(II) (III)

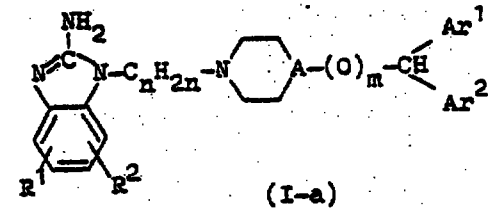
This condensation reaction is preferably carried out in an appropriate reaction-inert organic solvent such as, a lower alkanol, e.g., methanol, ethanol, propanol or butanol; an aromatic hydrocarbon e.g., benzene, methylbenzene or dimethylbenzene; an ether, e.g., 1,4-dioxane or 1,1'-oxybispropane; a ketone, e.g., 4-methyl-2-pentanone; N,N-dimethylformamide or nitrobenzene. The addition of an appropriate base such as, an alkali metal or earth alkali metal carbonate or hydrogen carbonate, may be utilized to pick up the acid which is liberated during the course of the reaction. A small amount of an appropriate metal iodide, e.g., sodium or potassium iodide may be added as a reaction promoter. Somewhat elevated temperatures are appropriate to enhance the rate of the reaction and preferably the reaction is carried out at the reflux temperature of the reaction mixture.

In this and following preparations, the reaction products are separated from the reaction mixture and, if necessary, further purified using methods generally known in the art.

The compounds of formula (I) wherein B is a 2-amino-1H-benzimidazol-1-yl radical, (I—a), are easily prepared starting from the corresponding compounds (I) wherein B is a 2-(lower alkyloxycarbonylamino)-1H-benzimidazol-1-yl radical, (I—b), by decarboxylating the latter under hydrolytic conditions, for example, by acid hydrolysis using an appropriate strong acid, such as hydrochloric, hydrobromic or sulfuric acid, or by alkaline hydrolysis using an appropriate strong base such as, sodium or potassium hydroxide.

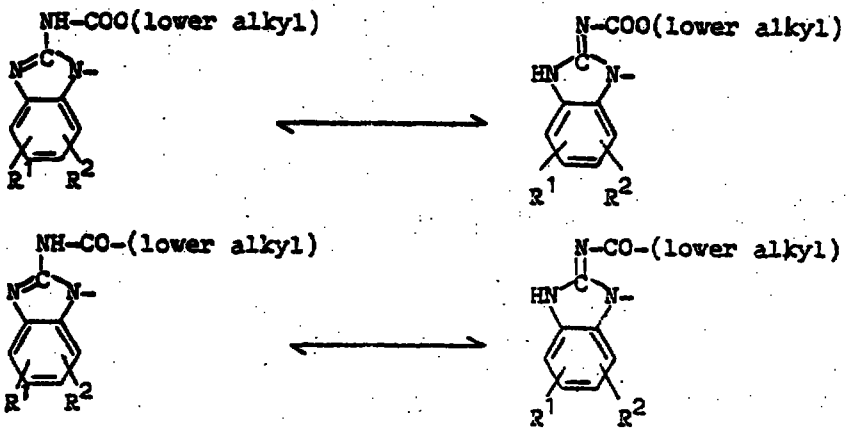


(I-b)



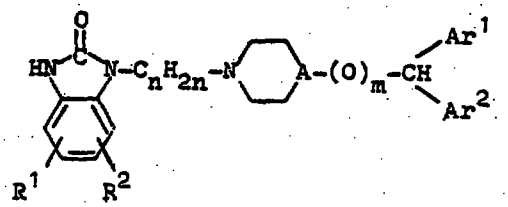
(I-a)

It is to be noted that when the B-group in compounds of formula (I) or in intermediates therefor is a 2-(lower alkloxycarbonylamino)-1H-benzimidazol-1-yl or a 2-(lower alkylcarbonylamino)-1H-benzimidazol-1-yl group, then the groups may exist in different tautomeric forms as is illustrated below:



The tautomeric forms of compounds of formula (I) are included within the scope of this invention.

Compounds of formula (I) which may be represented by the formula (I—c):



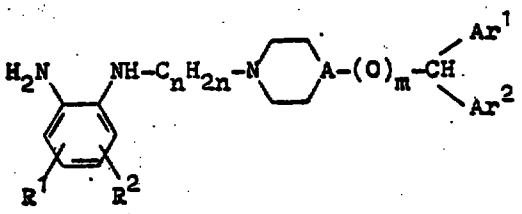
(I-c)

wherein R^1, R^2 n, A, Ar^1 and Ar^2 are as previously defined may alternatively be prepared by ring closure of an appropriate intermediate of formula (IV) with an appropriate cyclizing agent as known in the art for the preparation of 1,3-dihydro-2H-benzimidazol-2-ones starting from 1,2-benzenediamines.

Suitable cyclizing agents which may advantageously be employed include urea carbonyl dichloride and alkali metal isocyanates, and the cyclization reaction may be performed by methods generally known in the art. For example by methods

generally known in the art. For example, when urea is used as the cyclizing agent the compounds (I—c) are easily obtained by stirring and heating the reactants together in the absence of any solvent.

The foregoing preparations may be illustrated as follows:—

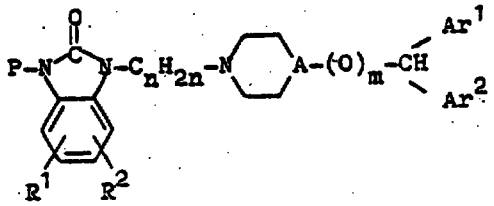


(IV)

cyclizing agent

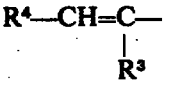
(I-c)

The compounds of formula (I—c) may also be prepared starting from the corresponding formula (V).



(V)

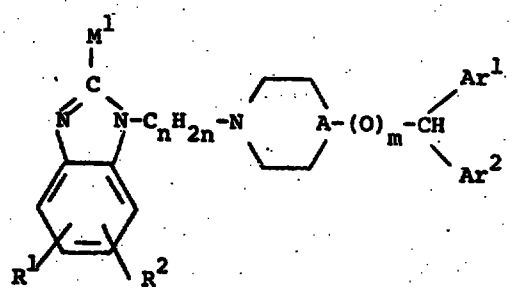
wherein R^1, R^2, n, A, m, Ar^1 and Ar^2 are as previously defined and P is an appropriate protecting group, by the removal of the protecting group according to conventional procedures. Examples of such protecting groups are lower alkyloxycarbonyl and, a substituted ethenyl group of the formula:



wherein R^3 and R^4 may represent different groups but wherein R^3 is preferably lower alkyl and R^4 is preferably hydrogen, lower alkyl or phenyl.

When the protecting group is lower alkyloxycarbonyl, it may easily be removed by alkaline hydrolysis, and when the protecting group is a substituted ethenyl group it is conveniently eliminated by subjecting the appropriate intermediate (V) to acid hydrolysis. In carrying out this acid hydrolysis a wide variety of protonic acids may be employed, including mineral acids such as, hydrochloric, hydrobromic, sulfuric, nitric and phosphoric acid, and organic acids such as, acetic, propanoic and ethanedioic acid. Further the reaction may be carried out in reaction-inert organic solvents as commonly employed in such a type of hydrolytic reactions, e.g. lower alkanols such as, methanol, ethanol or 2-propanol.

In a procedure similar to that described for the preparation of the compounds (I—c) starting from (IV) compounds of the formula (I—d) may also be prepared



(I-d)

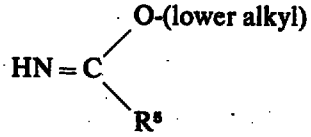
wherein R^1, R^2, n, A, m, Ar^1 and Ar^2 are as previously defined, and M^1 is a hydrogen atom or a lower alkyl, phenyl, phenylmethyl, mercapto, amino, lower alkyloxycarbonylamino or cycloalkyl group, by the reaction of (IV) with an appropriate cyclizing agent, using techniques known for preparing 1H-benzimidazoles starting from 1,2-benzenediamines. Depending on the nature of M^1 in the compounds (I—d) the following cyclizing agents may, for example, be employed.

When M^1 is a hydrogen atom formic acid or an appropriate tri(alkyloxy)-methane may be used as a cyclizing agent.

When M^1 is a lower alkyl, phenyl, phenylmethyl or cycloalkyl group, a carboxylic acid of the formula:

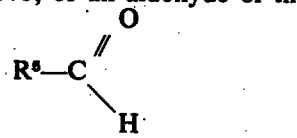
$$R^5—COOH \qquad (VI)$$

wherein R^5 is a lower alkyl, phenyl, phenylmethyl, or cycloalkyl group, or a functional derivative thereof such as, an acyl halide, an ester, an amide or a nitrile derived from such acid or an iminoester of the formula:



(VII)

wherein R^5 is as defined hereabove; or an aldehyde of the formula:



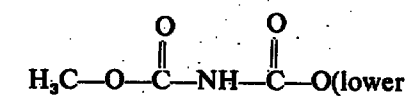
(VIII)

or an addition product thereof with an alkali metal hydrogen sulfite, may be used. When the cyclizing agent is an aldehyde an appropriate oxidizing agent such as nitrobenzene, mercuric oxide, Cu(II) or Pb(II) salts or other known suitable oxidants may be added to the reaction mixture, or the aldehyde itself, when added in excess, may serve as the oxidant.

When M^1 is a mercapto group cyclizing agents such as carbon disulfide, thiourea, carbothioic dichloride or ammonium thiocyanate may be used.

When M^1 is an amino group, ring closure may be performed with cyanamide, or a metal salt thereof, preferably an alkali or earth alkali metal salt, or with BrCN.

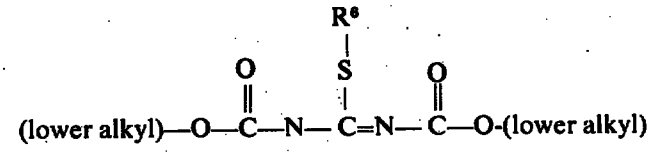
When M^1 is a lower alkyloxycarbonylamino group, an appropriate lower alkyl (iminomethoxymethyl)-carbamate of the formula (IX):



(IX)

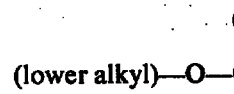
or

a lower alkyl [(lower alkoxycarbonylamino)(R^6-thio)-methylene]carbamate of the formula (X)



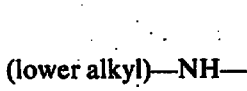
(X)

wherein R^6 is a hydrogen atom or a methyl group; or
a lower alkyl carbonoisothiocyanatidate of the formula (XI)



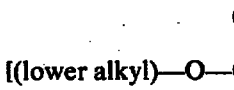
(XI)

a lower alkyl lower alkylcarbamothioate of the formula (XII)



(XII)

a dilower alkyl cyanimidodicarbonate of the formula (XIII)

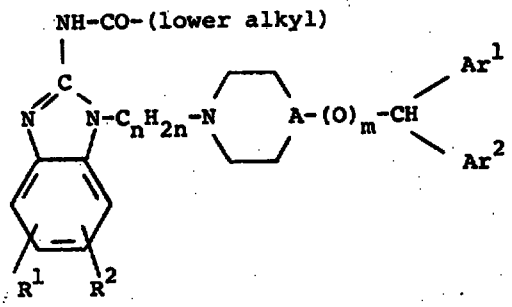


(XIII)

may be used as the cyclizing agent.

The foregoing cyclization reactions may all be performed by methods described in the literature.

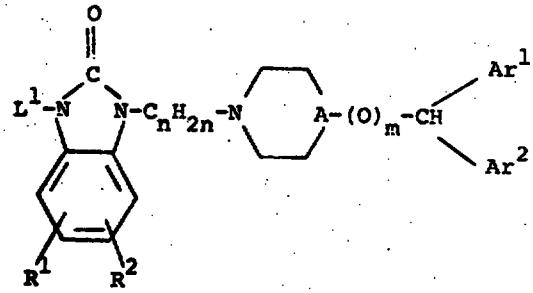
Compounds of the formula (I—e)



(I—e)

may alternatively be prepared by the acylation of an appropriate 2-amino-1H-benzimidazol-1-yl derivative of formula (I—a) following standard N-acylating procedures, e.g., by the reaction of (I—a) with an appropriate lower alkylcarbonyl halide or with an anhydride derived from a lower alkylcarboxylic acid.

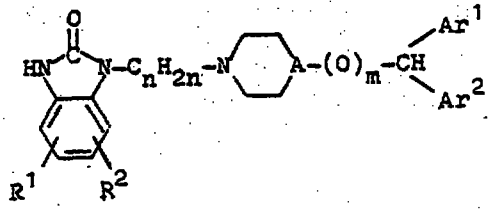
Compounds of the formula (I—f)



(I-f)

wherein R^1, R^2, n, A, m, Ar^1 and Ar^2 are as previously defined and L^1 is a lower alkyl, lower alkylcarbonyl, lower alkyloxycarbonyl-lower alkyl, carboxy-lower alkyl, phenylmethyl, lower alkylaminocarbonyl, hydroxymethyl or lower alkenyl

group, provided that the unsaturation in the lower alkenyl group is located in a position other than α, may be prepared by the introduction of L^1 into a compound of formula (I—c)



(I—c)

Depending on the nature of the L^1 group to be introduced the following methods may be utilized therefor.

When L^1 is a lower alkyl, lower alkyloxycarbonyl-lower alkyl, phenylmethyl or lower alkenyl group, in which case the symbol L^1_a is used therefor, the introduction of L^1_a into (I—c) may be performed by the reaction of (I—c) with an appropriate reactive ester of the formula L^1_a—W, (XIV), wherein L^1_a is as defined hereabove and W has the same meaning as given in the definition of the starting materials of formula (II).

The condensation of (XIV) with (I—c) may be carried out under conditions similar to those described for the condensation of the reactive esters (II) with the intermediates of formula (III).

In order to enhance the reaction rate it may be appropriate in some cases to add to the reaction mixture a small amount of an appropriate macrocyclic polyether such as, 2,3;11,12-dibenzo-1,4,7,10,12,16-hexaoxacyclooctadeca-2,11-diene as a reaction promotor.

When the L^1 group which is to be introduced is a lower alkyloxycarbonylethyl group, the introduction of the group may alternatively be performed by reacting (I—c) with a (lower alkyl) 2-propenoate of formula (XV)

(lower alkyl)OOC—CH=CH_2 (XV)

This reaction may conveniently be carried out in a reaction-inert organic solvent such as, an aromatic hydrocarbon, e.g., benzene, methylbenzene or dimethylbenzene; an ether, e.g., 1,1'-oxybisethane, 2,2'-oxybispropane, tetrahydrofuran or 1,4-dioxane. Preferably in the presence of an appropriate aminium hydroxide such as, N,N,N-triethylbenzenemethanaminium hydroxide.

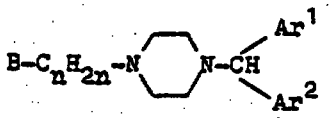
Compounds of formula (I—f) wherein L^1 is a carboxy-lower alkyl can easily be derived from the corresponding lower alkyloxycarbonyl-lower alkyl substituted compounds by hydrolyzing the latter in the usual manner, e.g., with aqueous alkali, to liberate the acid from the ester.

When L^1 is lower alkylcarbonyl the group may conveniently be introduced by the reaction of (I—c) with an appropriate acylating agent derived from the corresponding lower alkylcarboxylic acid such as, a halide, preferably, the chloride, or an anhydride, following standard N-acylating procedures.

When L^1 is lower alkylaminocarbonyl it may be introduced by the reaction of (I—c) with an appropriate isocyanatoalkane in an appropriate reaction-inert organic solvent such as, an ether, e.g., 1,1'-oxy-bisethane, 2,2'-oxybispropane or 1,4-dioxane.

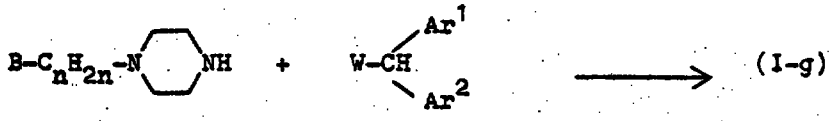
When L^1 is a hydroxymethyl group its introduction is conveniently performed by the reaction of (I—c) with formaldehyde in an appropriate organic solvent such as, N,N-dimethylformamide.

Compounds of the formula (I—g)



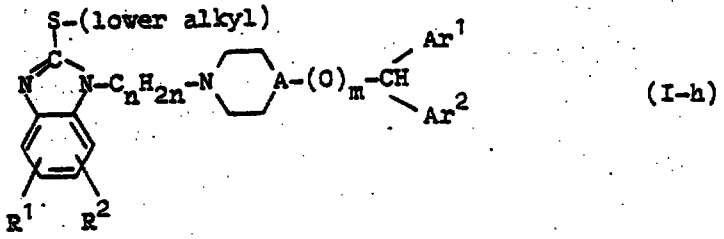
(I—g)

wherein B, n, Ar^1 and Ar^2 are as previously defined may alternatively be prepared by the condensation of a piperazine derivative of formula (XVI) with an appropriate reactive ester of formula (XVII) wherein Ar^1, Ar^2 and W are as previously defined, under conditions similar to those described for the preparation of the compounds (I) starting from (II) and (III).



(XVI) (XVII) (I-g)

Compounds of the formula (I—h)

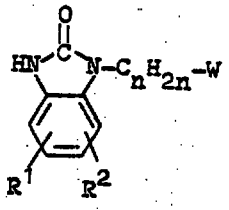


(I-h)

are also conveniently prepared starting from the corresponding —SH substituted analogs by standard S-alkylating procedures, e.g., by the reaction of the mercapto compound with an appropriate halo-lower alkane in an appropriate organic solvent such as, a lower alkanol, e.g., ethanol, propanol, 2-propanol or butanol.

A number of the intermediates of formula (II) are known compounds. Depending on the nature of B in the intermediates (II) the following procedures may be utilized for preparing them.

Intermediates of the formula (II—a)

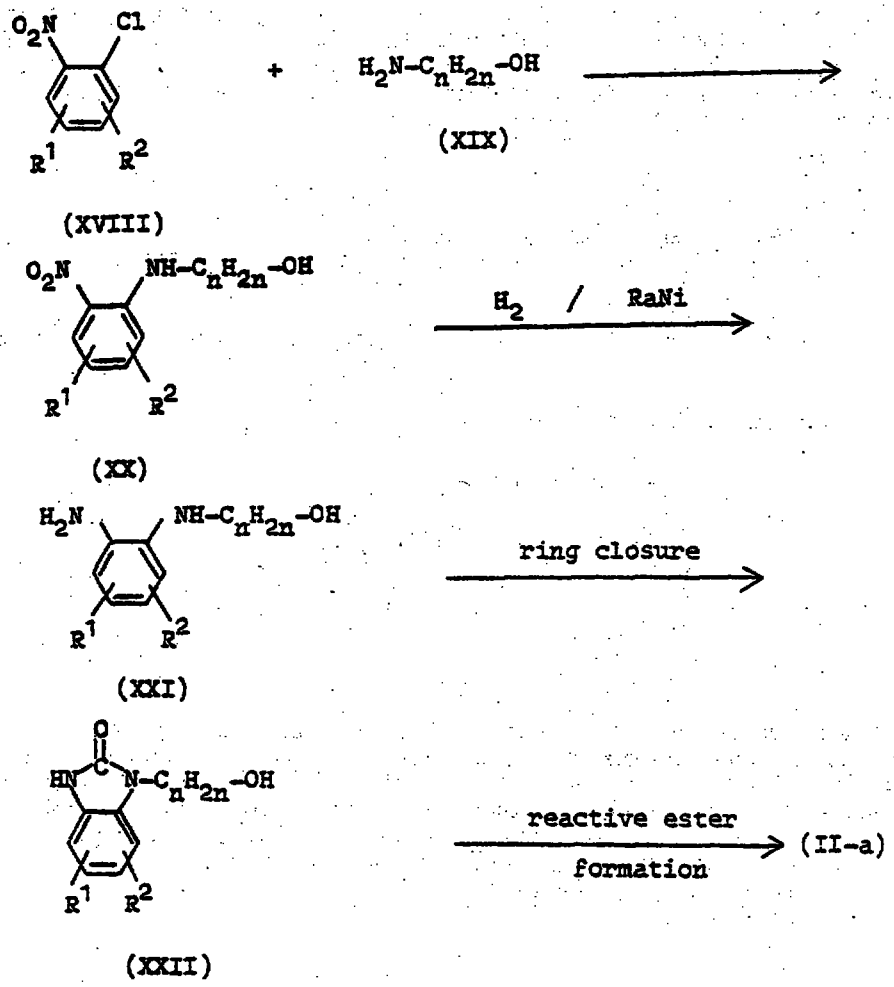


(II-a)

may be prepared as follows:

An appropriately substituted 2-chloronitrobenzene of formula (XVIII) is reacted with an appropriate aminoalkanol (XIX) by refluxing the reactants together in an appropriate reaction-inert organic solvent such as, a lower alkanol, e.g., ethanol, propanol, 2-propanol or butanol, whereupon a [(2-nitrophenyl)amino]alkanol of formula (XX) is obtained, which in turn is subjected to a nitro-to-amine reduction, e.g., by catalytic hydrogenation using Raney-nickel catalyst. The so-obtained intermediate (XXI) is then reacted with an appropriate cyclizing agent as described hereinbefore for the preparation of the compounds (I—c) starting from (IV), and the thus-obtained alcohol of formula (XXII) is subsequently converted into the desired reactive ester (II—a) by the known methods. Halides are conveniently prepared by the reaction of (XXII) with an appropriate halogenating agent such as, sulfinyl chloride, sulfuryl chloride, phosphor pentachloride, phosphor pentabromide or phosphoryl chloride. When the reactive ester is an iodide, it is preferably derived from the corresponding chloride or bromide by the replacement of that halogen with iodine. Other reactive esters such as methanesulfonates and 4-methylbenzenesulfonates are obtained by the reaction of the alcohol with an appropriate sulfonyl halide such as, methanesulfonyl chloride and 4-methylbenzenesulfonyl chloride, respectively.

The foregoing reactions are more clearly illustrated in the following schematic representation.



Alternatively the intermediates of formula (II—a) may also be prepared by:

i) reacting a compound of formula (XXIII) wherein R^3 and R^4 are as previously defined with a haloalkanol of formula (XXIV) by conventional N-alkylating procedures to obtain an alcohol of formula (XXV);

ii) converting the hydroxyl function of (XXV) into a reactive ester group in the usual manner as previously described; and

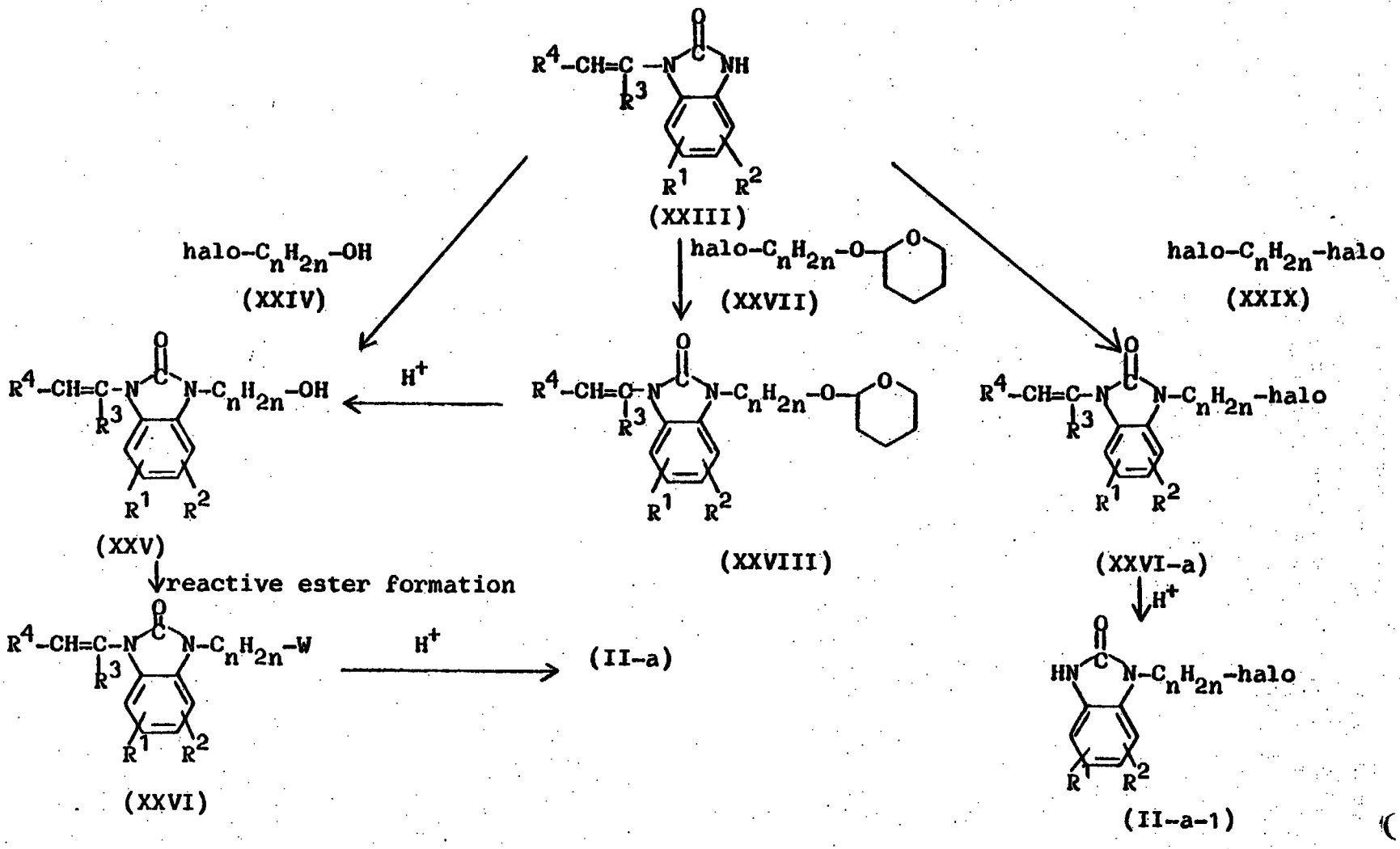
iii) eliminating the substituted ethenyl group of the thus obtained (XXVI) by acid hydrolysis as described hereinbefore for the preparation of (I—c) starting from (V).

The introduction of the hydroxyalkyl chain in (XXIII) to obtain (XXVI) may also be performed by the reaction of (XXIII) with an appropriate 2-(haloalkyloxy)tetrahydro-2H-pyran of formula (XXVII), yielding an intermediate of formula (XXVIII), the ether function of which is hydrolytically split open, e.g., by the treatment with an aqueous hydrochloric acid solution.

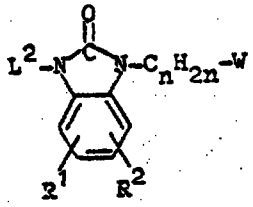
When the reactive ester (II—a) is a halide, (II—a—I), it may alternatively be prepared by the reaction of (XXIII) with an equivalent amount of an appropriate dihaloalkane, (XXIX) in the presence of an appropriate strong base such as, for example, sodium methoxide, or following a Mackosza procedure using aqueous alkali and a quaternary ammonium catalyst, e.g., N,N,N-triethylbenzenemethanaminium chloride, yielding an intermediate of formula (XXVI—a), the substituted ethenyl group of which is subsequently removed by acid hydrolysis, to yield the desired halide (II—a—1).

It is to be noted that the same procedures are also applicable when the substituted ethenyl group is replaced by another appropriate protecting group, except that removal thereof has to be performed following appropriate methods for the elimination of the particular group involved.

The foregoing reactions are more clearly illustrated in the following schematic representation.

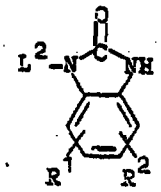

(XXIII)
halo-C_nH_{2n}-OH
(XXIV)
halo-C_nH_{2n}-O-THP
(XXVII)
halo-C_nH_{2n}-halo
(XXIX)
H^+
(XXV)
(XXVIII)
(XXVI-a)
reactive ester formation
(XXVI)
(II-a)
(II-a-1)

Intermediates of the formula (II—b)



(II-b)

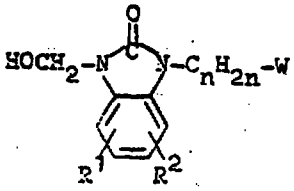
wherein R^1, R^2, n and W are as previously defined and L^2 is selected from the group consisting of lower alkyl, lower alkenyl, lower alkyloxycarbonyl-lower alkyl, phenyl, phenylmethyl and lower alkylaminocarbonyl, may conveniently be prepared by the introduction of the reactive ester side chain into a starting material of the formula (XXX).



(XXX)

following procedures similar to those described for the preparation of the intermediates (XXVI) starting from (XXIII).

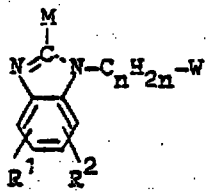
Intermediates of the formula (II—c)



(II-c)

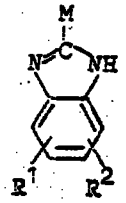
may be prepared starting from the corresponding (II—a) by hydroxymethylation of the latter in the usual manner with formaldehyde.

Intermediates of the formula (II—d)



(II-d)

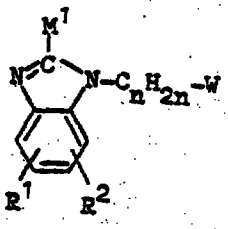
except those wherein M stands for a mercapto or lower alkylthio group, are conveniently obtained by the introduction of the reactive ester side chain into a starting material of the formula (XXXI)



(XXXI)

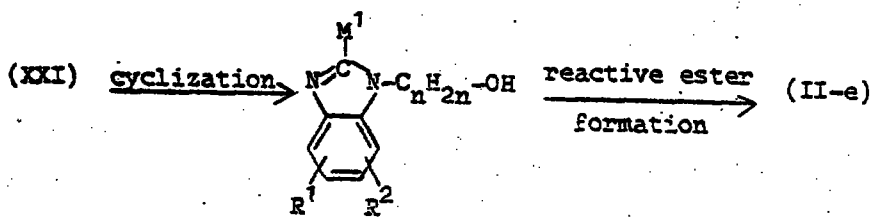
The introduction of the C_nH_{2n}—W group may be performed following procedures similar to those described for the introduction of the group into starting materials of formula (XXIII).

Intermediates of formula (II—e)



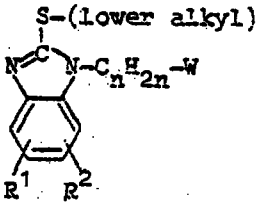
(II-e)

wherein R^1, R^2, M^1, *n* and W are as previously defined, may be prepared by subjecting an appropriate alcohol of formula (XXI) to ring closure with an appropriate cyclizing agent as described hereinbefore, followed by the conversion of the hydroxyl group of the thus obtained intermediate of formula (XXXII) into a reactive ester group.



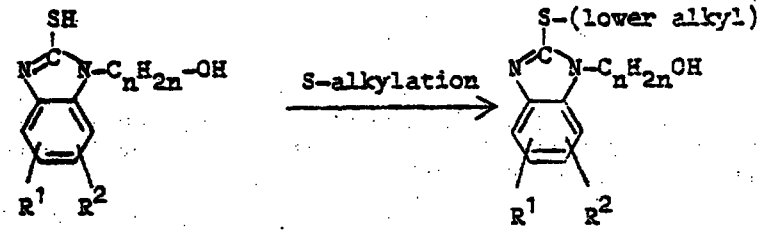
(XXXII)

The intermediates of the formula (II-f)

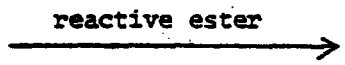


(II-f)

are conveniently obtained by S-alkylation of an appropriate intermediate of formula (XXXII), wherein M^1 is a mercapto group (XXXII—a), following standard S-alkylating procedures, e.g. with an appropriate halolower alkane and subsequent conversion of the hydroxyl function of the thus obtained (XXXIII) into a reactive ester group.

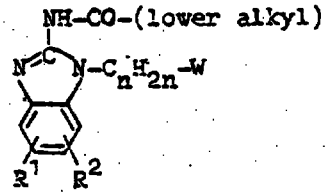


(XXXII-a) (XXXIII)



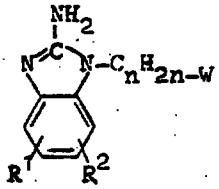
(II-f)

Intermediates of the formula (II-g)



(II-g)

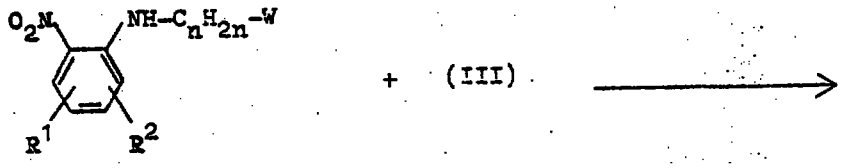
are conveniently prepared by N-acylation of the corresponding amino substituted analog, (II—h),



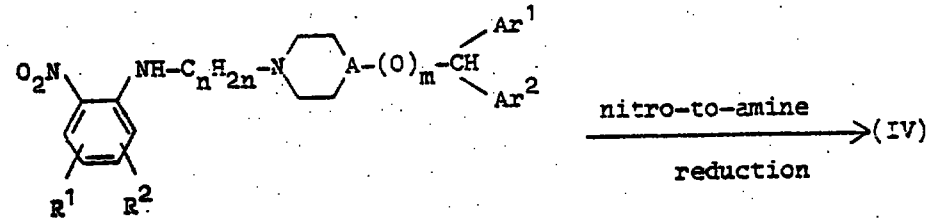
(II-h)

following procedures known in the art, e.g., by the reaction of (II—h) with an appropriate lower alkylcarbonyl halide or with an anhydride derived from an appropriate lower alkylcarboxylic acid.

The intermediates of formula (IV) are obtained by the condensation of an appropriate reactive ester of formula (XXXIV) with a piperazine or piperidine derivative of formula (III) followed by the reduction of the nitro group of the thus obtained intermediate (XXXV) to an amino group according to standard nitro-to-amine reduction procedures, e.g., by the reaction of the nitro compound with nascent hydrogen or by catalytic hydrogenation in the presence of an appropriate catalyst such as, Raney nickel.



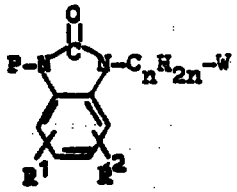
(XXXIV)



(XXXV)

The reactive esters of formula (XXXIV), used as starting materials herein are easily prepared from an alcohol of formula (XX) by the conversion of the hydroxyl function thereof into a reactive ester group following standard procedures as previously described herein.

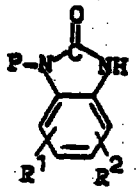
The intermediates of formula (V) may be obtained by the condensation of a reactive ester of formula (XXXVI) with a piperazine or piperidine derivative of formula (III)



(XXXVI)

+ (III) ⟶ (V)

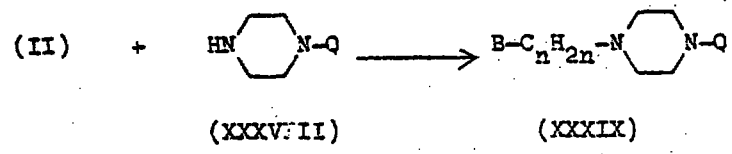
The reactive ester (XXXVI) used as a starting material herein is in turn prepared by introducing the $C_nH_{2n}W$ group into a starting material of formula (XXXVII).



(XXXVII)

following the procedures described hereinbefore.

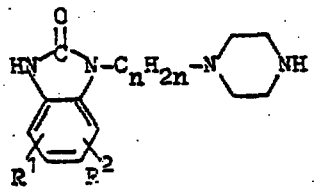
The intermediates of formula (XVI) may be prepared by the reaction of a reactive ester of formula (II) with a piperazine derivative of formula (XXXVIII) wherein Q is an appropriate protecting group such as, phenylmethyl or lower alkyloxycarbonyl, and subsequently eliminating the protecting group Q from the so-obtained intermediate (XXXIX) following standard known procedures, for example, by catalytic hydrogenation using palladium-on-charcoal catalyst when Q stands for phenylmethyl, or by alkaline hydrolysis when Q stands of lower alkoxycarbonyl.



(XXXVIII) (XXXIX)

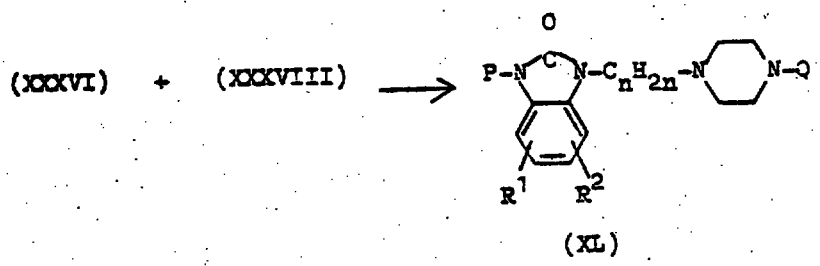
elimination of Q ⟶ (XVI)

Intermediates of formula (XVI-a)

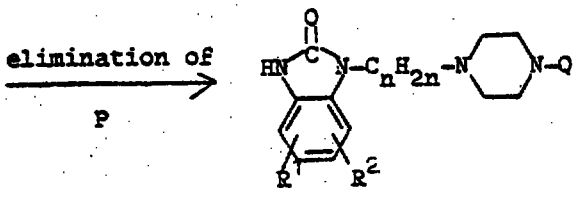


(XVI-a)

may alternatively be prepared by the reaction of (XXXVI) with (XXXVIII) to obtain an intermediate of formula (XL) and subsequently eliminating the protecting groups P and Q by appropriate procedures as generally known in the art.



(XXXVI) + (XXXVIII) → (XL)



elimination of P → (XXXIX-a)

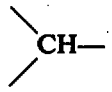
elimination of Q → (XVI-a)

Intermediates of formula (III) wherein A is

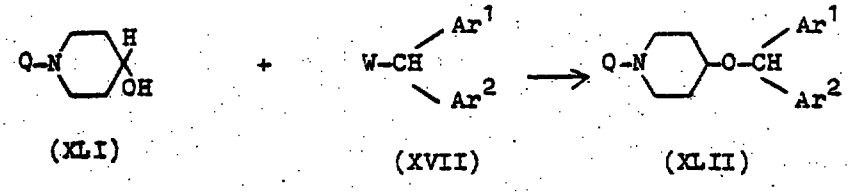


and *m* is 0, (III—a), are generally known and they may all be prepared by known methods. Such intermediates (III—a) may for example, be prepared by first subjecting an appropriate aroyl halide to a Friedel-Crafts reaction with an appropriate arene to obtain an Ar^1, Ar^2-methanone which in turn is reduced in the usual manner, e.g., with sodium borohydride to the corresponding methanol. The latter is then converted into a reactive ester (XVII) following standard procedures of preparing reactive esters starting from alcohols and the desired intermediates (III—a) are subsequently obtained by the reaction of XVII) with piperazine.

The intermediates of formula (III) wherein A is

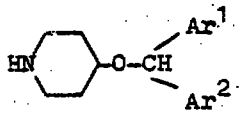


and *m* is 1, (III—b), may conveniently be prepared by O-alkylation of a 4-piperidinol of formula (XLI) wherein Q is an appropriate protecting group as previously defined with an appropriate reactive ester of formula (XVII), followed by the removal of the protecting group of the so-obtained (XLII) in the usual manner.



(XLI) + (XVII) → (XLII)

removal of Q →



(III-b)

The primary starting materials used in all of the foregoing preparations are generally known and they may all be prepared by known methods.

The compounds of formula (I) may be converted to the therapeutically active non-toxic acid addition salt form by treatment with an appropriate acid, such as, an inorganic acid, such as hydrohalic acid, e.g., hydrochloric or hydrobromic, and sulfuric acid, nitric acid or phosphoric acid; or an organic acid, such as, acetic, propanoic, hydroxy-acetic, 2-hydroxypropanoic, 2-oxopropanoic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, benzoic, 3-phenyl-2-propenoic, α-hydroxybenzeneacetic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic or 4-amino-2-hydroxybenzoic acid. Conversely, the salt form can be converted by treatment with alkali into the free base form.

The compounds of formula (I) and the pharmaceutically acceptable acid addition salts thereof possess strong anti-anaphylactic and antihistaminic properties and as such they are useful agents in human and animal therapy. The useful anti-anaphylactic and antihistaminic properties of the compounds of this invention are clearly demonstrated by the results obtained in the test procedures described hereafter.

It is emphasized that the compounds listed in the accompanying tables are not given for the purpose of limiting the invention thereto, but only to exemplify the useful anti-anaphylactic and antihistaminic properties of all the compounds within the scope of formula (I).

A. Materials and methods.

a) Anti-anaphylactic and antihistaminic effects in "vivo".

The anti-anaphylactic and antihistaminic effects of the subject compounds (I) and salts thereof are studied "in vivo" in guinea pigs.

Guinea pigs weighing between 400 and 500 g, are sensitized to ovalbumin by subplanter (s.p.) injection of 0.05 ml of antiserum in the left hind paw. The animals are then starved and orally treated, 24 hours after the sensitization, with saline (= control animals) or a particular dose of the compound under investigation.

The histamine injection (at a dose of 50 μg) was given s.p. in the right hind paw 2 hours after the oral pretreatment with the compound. The diameters of both hind paws are first measured before the histamine injection is given and again 10 minutes thereafter. The animals are challenged intravenously with 0.6 gm of ovalbumin 30 minutes after the histamine injection. All control animals develop typical primary anaphylactic shock symptoms (coughing, difficult breathing, convulsions) and 85% of these control animals die within 15 minutes after the ovalbumin injection. Protection against death is used as the criterion for possible drug effects and the estimated ED_{50}-value, i.e. the oral dose whereby the protection is observed in 50% of the guinea pigs, is listed in the tables below.

The median histamine paw œdema in 200 control animals 10 minutes after the histamine injection is 15 units (1 unit = 0.1 mm). Reactions below 10 units, occurring in less than 5% of the control animals are defined as effective inhibition of histamine œdema in the compound-treated animals and the oral dose-levels whereby this effective inhibition is seen, is also listed in the following tables.

b) Anti-histamine activity in "vitro".

Guinea-pig ileum strips are suspended in a 100 ml Tyrode bath at 37.5°C with a preload of 0.75 g and gassed with 95% O_2 and 5% CO_2.

The histamine—(0.5 mg/liter) induced spasms are recorded Kymographically with an isotonic lever giving a 5-fold magnification. The interaction of the compound to be tested (5 minutes incubation time) with the agonist is studied and the tables below give the effective concentration (in mg/l) of the different compounds whereby a significant inhibition (50%) of the histamine-induced contraction is measured.

As a result of the foregoing tests, the subject compounds (I) and pharmaceutically acceptable salts thereof are generally found active as anti-allergic agents in doses ranging from about 0.25 to about 20 mg/kg body weight upon systemic administration to warm-blooded animals.

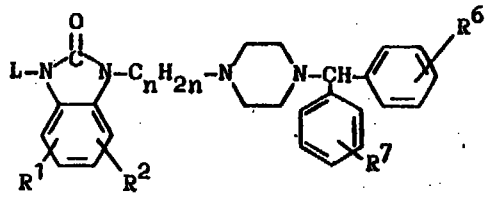
In view of their useful antihistaminic and antianaphylactic activity, the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the pharmaceutical compositions of this

invention, an effective antihistaminic or anti-anaphylactic amount of the particular compound, in base or acid-addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable diluent or carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration.

These pharmaceutical compositions are desirable in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils and alcohols in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders and disintegrating agents in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Acid addition salts of (I), due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonsful and tablespoonsful; and segregaged multiples thereof.

TABLE I-a



L	R^1	R^2	C_nH_{2n}	R^6	R^7	Base or Salt form	Histamine in "vitro" (ileum) effective conc. in mg/l	Anaphylaxis in guinea pigs oral effective dose in mg/kg	
								Survival	Histamine oedema
H	H	H	$(CH_2)_2$	H	H	base	0.01	0.63	1.25
H	5-Cl	H	$(CH_2)_2$	H	H	base	0.01	0.63	1.25
H	H	6-Cl	$(CH_2)_2$	H	H	base	0.02	2.5	2.5
H	5-CF_3	H	$(CH_2)_2$	H	H	base	0.02	0.31	1.25
H	5-CH_3	H	$(CH_2)_2$	H	H	base	0.01	1.25	1.25
H	H	H	$(CH_2)_2$	4-F	H	base	0.02	0.31	0.16
H	H	H	$(CH_2)_2$	4-F	4-F	base 1/2H_2O	0.02	0.63	0.63
H	H	H	$(CH_2)_3$	H	H	base	0.005	0.10	0.31
H	5-Cl	H	$(CH_2)_3$	H	H	base	0.01	0.63	1.25
H	5-CH_3	H	$(CH_2)_3$	H	H	base	0.01	0.08	0.16
H	H	6-Cl	$(CH_2)_3$	H	H	base	0.04	0.63	0.63
H	H	6-CH_3	$(CH_2)_3$	H	H	base	0.01	0.16	0.31
H	H	7-Cl	$(CH_2)_3$	H	H	base	0.08	≥2.5	—
H	5-Cl	6-Cl	$(CH_2)_3$	H	H	base	≥0.16	2.5	2.5
H	5-CF_3	H	$(CH_2)_3$	H	H	base	0.02	0.31	0.31
$CH_2=C(CH_3)-$	H	H	$(CH_2)_3$	H	H	base	0.01	0.16	0.31

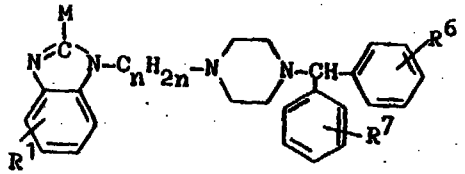
TABLE I-a (cont'd)

L	R^1	R^2	C_nH_{2n}	R^6	R^7	Base or Salt form	Histamine in "vitro" (ileum) effective conc. in mg/l	Anaphylaxis in guinea pigs oral effective dose in mg/kg	
								Survival	Histamine oedema
C_2H_5-OOC-$(CH_2)_2$	H	H	$(CH_2)_3$	H	H	$2HCl.2H_2O$	0.005	0.63	0.63
C_6H_5-CH_2-	H	H	$(CH_2)_3$	H	H	2 HCl	0.16	1.25	1.25
CH_3-CO-	H	H	$(CH_2)_3$	H	H	base	0.005	0.10	0.31
CH_3-NH-CO-	H	H	$(CH_2)_3$	H	H	base	0.02	–	–
CH_3-	H	H	$(CH_2)_3$	H	H	$2HCl.H_2O$	0.01	1.25	2.5
$HOCH_2$-	H	H	$(CH_2)_3$	H	H	base	0.01	0.31	0.31
C_6H_5-	5-Cl	H	$(CH_2)_3$	H	H	$2HCl.1/2H_2O$	0.08	–	–
H	H	H	$(CH_2)_3$	4-F	H	base	0.01	0.31	0.31
H	H	H	$(CH_2)_3$	4-Cl	H	base	0.01	1.25	0.63
H	H	H	$(CH_2)_3$	3-Cl	H	base	0.01	0.63	1.25
H	H	H	$(CH_2)_3$	4-F	4-F	base	0.01	0.31	0.16
H	5-Cl	H	$(CH_2)_3$	4-F	4-F	base	0.04	1.25	1.25
H	H	6-Cl	$(CH_2)_3$	4-F	4-F	$base.H_2O$	0.02	0.63	1.25
H	H	H	$(CH_2)_3$	2-F	4-Cl	base	0.02	0.31	1.25
H	H	H	$(CH_2)_4$	H	H	base	0.01	0.16	0.31
H	H	H	$(CH_2)_4$	4-F	4-F	$2HCl.H_2O$ $1/2C_2H_5OH$	0.01	0.16	0.31
H	H	H	$(CH_2)_5$	H	H	$2HCl.H_2O$	0.01	0.63	2.5
H	H	H	$(CH_2)_5$	4-F	4-F	$2HCl.H_2O$	0.01	1.25	2.5

TABLE I-a (cont'd)

L	R^1	R^2	C_nH_{2n}	R^6	R^7	Base or Salt form	Histamine in "vitro" (ileum) effective conc. in mg/l	Anaphylaxis in guinea pigs oral effective dose in mg/kg	
								Survival	Histamine oedema
H	H	H	$(CH_2)_6$	H	H	base	0.01	1.25	2.5
H	H	H	$-CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-$	4-F	4-F	base	0.02	1.25	1.25
H	H	H	$(CH_2)_3$	H	2-Cl	base	0.08	–	–
H	H	H	$(CH_2)_3$	4-Cl	4-Cl	base	0.16	<2.5	<2.5
H	H	H	$(CH_2)_3$	H	4-Br	base	0.16	<2.5	<2.5
H	H	H	$(CH_2)_3$	H	2-F	base	0.02	<2.5	<2.5
H	H	H	$(CH_2)_3$	4-F	$4-CH_3$	base	0.16	<2.5	<2.5
H	H	H	$(CH_2)_3$	H	$4-CH_3$	base	0.08	<2.5	<2.5
H	H	H	$(CH_2)_3$	H	$4-NO_2$	base	0.16	<2.5	<2.5
$HOOC-CH_2$	H	H	$(CH_2)_3$	H	H	base $1/2H_2O$	0.08	<2.5	<2.5

TABLE I-b

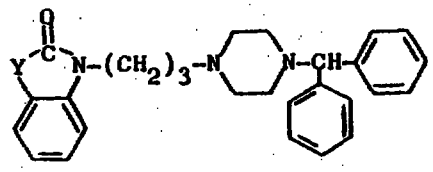


M	R^1	C_nH_{2n}	R^6	R^7	Base or Salt form	Histamine in "vitro" (ileum) effective conc. in mg/.l	Anaphylaxis in guinea pigs oral effective dose in mg/kg	
							Survival	Histamine oedema
H	H	$(CH_2)_2$	H	H	Base	0.005	1.25	1.25
C_2H_5–	H	$(CH_2)_2$	H	H	$3HCl.H_2O$	⩾0.16	–	–
H	H	$(CH_2)_3$	H	H	base	0.0025	0.08	0.16
CH_3–S–	H	$(CH_2)_3$	H	H	$3HCl.H_2O$	0.16	1.25	1.25
CH_3–	H	$(CH_2)_3$	H	H	base	0.02	2.5	2.5
C_6H_5–	H	$(CH_2)_3$	H	H	base	0.08	–	–
HS–	H	$(CH_2)_3$	H	H	base	0.01	0.63	1.25
cyclohexyl-	H	$(CH_2)_3$	H	H	base	⩾0.16	2.5	2.5
C_6H_5-CH_2–	H	$(CH_2)_3$	H	H	$3HCl.H_2O$	⩾0.16	–	–
CH_3OOC–NH–	H	$(CH_2)_3$	H	H	base	⩽0.16	2.5	2.5
H_2N–	H	$(CH_2)_3$	H	H	base	⩽0.16	2.5	2.5
CH_3–CO–NH–	H	$(CH_2)_3$	H	H	base	⩾0.16	2.5	–
C_2H_5–	H	$(CH_2)_3$	H	H	$3HCl.H_2O$	0.01	2.5	2.5
cyclohexyl-	5-Cl	$(CH_2)_3$	H	H	base	–	0.63	2.5
C_2H_5–	5-Cl	$(CH_2)_3$	H	H	$3HCl.H_2O$	0.01	–	–
C_6H_5-CH_2–	5-Cl	$(CH_2)_3$	H	H	$3HCl.H_2O$	–	2.5	–

TABLE I-b (cont'd)

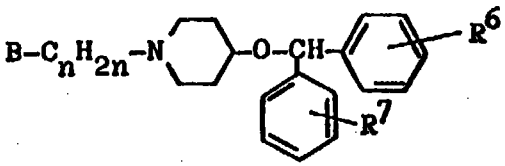
M	R^1	C_nH_{2n}	R^6	R^7	Base or Salt form	Histamine in "vitro" (ileum) effective conc. in mg/l	Anaphylaxis in guinea pigs oral effective dose in mg/kg	
							Survival	Histamine oedema
C_6H_5–	6-Cl	$(CH_2)_3$	H	H	base	–	2.5	–
cyclohexyl-	6-Cl	$(CH_2)_3$	H	H	base	–	2.5	–
H	H	$(CH_2)_3$	4-F	H	base	0.005	0.31	0.31
H	H	$(CH_2)_3$	2-Cl	H	$3HCl2H_2O$	0.01	1.25	1.25
H	H	$(CH_2)_3$	4-Cl	H	base	0.01	0.08	0.31
H	H	$(CH_2)_3$	4-F	4-F	base H_2O	0.02	0.16	0.31
H	H	$(CH_2)_4$	H	H	base	0.0025	0.16	0.16
CH_3	H	$(CH_2)_4$	H	H	base	0.005	1.25	1.25
H	H	$(CH_2)_4$	4-F	H	base	0.005	0.08	0.16
H	H	$(CH_2)_4$	3-Cl	H	$3HCl.H_2O$ $1/2CH_3CHOHCH_3$	0.01	1.25	1.25
H	H	$(CH_2)_4$	4-F	4-F	base	0.005	0.31	0.31
H	H	CH_2–$CH(CH_3)$–CH_2	H	H	$3HCl1/2H_2O$	0.02	–	–
H	H	CH_2–$CH(CH_3)$–CH_2	4-F	4-F	$3HCl1/2H_2O$	0.02	0.63	1.25

TABLE I-c



Y	Base or Salt form	Histamine in "vitro" ileum effective conc. in mg/l	Anaphylaxis in guinea pigs oral effective dose in mg/kg	
			Survival	Histamine oedema
S	2 HCl . 1/2 H_2O	0.01	1.25	1.25
O	2 HCl	0.01	0.63	2.5

Table I-d



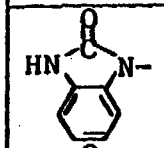
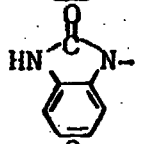
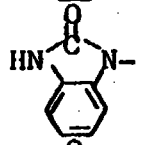
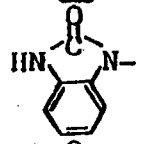
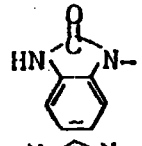
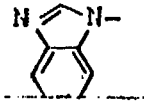
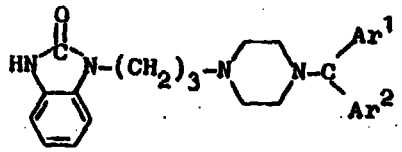
B	C_nH_{2n}	R^6	R^7	Base or Salt form	Histamine in "vitro" (ileum) effective dose in mg/l	Anaphylaxis in guinea pigs oral effective dose in mg/kg	
						Survival	Histamine œdema
	$(CH_2)_2$	H	H	HCl	0,0025	0.31	0.16
	$(CH_2)_3$	H	H	base	0,0025	0,63	1.25
	$(CH_2)_4$	H	H	base	0.005	0.63	0.31
	$(CH_2)_2$	4-F	4-F	HCl.1/2H_2O	0.0025	0.31	0.31
	$(CH_2)_3$	4-F	4-F	HCl.1/2H_2O	0.0025	0.63	0.63
	$(CH_2)_3$	H	H	base	0.0025	0.16	0.16

TABLE I-e



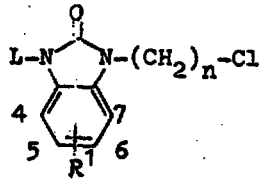
Ar^1	Ar^2	Base or Salt Form	Histamine in "vitro" (ileum) effective dose in mg/l	Anaphylaxis in guinea pigs oral effective dose in mg/kg	
				Survival	Histamine oedema
C_6H_5	2-pyridinyl	base	0.16	–	2.5
C_6H_5	3-pyridinyl	base	0.08	–	<2.5
C_6H_5	2,5-$(CH_3)_2$-C_6H_3	base	0.16	–	–
4-Cl-C_6H_4	3-pyridinyl	base	0.08	1.25	2.5
4-F-C_6H_4	3-pyridinyl	base	0.08	<2.5	<2.5
4-F-C_6H_4	4-pyridinyl	base	0.16	–	<2.5

The following examples are intended to illustrate but not to limit the scope of the present invention. Unless otherwise stated all parts therein are by weight.

Example I.

To a stirred and hot mixture of 54 parts of 1,3-dihydro-1-(phenylmethyl)-2H-benzimidazol-2-one, 47.25 parts of 1-bromo-3-chloropropane and 6 parts of N,N,N-triethylbenzenemethanaminium chloride are added dropwise 450 parts of sodium hydroxide solution 60% at 60°C. Upon completion, stirring is continued for 6 hours at 60°C. The reaction mixture is cooled and poured onto water. The oily product is extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is crystallized from 2,2'-oxybispropane, yielding, after drying, 42 parts (58%) of 1-(3-chloropropyl)-1,3-dihydro-3-(phenylmethyl)-2H-benzimidazol-2-one.

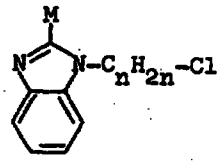
Similarly were prepared:



L	R^1	n	boiling point
$CH_2=C(CH_3)$	5-CH_3	3	140°C at 0.015 mm. pressure
$CH_2=C(CH_3)$	6-CH_3	3	140°C at 0.02 mm. pressure
C_6H_5	5-Cl	3	-
$CH_2=C(CH_3)$	H	4	-
$CH_2=C(CH_3)$	H	5	-
$CH_2=C(CH_3)$	H	6	-

Example II.

Following the procedure of Example I and using an equivalent amount of an appropriate 1H-benzimidazole as a starting material there were obtained as a residue:



M	C_nH_{2n}
CH_3	$(CH_2)_3$
H	$(CH_2)_3$
C_2H_5	$(CH_2)_3$
H	$CH_2-CH(CH_3)-CH_2$
C_6H_5	$(CH_2)_3$
CH_3	$(CH_2)_4$

Example III.

A mixture of 20 parts of 3-[(2-amino-4-chlorophenyl)amino]-1-propanol, 50 parts of acetic acid and 150 parts of hydrochloric acid solution 4N is stirred and refluxed overnight. The reaction mixture is cooled and evaporated. The residue is dissolved in water and the solution is alkalized with ammonium hydroxide. The product is extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is crystallized from a mixture of 4-methyl-2-pentanone and 2,2'-oxybispropane, yielding 6.5 parts (28%) of 5-chloro-2-methyl-1H-benzimidazole-1-propanol.

Similarly there was prepared 5-chloro-2-ethyl-1H-benzimidazole-1-propanol by the reaction of 3-[(2-amino-4-chlorophenyl)amino]-1-propanol with propanoic acid.

Example IV.

To a stirred and refluxing (water-separator) mixture of 30 parts of 3-[(2-amino-4-chlorophenyl)amino]-1-propanol and 0.1 parts of 4-methylbenzenesulfonic acid in 405 parts of methylbenzene is added dropwise a solution of 34 parts of cyclohexanecarboxaldehyde in 45 parts of methylbenzene. Upon completion, stirring is continued for 1 hour at reflux temperature and with water-separator. The methylbenzene is removed by evaporation in vacuo and the residue is triturated in 2,2'-oxybispropane. The product is filtered off and dried, yielding 16.5 parts (38%) of 5-chloro-2-cyclohexyl-1H-benzimidazole-1-propanol; m.p. 95°C.

Example V.

A mixture of 30 parts of 3-[(2-amino-4-chlorophenyl)amino]-1-propanol, 44.8 parts of sodium α-hydroxybenzeneethanesulfonate and 120 parts of ethanol is stirred and refluxed for 30 minutes. The reaction mixture is evaporated and the residue is taken up in water. The oily product is extracted with trichloromethane. The extract is dried, filtered and evaporated, yielding 45 parts (100%) of 5-chloro-2-(phenylmethyl)-1H-benzimidazole-1-propanol as a residue.

Similarly there was prepared 6-chloro-2-cyclohexyl-1H-benzimidazole-1-propanol; mp. 120.1°C by the reaction of 3-[(2-amino-5-chlorophenyl)amino]-1-propanol with sodium α-hydroxycyclohexanemethanesulfonate.

Example VI.

To a stirred mixture of 93 parts of 3-(2-aminophenyl)amino-1-propanol, 45.5 parts of potassium hydroxide and 600 parts of ethanol 85% in water are added dropwise 60.8 parts of carbon disulfide. Upon completion, stirring is continued for 6 hours at reflux temperature. The reaction mixture is evaporated and the residue is taken up in 1500 parts of water. The whole is filtered over Hyflo (Registered Trade Mark) and the filtrate is acidified with acetic acid. The oily product solidifies on scratching. It is filtered off, washed with water and dried, yielding 92 parts (78.9%) of 2-mercapto-1H-benzimidazole-1-propanol; mp. 110°C.

A mixture of 20.8 parts of 2-mercapto-1H-benzimidazole-1-propanol, 15.62 parts of iodomethane and 120 parts of methanol is stirred overnight at room temperature. The reaction mixture is evaporated and the residue is dissolved in 500 parts of water. The solution is filtered over hyflo and the filtrate is alkalized with solid potassium hydroxide. The oily product is extracted with trichloromethane. The extract is dried, filtered and evaporated, yielding 19 parts (85.5%) of 2-(methylthio-1H-benzimidazole-1-propanol as a residue.

To a stirred mixture of 19 parts of 2-(methylthio)-1H-benzimidazole-1-propanol, 15.2 parts of N,N-diethylethanamine and 195 parts of dichloromethane are added dropwise 11.5 parts of methanesulfonyl chloride. Upon completion, stirring is continued for 1 hour at reflux. After cooling, water is added and the layers are separated. The organic phase is dried, filtered and evaporated, yielding 19 parts of 3-[(2-methylthio)-1H-benzimidazole-1-yl]propyl methanesulfonate as an oily residue.

Example VII.

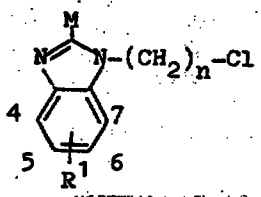
A mixture of 30 parts of 1H-benzimidazole, 49 parts of 2-(4-chlorobutoxy)-tetrahydro-2H-pyran, 21 parts of potassium hydroxide and 200 parts of ethanol is stirred and refluxed overnight. The reaction mixture is cooled to room temperature, filtered and the filtrate is evaporated. The residue is stirred in water and acidified with a diluted hydrochloric acid solution. The whole is stirred and heated for 30 minutes in a water-bath. After cooling to room temperature, the product is extracted with methylbenzene. The aqueous phase is separated and alkalized with ammonium hydroxide. The product is extracted with dichloromethane. The extract is dried, filtered and evaporated, yielding 50 parts of 1H-benzimidazole-1-butanol as an oily residue.

Example VIII.

To a stirred mixture of 5 parts of 4-chloro-1,3-dihydro-3-(3-hydroxypropyl)-2H-benzimidazol-2-one and 75 parts of trichloromethane are added dropwise 8 parts of sulfinyl chloride. Upon completion, stirring is continued for 3 hours at

reflux temperature. The reaction mixture is cooled and evaporated. The residue is stirred in a small amount of 4-methyl-2-pentanone. The product is filtered off and dried, yielding 3.5 parts of 4-chloro-3-(3-chloropropyl)-1,3-dihydro-2H-benz-imidazol-2-one.

In a similar manner the following 1-(chloroalkyl)-1H-benzimidazoles were prepared:



M	n	R^1	Base or Salt form	Melting Point
$C_6H_5-CH_2$	3	5-Cl	base	-
CH_3	3	5-Cl	base	-
C_2H_5	3	5-Cl	base	-
	3	5-Cl	HCl	211.7°C
$C_6H_5-CH_2$	3	H	base	112°C
	3	6-Cl	HCl	227.5°C
C_2H_5	2	H	base	-
H	4	H	base	-

Example IX.

A mixture of 113.2 parts of 1,2,4-trichloro-5-nitrobenzene, 75 parts of 3-amino-1-propanol, 0.2 parts of potassium iodide and 200 parts of butanol is stirred and refluxed overnight. The butanil is removed by evaporation in vacuo and water is added to the residue. The product is extracted with 4-methyl-2-pentanone. The extract is washed a few times with water, dried, filtered and evaporated. The oily residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and 5% of methanol as eluent. The pure fractions are collected and the eluent is evaporated. The residue is triturated in 2,2'-oxybispropane. The product is filtered off and crystallized from a mixture of 2,2'-oxybispropane and 2-propanol, yielding 31.7 parts of 3-[(4,5-dichloro-2-nitrophenyl)amino]-1-propanol; mp. 97°C.

Similarly were prepared:

3-[[2-nitro-4-(trifluoromethyl)phenyl]amino]-1-propanol; and

2-[[2-nitro-4-(trichloromethyl)phenyl]amino]ethanol; mp. 74.9°C.

Example X.

To a stirred mixture of 39.2 parts of 3-(2-nitrophenyl)amino-1-propanol and 225 parts of trichloromethane are added dropwise 35.7 parts of sulfinyl chloride (exothermic reaction: temperature rises to 45°C). Upon completion, stirring is continued for 6 hours at reflux temperature. The reaction mixture is evaporated, yielding 43 parts (100%) of N-(3-chloropropyl)-2-nitrobenzenamine as a residue.

Similarly were prepared:

N-(3-chloropropyl)-2-nitro-4-(trifluoromethyl)benzenamine as a residue;

4,5-dichloro-N-(3-chloropropyl)-2-nitrobenzenamine; mp. 78°C; and

N-(2-chloroethyl)-2-nitro-4-(trifluoromethyl)benzenamine.

Example XI.

A mixture of 21.5 parts of N-(3-chloropropyl)-2-nitrobenzenamine, 22.68 parts of 1-(diphenylmethyl)-piperazine, 20 parts of N,N-diethylethanamine and 180 parts of N,N-dimethylacetamide is stirred and heated for 6 hours at 100°C. The reaction mixture is evaporated and the residue is taken up in water. The oily product is extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is crystallized from a mixture of 2-propanol, ethanol and 2,2'-oxybispropane. The product is filtered off and dried, yielding 15.5 parts (36.9%) of 4-(diphenylmethyl)-N-(2-nitrophenyl)-1-piperazinepropanamine hydrochloride; mp. 228°C.

Similarly were prepared:

N-(4,5-dichloro-2-nitrophenyl)-4-(diphenylmethyl)-1-piperazinepropanamine as a residue;

4-(diphenylmethyl)-N-[2-nitro-4-(trifluoromethyl)-phenyl] - 1 - piperazinepropan - amine; mp. 113.7°C; and

4-(diphenylmethyl)-N-[2-nitro-4-(trifluoromethyl)-phenyl]-1-piperazineethan-amine; mp. 152.1°C.

Example XII.

A mixture of 15 parts of 4-(diphenylmethyl)-N-(2-nitrophenyl)-1-piperazinepropanamine hydrochloride in 160 parts of methanol is hydrogenated at normal pressure and at room temperature with 5 parts of Raney-nickel catalyst. After the calculated amount of hydrogen is taken up, the catalyst is filtered off over Hyflo and the filtrate is evaporated. The solid residue is crystallized from a mixture of 2-propanol and 2,2'-oxybispropane. The product is filtered off and dried, yielding 12 parts (78.9%) of N-(2-aminophenyl)-4-(diphenylmethyl)-1-piperazinepropanamine hydrochloride; mp. 223.1°C.

Similarly were prepared:

4,5-dichloro-N^1-[3-[4-(diphenylmethyl)-1-piperazinyl]-propyl]-1,2-benzene-diamine as an oily residue

N^1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-4-(trifluoromethyl)-1,2-benzene-diamine; and

N^1-[2-[4-(diphenylmethyl)-1-piperazinyl]ethyl]-4-(trifluoromethyl)-1,2-benzene-diamine as an oily residue.

Example XIII.

A mixture of 60.5 parts of 1-(3-chloropropyl)-1,3-dihydro-3-(1-methyl-ethenyl)-2H-benzimidazol-2-one, 31.68 parts of 1-(phenylmethyl)piperazine, 21.2 parts of sodium carbonate, 0.1 parts of potassium iodide and 400 parts of 4-methyl-2-pentanone is stirred and refluxed for 20 hours with water-separator. The reaction mixture is cooled, water is added and the layers are separated. The organic phase is dried, filtered and evaporated, yielding 70 parts (100%) of 1,3-dihydro-1-(1-methyl-ethenyl)-3-[3-[4-(phenylmethyl)-1-piperazinyl]propyl]-2H-benzimidazol-2-one as a residue.

Similarly was prepared 1,3-dihydro-1-[2 - [4 - (phenylmethyl) - 1 - piper - azinyl]ethyl]-2H-benzimidazol-2-one; mp. 136.5°C.

Example XIV.

To a stirred solution of 70 parts of 1,3-dihydro-1-(1-methylethenyl)-3-[3-[4-(phenylmethyl)-1-piperazinyl]-propyl]-2H-benzimidazol-2-one in 240 parts of ethanol are added 55 parts of hydrochloric acid solution 6N. The whole is stirred for 2 hours at 40—50°C. The reaction mixture is evaporated and the residue is taken up in a diluted ammonium hydroxide solution. The oily product is extracted

with trichloromethane. The extract is dried, filtered and evaporated, yielding 63 parts (100%) of 1,3-dihydro-1-[3-[4-(phenylmethyl)-1-piperazinyl]propyl]-2H-benzimidazol-2-one as a residue.

Example XV.

A mixture of 63 parts of 1,3-dihydro-1-[3-[4-(phenylmethyl)-1-piperazinyl]propyl]-2H-benzimidazol-2-one in 400 parts of methanol is hydrogenated at normal pressure and at room temperature with 10 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off over Hyflo and the filtrate is evaporated. The residue is crystallized from a mixture of 4-methyl-2-pentanone and 2-propanol. The product is filtered off and dried, yielding 29.5 parts (63%) of 1,3-dihydro-1-[3-(1-piperazinyl)propyl]-2H-benzimidazol-2-one; mp. 157.5°C.

Similarly was prepared:

1,3-dihydro-1-[2-(1-piperazinyl)ethyl]-2H-benzimidazol-2-one; mp. 122.6°C.

Example XVI.

To a stirred mixture of 20 parts of aluminium chloride and 100 parts of fluorobenzene are added dropwise 20.5 parts of 2,4-dichlorobenzoyl chloride. Upon completion;, the mixture is heated to reflux and stirred at reflux temperature for 5 minutes. The reaction mixture is poured onto crushed ice and the product is extracted with 1,1'-oxybisethane. The extract is dried and evaporated, yielding 30 parts of (2,4-dichlorophenyl)(4-fluorophenyl)methanone as an oily residue.

Similarly was prepared:

(4-fluorophenyl) (4-pyridinyl)methanone; mp. 85.5°C.

Example XVII.

To a stirred and refluxing mixture of 23.4 parts of (4-chlorophenyl)(2-fluorophenyl)methanone in 280 parts of 2-propanol are added portionwise 3.7 parts of sodium borohydride. Upon completion, stirring is continued for 2 hours at reflux temperature (±80°C). The reaction mixture is cooled and decomposed by the addition of water. The 2-propanol is evaporated and the residual product is extracted with trichloromethane. The extract is dried, filtered and evaporated, yielding 23.6 parts of 4-chloro-α-(2-fluorophenyl)benzenemethanol as a residue.

Similarly were prepared:

2,4-dichloro-α-(4-fluorophenyl)benzenemethanol as a residue;

α-(4-fluorophenyl)-4-pyridinemethanol; mp. 138.2°C.

α-(4-fluorophenyl)-3-pyridinemethanol hydrochloride; mp. 158.3°C. and

4-methoxy-α-[3-(trifluoromethyl)phenyl]benzenemethanol as a residue.

Example XVIII.

A mixture of 22 parts of 2,4-dichloro-α-(4-fluorophenyl)benzenemethanol and 240 parts of hydrochloric acid solution 12N is stirred for 40 hours at room temperature. The reaction mixture is poured onto ice-water and the product is extracted with trichloromethane. The extract is washed with water, dried, filtered and evaporated. The residue is distilled, yielding 13.2 parts of 2,4-dichloro-1-[α-chloro-α-(4-fluorophenyl)methyl]benzene; bp. 146°C at 0.15 mm. pressure.

Similarly were prepared:

1-[α-chloro-α-(4-methoxyphenyl)methyl]-3-(trifluoromethyl)benzene as a residue; and

1-[α-chloro-α-(4-methylphenyl)methyl]-4-fluorobenzene as a residue.

Example XIX.

To a stirred mixture of 23.6 parts of 4-chloro-α-(2-fluorophenyl)benzenemethanol in 108 parts of benzene are added dropwise 24 parts of sulfinyl chloride. Upon completion, the whole is heated to reflux and stirring is continued first for 5 hours at reflux temperature and further overnight at room temperature. The

benzene is evaporated and the residue is distilled, yielding 16.5 parts of 1-chloro-4-[α-chloro-α-(2-fluorophenyl)-methyl]benzene; bp. 122—125°C at 0.1 mm. pressure.

Similarly were prepared:

3-[α-chloro-α-(4-fluorophenyl)methyl]pyridine hydrochloride as an oily residue;

3-[α-chloro-α-(4-chlorophenyl)methyl]pyridine hydrochloride as a residue;

4-[α-chloro-α-(4-fluorophenyl)methyl]pyridine hydrochloride; mp. 198—200°C;

1-(α-chloro-α-methylphenyl)-2,3-dimethylbenzene; bp. 137° at 0.7 mm. pressure;

1-(α-chloro-α-methylphenyl)-2,4-dimethylbenzene; bp. 137° at 0.7 mm. pressure;

2-(α-chloro-α-methylphenyl)-1,4-dimethylbenzene; bp. 136°C at 0.7 mm. pressure;

1-(α-chloro-α-methylphenyl)-2-fluorobenzene; bp. 108—109°C at 0.4 mm. pressure.

Example XX.

A mixture of 121 parts of piperazine, 54 parts of 3-(α-chloro-α-(4-chlorophenyl)methyl]pyridine hydrochloride and 315 parts of N,N-dimethylformamide is stirred for 20 hours at room temperature. The reaction mixture is evaporated and 250 parts of water are added to the residue. The product is extracted with methylbenzene. The organic phase is washed with water and extracted with an acetic acid solution 10%. The acid aqueous phase is alkalized with a sodium hydroxide solution 60% and the product is extracted again with methylbenzene. The extract is dried, filtered and evaporated. The oily residue is converted into the nitrate salt in ethanol. The salt is filtered off, washed with ethanol and with 2,2'-oxybispropane and crystallized from ethanol, yielding 48 parts of 1-[α-(4-chlorophenyl)-α-(3-pyridinyl)methyl]piperazine trinitrate; mp. 132.9°C.

Similarly were prepared:

1-[α-(4-chlorophenyl)-α-(2-fluorophenyl)methyl]piperazine;

1-[α-(4-fluorophenyl)-α-(4-pyridinyl)methyl]piperazine; mp. 108.4°C;

1[-(2-chlorophenyl)(3-chlorophenyl)methyl]piperazine;

1[-(2-fluorophenyl)phenylmethyl]piperazine ethanedioate (1:1); mp. 195.5°C;

1-[(4-fluorophenyl)(4-methoxyphenyl)methyl]piperazine ethanedioate (1:2); mp. 280.1°C; and

1-[(4-nitrophenyl)phenylmethyl]piperazine dihydrochloride.

Example XXI.

A mixture of 21.5 parts of ethyl 4-hydroxy-1-piperidinecarboxylate, 35.2 parts of bis(4-fluorophenyl)bromomethane and 8.6 parts of potassium carbonate is stirred and heated in an oil-bath at 140°C for 3 hours. The reaction mixture is allowed to cool to room temperature and water is added. The product is extracted with methylbenzene. The extract is washed successively with water, a diluted hydrochloric acid solution and a sodium bicarbonate solution, dried, filtered and evaporated. The forerun is distilled off (bp. till 143°C at 0.5—1 mm. pressure), yielding 29 parts of ethyl 4-[bis(4-fluorophenyl)methoxy]-1-piperidinecarboxylate as an oily residue.

Similarly was prepared:

ethyl 4-(diphenylmethoxy)-1-piperidinecarboxylate; bp. 150°C at 0.4 mm. pressure.

Example XXII.

A mixture of 29 parts of ethyl 4-[bis(4-fluorophenyl)methoxy]-1-piperidinecarboxylate, 25 parts of potassium hydroxide, 1 part of water and 160 parts of 2-propanol is stirred and refluxed for 4 hours. The solvent is evaporated and water is

added to the residue. The product is extracted with methylbenzene. The extract is washed a few times with water, dried, filtered and evaporated. The oily residue is converted into the hydrochloride salt in 4-methyl-2-pentanone and 2-propanol at room temperature. The salt is filtered off and dried, yielding; 20.5 parts (78%) of 4-[bis(4-fluorophenyl)-methoxy]piperidine hydrochloride; mp. 161.8°C.

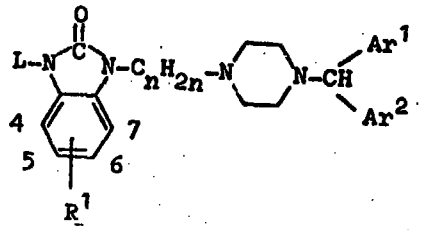
Similarly was prepared:

4-(diphenylmethoxy)piperidine hydrochloride; mp. 209.8°C.

Example XXIII.

A mixture of 5.3 parts of 1-(3-chloropropyl)-1,3-dihydro-2H-benzimidazol-2-one, 5 parts of 1-(diphenylmethyl)piperazine, 6.4 parts of sodium carbonate and 200 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. After cooling, water is added and the layers are separated. The 4-methyl-2-pentanone-phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and 5% of methanol as eluent. The pure fractions are collected and the eluent is evaporated. The oily residue is crystallized from a mixture of 2,2'-oxybispropane and a small amount of 2-propanol. The product is filtered off and dried, yielding 2 parts (23%) of 1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1,3-dihydro-2H-benzimidazol-2-one; mp. 153.6°C.

In a similar manner the following compounds were prepared in free base form or in the form of an acid addition salt after treatment of the free base with an appropriate acid:



L	R^1	C_nH_{2n}	Ar^1	Ar^2	Base or Salt form	Melting Point in °C
H	5-Cl	$(CH_2)_3$	C_6H_5	C_6H_5	base	175
H	6-Cl	$(CH_2)_3$	C_6H_5	C_6H_5	base	206.1
H	H	$(CH_2)_2$	4-F-C_6H_4	4-F-C_6H_4	base 1/2 H_2O	132
H	H	$(CH_2)_2$	C_6H_5	4-F-C_6H_4	base	172.4
H	5-CH_3	$(CH_2)_2$	C_6H_5	C_6H_5	base	214.6
CH_2=C(CH_3)	H	$(CH_2)_3$	C_6H_5	C_6H_5	base	–
CH_2=C(CH_3)	5-CH_3	$(CH_2)_3$	C_6H_5	C_6H_5	base	–
CH_2=C(CH_3)	6-CH_3	$(CH_2)_3$	C_6H_5	C_6H_5	base	–
H	H	$(CH_2)_2$	C_6H_5	C_6H_5	base	218
H	H	$(CH_2)_3$	C_6H_5	4-F-C_6H_4	base	153.6
H	H	$(CH_2)_3$	C_6H_5	4-Cl-C_6H_4	base	180.2
H	H	$(CH_2)_3$	4-Cl-C_6H_4	2-F-C_6H_4	base	136
H	5-Cl	$(CH_2)_3$	4-F-C_6H_4	4-F-C_6H_4	base	205.8
H	6-Cl	$(CH_2)_3$	4-F-C_6H_4	4-F-C_6H_4	base. H_2O	132.9
H	H	$(CH_2)_4$	C_6H_5	C_6H_5	base	196.6
H	6-Cl	$(CH_2)_2$	C_6H_5	C_6H_5	base	204.1
H	5-Cl	$(CH_2)_2$	C_6H_5	C_6H_5	base	203,6

L	R^1	C_nH_{2n}	Ar^1	Ar^2	Base or Salt form	Melting Point in °C
H	H	$(CH_2)_4$	C_6H_5	C_6H_5	base 1/2 H_2O	197.8
C_6H_5-CH_2	H	$(CH_2)_3$	C_6H_5	C_6H_5	2 HCl	199.6
H	H	$(CH_2)_4$	4-F-C_6H_4	4-F-C_6H_4	2HCl.H_2O	184.4
CH_2=C(CH_3)	H	CH_2–CH(CH_3)–CH_2	4-F-C_6H_4	4-F-C_6H_4	base	–
CH_2=C(CH_3)	H	$(CH_2)_3$	3-pyridinyl	4-Cl-C_6H_4	base	–
CH_2=C(CH_3)	H	$(CH_2)_3$	4-pyridinyl	4-F-C_6H_4	base	–
CH_2=C(CH_3)	H	$(CH_2)_3$	4-Cl-C_6H_4	4-OCH_3-C_6H_4	base	–
H	H	$(CH_2)_3$	C_6H_5	4-NO_2-C_6H_4	base	103.6
CH_2=C(CH_3)	H	$(CH_2)_3$	C_6H_5	2-F-C_6H_4	base	–
H	H	$(CH_2)_3$	4-OCH_3-C_6H_4	4-F-C_6H_4	base	157.4
H	H	$(CH_2)_3$	C_6H_5	4-Br-C_6H_4	base	189.7
H	H	$(CH_2)_4$	4-F-C_6H_4	4-F-C_6H_4	2 HCl.H_2O 1/2 C_2H_5OH	172.9
H	H	$(CH_2)_3$	C_6H_5	3-Cl-C_6H_4	base	112.7
H	7-Cl	$(CH_2)_3$	C_6H_5	C_6H_5	base	196.9
C_6H_5	5-Cl	$(CH_2)_3$	C_6H_5	C_6H_5	2HCl.1/2H_2O	184.2
H	H	$(CH_2)_3$	C_6H_5	C_6H_5	base. H_2O	156.6

Example XXIV.

In an analogous manner as described in Example XXIII there were prepared:

1-[3-[4-bis(4-fluorophenyl)methyl]-1-piperazinyl]-propyl]-1,3-dihydro-2H-benzimidazol-2-one; mp. 197.3°C by the reaction of 1,3-dihydro-1-(3-hydroxypropyl)-2H-benzimidazol-2-one methanesulfonate with 1-[bis(4-fluorophenyl)methyl]piperazine;

1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1,3-dihydro-3-methyl-2H-benzimidazol-2-one dihydrochloride hydrate; mp. 201.8°C by the reaction of 1,3-dihydro-1-(3-iodopropyl)-3-methyl-2H-benzimidazol-2-one with 1-(diphenylmethyl)piperazine;

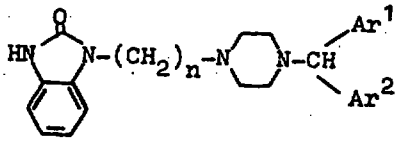
3-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-2(3H)-benzothiazolone dihydrochloride. hemihydrate; mp. 186.1°C by the reaction of 3-(3-bromopropyl)-2(3H)-benzothiazolone with 1-(diphenylmethyl)-piperazine; and

3-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-2(3H)-benzoxazolone dihydrochloride; mp. 212.4°C by the reaction of 3-(3-chloropropyl)-2(3H)-benzoxazolone with 1-(diphenylmethyl)piperazine.

Example XXV.

A mixture of 6.95 parts of 1-(5-chloropentyl)-1,3-dihydro-3-(1-methylethenyl)-2H-benzimidazol-2-one, 5.15 parts of 1-(diphenylmethyl)piperazine, 5.30 parts of sodium carbonate, 0.1 parts of potassium iodide and 160 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is cooled to room temperature, water is added and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is stirred and refluxed for 30 minutes with 12 parts of a hydrochloric acid solution in 40 parts of ethanol. The whole is evaporated and the residue is crystallized from ethanol, yielding 5 parts (46%) of 1-[5-[4-(diphenylmethyl)-1-piperazinyl]pentyl]-1,3-dihydro-2H-benzimidazol-2-one dihydrochloride hydrate; mp. 215.3°C.

Similarly were prepared:



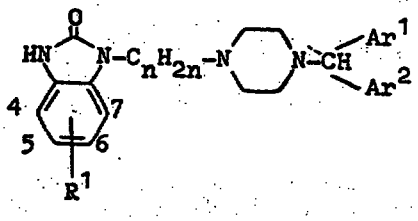
n	Ar^1	Ar^2	Base or Salt form	melting point in°C
5	4-F-C_6H_4	4-F-C_6H_4	2HCl.H_2O	203.7
4	C_6H_5	4-F-C_6H_4	base	172.3
3	C_6H_5	2-Cl-C_6H_4	base	149
3	3-Cl-C_6H_4	2-Cl-C_6H_4	base.H_2O	139.1
3	C_6H_5	2,4-Cl_2-C_6H_3	base	160.1
6	C_6H_5	C_6H_5	base	189.7
6	4-F-C_6H_4	4-F-C_6H_4	2HCl	204.5

Example XXVI.

To a stirred solution of 76 parts of 1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1,3-dihydro-3-(1-methylethenyl)-2H-benzimidazol-2-one in 280 parts of ethanol are added 120 parts of hydrochloric acid solution and 250 parts of water. The whole is stirred for 30 minutes at room temperature. Upon cooling in an ice-

bath, the product is precipitated. It is filtered off, washed with 2-propanone and with 2,2'-oxybispropane, and dried, yielding 43 parts (55%) of 1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1,3-dihydro-2H-benzimidazol-2-one dihydrochloride hydrate; mp. 237.5°C.

Similarly were prepared:



R^1	C_nH_{2n}	Ar^1	Ar^2	mp. in °C
H	$(CH_2)_3$	3-pyridinyl	$4\text{-Cl-}C_6H_4$	160.2
H	$(CH_2)_3$	4-pyridinyl	$4\text{-F-}C_6H_4$	183.2
H	$(CH_2)_3$	$4\text{-Cl-}C_6H_4$	$4\text{-OCH}_3\text{-}C_6H_4$	199.3
H	$(CH_2)_3$	C_6H_5	$2\text{-F-}C_6H_4$	157.7
5-CH_3	$(CH_2)_3$	C_6H_5	C_6H_5	178.3
6-CH_3	$(CH_2)_3$	C_6H_5	C_6H_5	195.7
H	$CH_3\text{-CH(CH}_3\text{)-CH}_2$	$4\text{-F-}C_6H_4$	$4\text{-F-}C_6H_4$	176

Example XXVII.

A mixture of 3.6 parts of N'-[2-[4-(diphenylmethyl)-1-piperazinyl]ethyl]-4-(trifluoromethyl)-1,2-benzenediamine and 1.8 parts of urea is stirred for 3 hours in an oil-bath at 190°C. The reaction mixture is cooled, water and trichloromethane are added and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5) as eluent. The pure fractions are collected and the eluent is evaporated, yielding 1.5 parts (41.5%) of 1-[2-[4-(diphenylmethyl)-1-piperazinyl]-ethyl]-1,3-dihydro-5-(trifluoromethyl)-2H-benzimidazol-2-one; mp. 163.7°C.

Similarly were prepared:

1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1,3-dihydro-5-(trifluoromethyl)-2H-benzimidazol-2-one; mp. 152.7°C; and

5,6-dichloro-1-[3-[4-(diphenylmethyl)-1-piperazinyl]-propyl]-1,3-dihydro-2H-benzimidazol-2-one; mp. 214.7°C.

Example XXVIII.

A mixture of 2.3 parts of 1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1,3-dihydro-2H-benzimidazol-2-one, 4.5 parts of formaldehyde solution 40% and 45 parts of N,N-dimethylformamide is stirred and heated for 2 hours at 100°C. The reaction mixture is cooled and diluted with water. The precipitated product is filtered off and crystallized from methylbenzene, yielding, after drying, 1.5 parts (66%) of 1-[3-[4-(diphenylmethyl)-1-piperazinyl]-propyl]-1,3-dihydro-3-(hydroxymethyl)-2H-benzimidazol-2-one; mp. 102.5°C.

Example XXIX.

A mixture of 1.55 parts of acetic acid anhydride, 3 parts of 1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1,3-dihydro-2H-benzimidazol-2-one and 22.5 parts of methylbenzene is stirred and refluxed overnight. Water is added to the reaction mixture and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using

a mixture of trichloromethane and methanol (95:5) as eluent. The pure fractions are collected and the eluent is evaporated, yielding 1.1 parts (33.5%) of 1-acetyl-3-[3-[4-(diphenylmethyl)-1-piperazinyl]-propyl]-1,3-dihydro-2H-benzimidazol-2-one; mp. 124.4°C.

Example XXX.

A mixture of 1.1 parts of ethyl 2-propenoate, 3 parts of 1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1,3-dihydro-2H-benzimidazol-2-one, a few drops of N,N,N-trimethylbenzenemethanaminium hydroxide solution 40% in methanol and 25 parts of 1,4-dioxane is stirred and refluxed for 24 hours. The reaction mixture is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5) eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the hydrochloride salt in 2-propanol and ethanol. the salt is filtered off and dried, yielding 1.4 parts (32.5%) of ethyl 3-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-2,3-dihydro-2-oxo-1H-benzimidazole - 1 - propanoate dihydrochloride. dihydrate; mp. 204°C.

Example XXXI.

A mixture of 3 parts of 1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1,3-dihydro-2H-benzimidazol-2-one, 1 part of isocyanatomethane and 25 parts of 1,4-dioxane is stirred and refluxed overnight. The reaction mixture is evaporated and the residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from a mixture of methylbenzene and 2,2'-oxybispropane, yielding 0.8 parts (23.5%) of 3-[3-[4-(diphenylmethyl)-1-piperazinyl]-propyl]-2,3-dihydro-N-methyl-2-oxo-1H-benzimidazole - 1 - carboxamide; mp. 153.1°C.

Example XXXII.

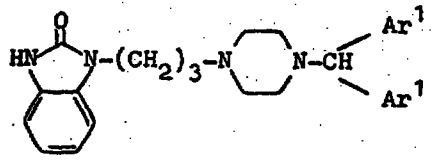
To a stirred mixture of 9.4 parts of 1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1,3-dihydro-2H-benzimidazol-2-one and 180 parts of methylbenzene are added 0.8 parts of sodium hydride dispersion 75% and the whole is stirred and heated for 60 minutes at 90°C. After cooling to 30°C, 0.2 parts of 2,3,11,12-dibenzo-1,4,7,10,13,16-hexaoxacyclooctadeca-2,11-diene are added and stirring is continued for 10 minutes. Then there are added 4.2 parts of ethyl 2-bromoacetate and the mixture is stirred and refluxed overnight. The reaction mixture is cooled to 90°C, 50 parts of water are added and the layers are separated while hot. The organic phase is evaporated, yielding 10 parts of ethyl 3-[3-[4-(diphenylmethyl)-1-piperazinyl]-propyl]-2,3-dihydro-2-oxo-1H-benzimidazole - 1 - acetate as a residue.

A mixture of 9.8 parts of ethyl 3-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-2,3-dihydro-2-oxo-1H-benzimidazole-1-acetate, 1.2 parts of sodium hydroxide and 150 parts of water is stirred and refluxed for 5 minutes (±80°C). The reaction mixture is filtered and the filtrate is acidified with acetic acid to pH 5.8—6: a sticky precipitate is formed. It is separated and crystallized from ethanol and water. The product is filtered off and dried in vacuo at 100°C for 3 hours, yielding 6 parts of 3-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-2,3-dihydro-2-oxo-1H-benzimidazole-1-acetic acid hemihydrate; mp. 138.7°C.

Example XXXIII.

A mixture of 5.2 parts of 1,3-dihydro-1-[3-(1-piperazinyl)propyl]-2H-benzimidazol-2-one, 5.28 parts of 2-(α-chloro-α-methylphenyl)pyridine hydrochloride, 5.3 parts of sodium carbonate and 90 parts of N,N-dimethylformamide is stirred and heated overnight at 50°C. The reaction mixture is cooled and poured onto ice-water. The product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is crystallized from a mixture of 4-methyl-2-pentanone and 2,2'-oxybispropane. The product is filtered off and dried, yielding 2 parts (23.4%) of 1,3-dihydro-1-[3-[4-[phenyl(2-pyridinyl)methyl]-1-piperazinyl]propyl]-2H-benzimidazol-2-one; mp. 141.7°C.

Similarly were prepared:

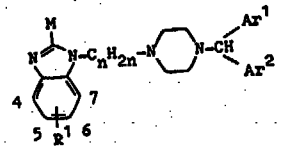


Ar^1	Ar^2	mp. in °C
3-pyridinyl	$4\text{-F-C}_6\text{H}_4$	154.1
3-pyridinyl	C_6H_5	162.6
$4\text{-F-C}_6\text{H}_4$	$4\text{-CH}_3\text{-C}_6\text{H}_4$	147.8
$4\text{-Cl-C}_6\text{H}_4$	$4\text{-Cl-C}_6\text{H}_4$	209.5
$4\text{-F-C}_6\text{H}_4$	$2,4\text{-Cl}_2\text{-C}_6\text{H}_3$	160.1
C_6H_5	$2,3\text{-(CH}_3)_2\text{-C}_6\text{H}_3$	169.8
$3\text{-CF}_3\text{-C}_6\text{H}_4$	$4\text{-OCH}_3\text{-C}_6\text{H}_4$	153.4
C_6H_5	$4\text{-CH}_3\text{-C}_6\text{H}_4$	178.3
C_6H_5	$2,4\text{-(CH}_3)_2\text{-C}_6\text{H}_3$	115.8
C_6H_5	$2,5\text{-(CH}_3)_2\text{-C}_6\text{H}_3$	156.3

Example XXXIV.

A mixture of 4.9 parts of 1-(3-chloropropyl)-1H-benzimidazole, 5.76 parts of 1-[bis(4-fluorophenyl)methyl]piperazine, 5.3 parts of sodium carbonate, 0.1 parts of potassium iodide and 200 parts of 4-methyl-2-pentanone is stirred and refluxed for 20 hours with water-separator. The reaction mixture is cooled, water is added and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is crystallized from a mixture of 4-methyl-2-pentanone and 2,2'-oxybispropane. The product is filtered off and dried, yielding 5.5 parts (59.3%) of 1-[3-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]propyl]-1H-benzimidazole hydrate; mp. 108.4°C.

Similarly were prepared:



M	R^1	C_nH_{2n}	Ar^1	Ar^2	Base or Salt form	melting point in °C
H	H	$(CH_2)_2$	C_6H_5	C_6H_5	base	192.3
H	H	$(CH_2)_3$	C_6H_5	3-Cl-C_6H_4	$3HCl.H_2O$ $1/2CH_3-CHOH-CH_3$	191.1
C_6H_5	H	$(CH_2)_3$	C_6H_5	C_6H_5	base	130.5
C_6H_5	5-Cl	$(CH_2)_3$	C_6H_5	C_6H_5	base	143.9
C_6H_5	H	$(CH_2)_2$	C_6H_5	C_6H_5	$3HCl.H_2O$	198.3
C_6H_5	5-Cl	$(CH_2)_3$	C_6H_5	C_6H_5	base	127.8
$C_6H_5-CH_2$	H	$(CH_2)_3$	C_6H_5	C_6H_5	$3HCl.3H_2O$	179.9
$C_6H_5-CH_2$	5-Cl	$(CH_2)_3$	C_6H_5	C_6H_5	$3HCl.H_2O$	198.2
H	H	$(CH_2)_3$	C_6H_5	C_6H_5	base	132.3
H	H	$(CH_2)_3$	C_6H_5	4-F-C_6H_4	base	102.5
H	H	$(CH_2)_3$	C_6H_5	4-Cl-C_6H_4	base	90.8
H	H	$(CH_2)_4$	C_6H_5	C_6H_5	base	106
H	H	$(CH_2)_4$	C_6H_5	4-F-C_6H_4	base	114.9
H	H	$(CH_2)_4$	4-F-C_6H_4	4-F-C_6H_4	base	86.3
H	H	$CH_2-CH(CH_3)-CH_2$	C_6H_5	C_6H_5	$3HCl1/2H_2O$	237.3
H	H	$CH_2-CH(CH_3)-CH_2$	4-F-C_6H_4	4-F-C_6H_4	$3HCl1/2\ H_2O$	223.4
CH_3	H	$(CH_2)_3$	C_6H_5	C_6H_5	base	121.2
CH_3	5-Cl	$(CH_2)_3$	C_6H_5	C_6H_5	$3HCl\ H_2O$	226.4
CH_3	H	$(CH_2)_4$	C_6H_5	C_6H_5	base	118.7

M	R^1	C_nH_{2n}	Ar^1	Ar^2	Base or Salt form	melting point in °C
	H	$(CH_2)_3$	C_6H_5	C_6H_5	base	106.5
	5-Cl	$(CH_2)_3$	C_6H_5	C_6H_5	base	114.9
	6-Cl	$(CH_2)_3$	C_6H_5	C_6H_5	base	173.6
H	H	$(CH_2)_3$	C_6H_5	3-Cl-C_6H_4	$3HCl.2H_2O$	182.9

Example XXXV.

Following the procedure of Example XXXIV there is prepared 1-[3-[4-(diphenylmethyl)-1-piperazinyl]-propyl]-2-(methylthio)-1H-benzimidazole trihydrochloride. hydrate; mp. 203.4°C by the reaction of 3-[2-(methylthio)-1H-benzimidazol-1-yl]propyl methanesulfonate with 1-(diphenylmethyl)piperazine.

Example XXXVI.

A mixture of 4.37 parts of N-(2-aminophenyl)-4-(diphenylmethyl)-1-piperazinepropanamine hydrochoride, 38 parts of carbon disulfide, 2 parts of sodium carbonate and 40 parts of ethanol is stirred and refluxed for 20 hours. The reaction mixture is evaporated and water is added to the residue. The precipitated product is filtered off, washed with water and dissolved in trichloromethane. The solution is dried, filtered and evaporated. The residue is crystallized from 4-methyl-2-pentanone, yielding 2 parts (45.5%) of 1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1,3-dihydro-2H-benzimidazole-2-thione; mp. 181.8°C.

Example XXXVII.

A mixture of 60 parts of N-(2-aminophenyl)-4-(diphenylmethyl)-1-piperazinepropanamine, 20 parts of methyl (iminomethoxymethyl)carbamate, 42 parts of acetic acid and 450 parts of trichloromethane is stirred and refluxed overnight. The reaction mixture is evaporated and the residue is stirred in water. The latter is decanted and the residue is taken up again in water. The whole is alkalized with a diluted ammonium hydroxide solution and the product is extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from a mixture of 4-methyl-2-pentanone and 2,2'-oxybispropane, yielding 13.5 parts of methyl [1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1H-benzimidazol-2-yl]carbamate; mp. 137.8°C.

A mixture of 12 parts of methyl [1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1H-benzimidazol-2-yl]-carbamate, 60 parts of a concentrated hydrochloric acid solution and 80 parts of ethanol is stirred and refluxed overnight. The reaction mixture is evaporated and water is added to the residue. The free base is liberated in the conventional manner with ammonium hydroxide and extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is crystallized from ethanol. The product is filtered off and dried, yielding 4.3 parts (40%) of 1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1H-benzimidazol-2-amine; mp. 228.7°C.

A mixture of 10.7 parts of 1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1H-benzimidazol-2-amine, 5.1 parts of acetic acid anhydride and 90 parts of methylbenzene is stirred and refluxed for 5 hours. The reaction mixture is evaporated and the residue is stirred in water. The whole is alkalized with ammonium hydroxide and the product is extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is crystallized from ethanol. The product is filtered off and dried, yielding 6.6 parts (56.5%) of N-[1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1,3-dihydro-2H-benzimidazol-2-ylidine acetamide; mp. 143.3°C.

Example XXXVIII.

A mixture of 13 parts of 1,3-dihydro-1-[3-(1-piperazinyl)propyl]-2H-benzimidazol-2-one, 12.4 parts of 1,1'-(bromomethylene)bis[benzene], 6.6 parts of sodium carbonate and 200 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. After cooling to room temperature, water is added and the layers are separated. The organic layer is dried, filtered and evaporated. The residue is crystallized from a mixture of 2,2'-oxybispropane and a small amount of 2-propanol, yielding 1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1,3-dihydro-2H-benzimidazol-2-one; mp. 153°C.

Example XXXIX.

Following the procedure of Example XXXVIII and using equivalent amounts of the appropriate starting materials, the following compounds are prepared:

1-[2-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]-ethyl]-1,3 - dihydro - 2H - benzimidazol-2-one hemihydrate; mp. 131.5°C;

1-[2-[4-(diphenylmethyl)-1-piperazinyl]ethyl]-1,3-dihydro-2H-benzimidazol-2-one; mp. 218°C; and

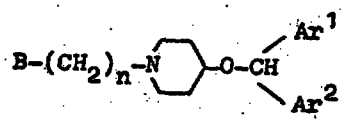
1-[3-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]-propyl]-1,3-dihydro - 3H - benzimidazol-2-one; mp. 198°C.

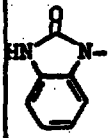
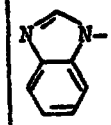
Example XL.

A mixture of 4.8 parts of 1-(3-chloropropyl)-1,3-dihydro-2H-benzimidazol-2-one, 6.1 parts of 4-(diphenylmethoxy)piperidine hydrochloride, 7.5 parts of sodium carbonate and 200 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is cooled and water is added. The layers are separated and the 4-methyl-2-pentanone-phase is dried, filtered and evaporated. The oily residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and 5% of methanol as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 4-methyl-2-pentanone, yielding 4.2 parts (48%) of 1-[3-[4-(diphenylmethoxy)-

1-piperidinyl]propyl]-1,3-dihydro-2H-benzimidazol-2-one; mp. 149.2°C.

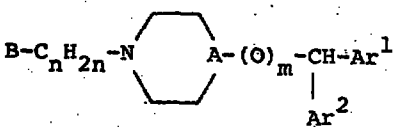
Similarly were prepared:



B	n	Ar^1	Ar^2	Base or Salt form	mp. in °C
	2	C_6H_5	C_6H_5	HCl	253.1
"	3	$4\text{-}F\text{-}C_6H_4$	$4\text{-}F\text{-}C_6H_4$	HCl 1/2 H_2O	167.2
"	2	$4\text{-}F\text{-}C_6H_4$	$4\text{-}F\text{-}C_6H_4$	HCl 1/2 H_2O	251.4
"	4	C_6H_5	C_6H_5	base	152
	3	C_6H_5	C_6H_5	base	110.2

WHAT WE CLAIM IS:—

1. A compound having the general formula:



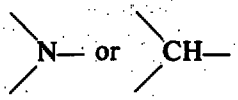
(I)

wherein:

Ar^1 and Ar^2 are each independently a pyridinyl, phenyl or substituted phenyl group, the substituted phenyl group having 1 or 2 substituents which are each independently a halogen atom, a lower alkyl, lower alkyloxy, trifluoromethyl or nitro group;

m is 0 or 1;

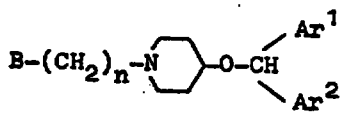
A is a

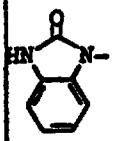
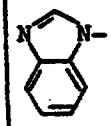


group, provided that when A is



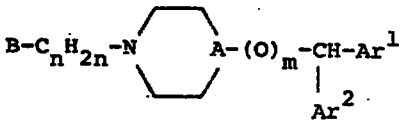
1-piperidinyl]propyl]-1,3-dihydro-2H-benzimidazol-2-one; mp. 149.2°C.
Similarly were prepared:



B	n	Ar^1	Ar^2	Base or Salt form	mp. in °C
	2	C_6H_5	C_6H_5	HCl	253.1
"	3	$4\text{-F-}C_6H_4$	$4\text{-F-}C_6H_4$	HCl 1/2 H_2O	167.2
"	2	$4\text{-F-}C_6H_4$	$4\text{-F-}C_6H_4$	HCl 1/2 H_2O	251.4
"	4	C_6H_5	C_6H_5	base	152
	3	C_6H_5	C_6H_5	base	110.2

WHAT WE CLAIM IS:—

1. A compound having the general formula:



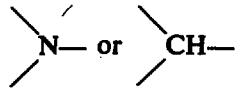
(I)

wherein:

Ar^1 and Ar^2 are each independently a pyridinyl, phenyl or substituted phenyl group, the substituted phenyl group having 1 or 2 substituents which are each independently a halogen atom, a lower alkyl, lower alkyloxy, trifluoromethyl or nitro group;

m is 0 or 1;

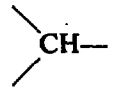
A is a



group, provided that when A is



then *m* is 0 and when A is

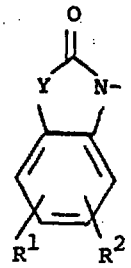


then *m* is 1;

n is an integer of from 2 to 6 inclusive, provided that when C_nH_{2n} represents a branched alkylene chain, then at least 2 carbon atoms are present in the linear portion of the chain linking B with the piperidine or piperazine nitrogen atom; and

B is:

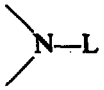
a) a group having the formula



wherein:

R^1 and R^2 are each independently a hydrogen or halogen atom, or a lower alkyl or trifluoromethyl group; and

Y is an oxygen or sulfur atom or a possibly substituted nitrogen atom of the formula



wherein L is a hydrogen atom or a lower alkyl, lower alkylcarbonyl, lower alkyloxy-carbonyl-lower alkyl, carboxy-lower alkyl, phenyl, phenylmethyl, lower alkylamino-carbonyl, hydroxymethyl or lower alkenyl group; or

b) a group having the formula

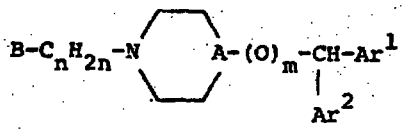


wherein:

R^1 and R^2 are as above defined; and

M is a hydrogen atom or a lower alkyl, phenyl, phenylmethyl, mercapto, lower alkylthio, amino, lower alkylcarbonylamino, lower alkyloxycarbonylamino or cycloalkyl group having from 3 to 6 carbon atoms.

2. A compound having the general formula:

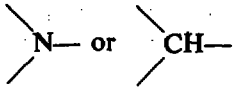


(I)

wherein: Ar^1 and Ar^2 are each independently a phenyl or halophenyl group;

m is 0 or 1;

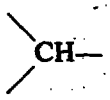
A is an



group, provided that when A is



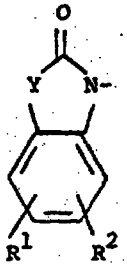
then *m* is 0 and when A is



then *m* is 1;

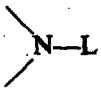
n is an integer of from 2 to 6 inclusive, provided that when C_nH_{2n} represents a branched alkylene chain, then at least 2 carbon atoms are present in the linear portion of the chain linking B with the piperidine or piperazine nitrogen atom; and B is:

a) a group having the formula



wherein: R^1 and R^2 are each independently a hydrogen or halogen atom, or a lower alkyl or trifluoromethyl group; and

Y is an oxygen or sulfur atom or a possibly substituted nitrogen of the formula



wherein L is a hydrogen atom or a lower alkyl, lower alkyl carbonyl, lower alkyloxycarbonyl-lower alkyl, phenyl, phenylmethyl, lower alkylaminocarbonyl, hydroxymethyl or lower alkenyl group; or

b) a group having the formula



wherein: R^1 and R^2 are as above defined; and

M is a hydrogen atom or a lower alkyl, phenyl, phenylmethyl, mercapto, lower alkylthio, amino, lower alkylcarbonylamino, lower alkyloxycarbonylamino or cycloalkyl group having from 3 to 6 carbon atoms.

3. 1-[3-[4-(Diphenylmethyl)-1-piperazinyl]propyl] - 1,3 - dihydro - 2H - benzimidazol-2-one.

4. 1-[3-[4-[Bis(4-fluorophenyl)methyl]-1-piperazinyl]propyl]-1,3-dihydro-2H-benzimidazol-2-one.

5. 1-[4-[4-[Bis(4-fluorophenyl)methyl]-1-piperazinyl]butyl]-1,3-dihydro-2H-benzimidazol-2-one.

6. 1-[4-[4-(Diphenylmethyl)-1-piperazinyl]butyl]-1,3-dihydro-2H-benzimidazol-2-one.

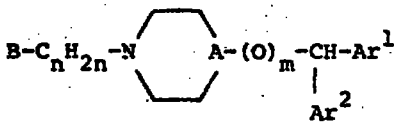
7. 1-[3-[4-(Diphenylmethyl)-1-piperazinyl]propyl]-1H-benzimidazole.

8. 1-[4-[4-[(4-Fluorophenyl)phenylmethyl]-1-piperazinyl]butyl]-1H-benzimidazole.

9. 1-[4-[4-[Bis(4-fluorophenyl)methyl]-1-piperazinyl]butyl]-1H-benzimidazole.

10. A pharmaceutically acceptable acid addition salt of a compound as claimed in any one of the preceding claims.

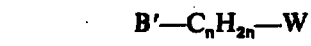
11. A process for preparing a compound having the general formula:



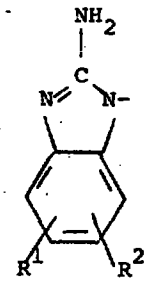
(I)

or a pharmaceutically acceptable acid addition salt thereof, wherein:

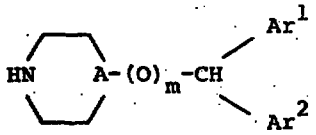
Ar^1, Ar^2, *m*, A, *n*, B are as defined in claim 1, which process comprises a) reacting an appropriate reactive ester of the formula:



wherein B' is the same as B defined above but is other than a 2-amino-1H-benzimidazol-1-yl group of the formula:

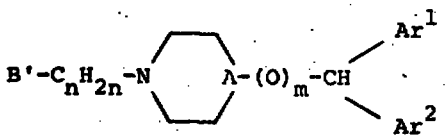


wherein R^1 and R^2 are as defined in claim 1 and W is an appropriate reactive ester function derived from the corresponding alcohol, with a compound of the formula:



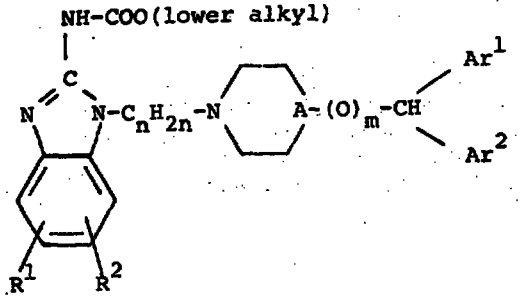
(III)

wherein Ar^1, Ar^2 and *m* are as above defined in order to prepare a compound of the formula:



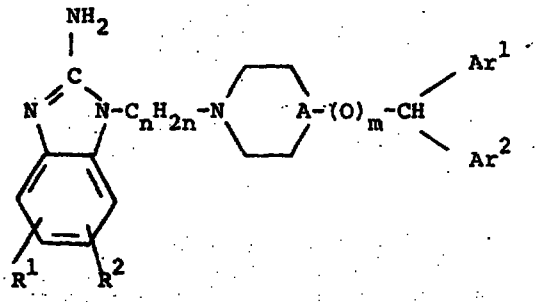
(i')

or b) decarboxylating a compound of the formula:



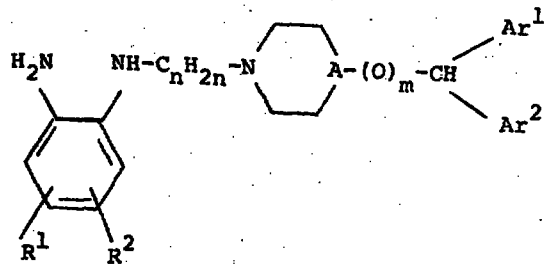
(I—b)

wherein Ar^1, Ar^2, *m*, A, *n*, R^1 and R^2 are as defined in claim 1 under hydrolytic conditions, in order to prepare a compound of the formula:



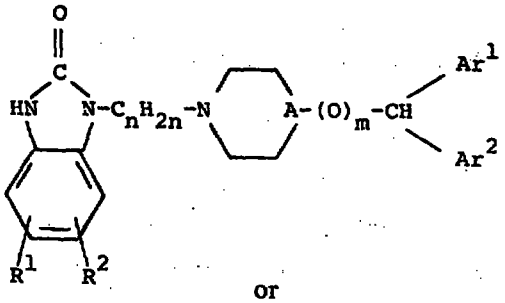
(I—a)

or c) ring closing a compound of the formula:



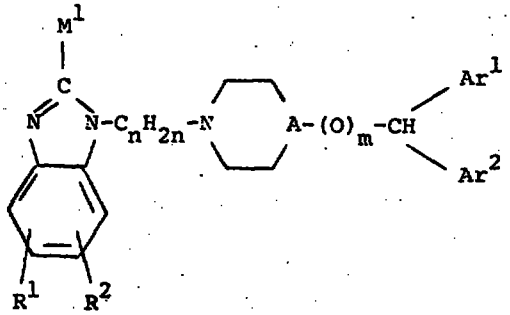
(IV)

wherein Ar^1, Ar^2, *m*, A, *n*, R^1 and R^2 are as defined in claim 1 with an appropriate cyclizing agent by known methods in order to prepare a compound of the formula:



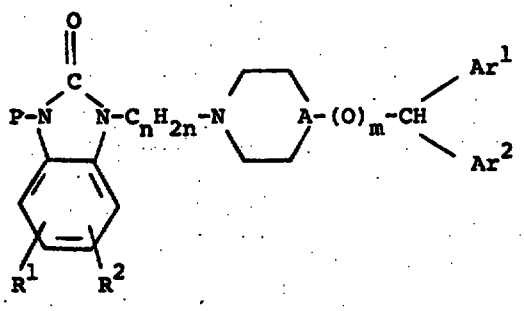
(I—c)

or



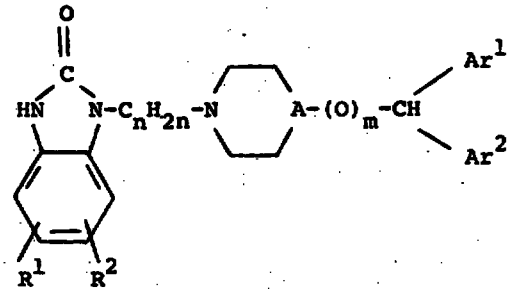
(I—d)

wherein M^1 is a hydrogen atom, a lower alkyl, phenyl, phenylmethyl, mercapto, amino, lower alkyloxycarbonylamino or cycloalkyl group, by the reaction of (IV) with an appropriate cyclizing agent, or d) removing a protecting group P by conventional procedures from a compound of the formula:



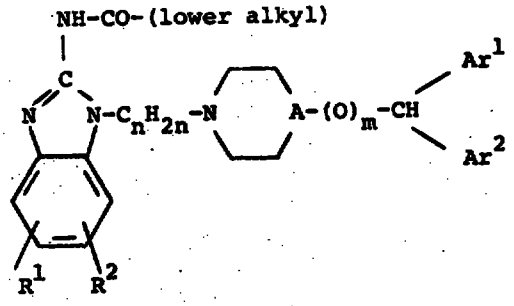
(V)

wherein Ar^1, Ar^2, *m*, A, *n*, R^1 and R^2 are as defined in claim 1 in order to prepare a compound of the formula:



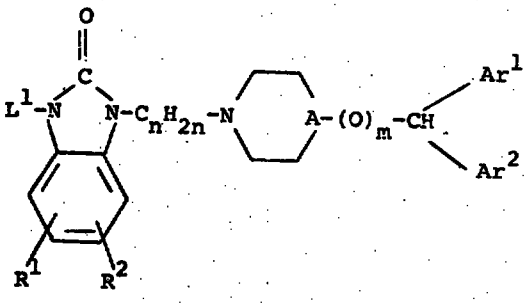
(I—c)

or e) acylating an appropriate compound of the formula (I—a) above, by standard N-acylating procedures in order to prepare a compound of the formula:



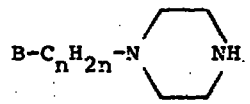
(I—e)

or f) introducing the group L^1 by known methods into a compound of the formula (I—c) above, in order to prepare a compound of the formula:



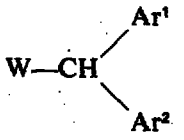
(I—f)

wherein L^1 is a lower alkyl, lower alkylcarbonyl, lower alkyloxycarbonyl-lower alkyl, carboxy-lower alkyl, phenylmethyl, lower alkylaminocarbonyl, hydroxymethyl or lower alkenyl group, provided that the unsaturation in the lower alkenyl is located in a position other than α, or g) condensing a compound of the formula:



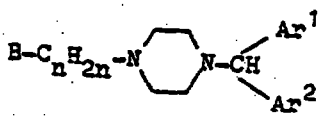
(XVI)

wherein B is as defined in claim 1 with an appropriate reactive ester of the formula:



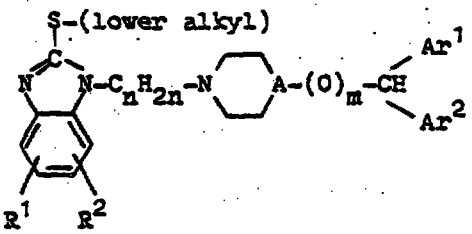
(XVII)

wherein Ar^1 and Ar^2 are as defined in claim 1 and W is defined hereinabove, in order to prepare a compound of the formula:



(I—g)

or h) preparing a compound of the formula:



(I—h)

by known S-alkylating procedures, starting from the corresponding —SH substituted analog; and, if desired, preparing pharmaceutically acceptable acid addition salts of the products of steps a) to h).

12. A process as claimed in claim 11 wherein steps (a) and (g) are effected at an elevated temperature in the presence of a reaction-inert organic solvent and an appropriate base.

13. A process for preparing 1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1,3-dihydro-2H-benzimidazol-2-one which comprises reacting 1-(3-chloropropyl)-1,3-dihydro-2H-benzimidazol-2-one with 1-(diphenylmethyl)piperazine.

14. A process for preparing 1-[3-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]propyl]-1,3-dihyro-2H-benzimidazol-2-one which comprises reacting 1,3-dihydro-1-(3-hydroxypropyl)-2H-benzimidazol-2-one methanesulfonate with 1-[bis(*p*-fluorophenyl)methyl]piperazine.

15. A process for preparing 1-[4-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]butyl]-1,3-dihydro-2H-benzimidazol-2-one which comprises reacting 1-(4-chlorobutyl)-1,3-dihydro-2H-benzimidazol - 2 - one with 1 - [bis(*p* - fluorophenyl) - methyl]piperazine.

16. A process for preparing 1-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-1,3-dihydro-2H-benzimidazol-2-one which comprises reacting 1-(4-chlorobutyl)-1,3-dihydro-2H-benzimidazol-2-one with 1-(diphenylmethyl)-piperazine.

17. A process for preparing 1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1H-benzimidazole which comprises reacting 1-(3-chloropropyl)-1H-benzimidazole with 1-(diphenylmethyl)piperazine.

18. A process for preparing 1-[4-[4-[(4-fluorophenyl)phenylmethyl]-1-piperazinyl]butyl]-1H-benzimidazole which comprises reacting 1-(4-chlorobutyl)-1H-benzimidazole with 1-[(4-fluorophenyl)phenylmethyl]piperazine.

19. A process for preparing 1-[4-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]butyl]-1H-benzimidazole which comprises reacting 1-(4-chlorobutyl)-1H-benzimidazole with 1-[bis(*p*-fluorophenyl)methyl]piperazine.

20. A process for preparing a compound of formula I as claimed in claim 1 substantially as hereinbefore described with reference to any one of the specific Examples.

21. A compound of formula I whenever prepared by a process as claimed in any one of claims 11 to 20.

22. A pharmaceutical composition which comprises at least one compound as claimed in any one of claims 1 to 9 or 21, or a pharmaceutically acceptable salt as claimed in claim 10, together with a pharmaceutically acceptable diluent or carrier.

23. A pharmaceutical composition as claimed in claim 22 which is in unit dosage form.

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