(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 288 640 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **09.09.92**

(51) Int. Cl.5: **C07D 401/04**, A61K 31/445

(21) Application number: **87309349.6**

(22) Date of filing: **22.10.87**

The file contains technical information submitted after the application was filed and not included in this specification

(54) **6,11-Dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta-[1,2-b]pyridines and compositions and methods of use.**

(30) Priority: **28.04.87 US 43409**

(43) Date of publication of application:
02.11.88 Bulletin 88/44

(45) Publication of the grant of the patent:
09.09.92 Bulletin 92/37

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 042 544
EP-A- 0 152 697
EP-A- 0 208 855
EP-A- 0 270 818
DE-B- 1 470 314
US-A- 4 273 780

CHEMICAL ABSTRACTS, vol. 77, no. 15, 9th October 1972, page 22, abstract no. 96881b, Columbus, Ohio, US; F.J. VILLANI et al.: "Derivatives of 10,11-dihydro-5H-dibenzo[a,d]cycloheptene and related compounds. 6. Aminoalkyl derivatives of the aza isosteres"

(73) Proprietor: **SCHERING CORPORATION**
2000 Galloping Hill Road
Kenilworth New Jersey 07033(US)

(72) Inventor: **Piwinsky, John J.**
19 Pitman Road
Parsippany,New Jersey 07054(US)
Inventor: **Green, Michael John**
43 Meadow Run Drive
Skillman, New Jersey 08558(US)
Inventor: **Ganguly, Ashit Kumar**
96 Cooper Avenue
Upper Montclair, New Jersey 07043(US)
Inventor: **Wong, Jesse Kwok-Keung**
547 Andress Terrace
Union, New Jersey 07083(US)
Inventor: **Katchen, Bernard**
18 Chestnut Street
Livingston, New Jersey 07039(US)
Inventor: **Cramer, Jeffrey Abbott**
246 Maryland Street
Westfield, New Jersey 07090(US)

(74) Representative: **Ritter, Stephen David et al**
Mathys & Squire 10 Fleet Street
London EC4Y 1AY(GB)

Rank Xerox (UK) Business Services

CHEMICAL ABSTRACTS, vol. 107, no. 7, 17th August 1987, page 714, abstract no. 58815p, Columbus, Ohio, US; F.J. VILLANI et al.: "N-Substituted 11-(4-piperidylene)-5,6-dihydro-11H-benzo[5,-6]cyclohepta[1,2-b]pyridines. Antihistamines with no sedating liability"

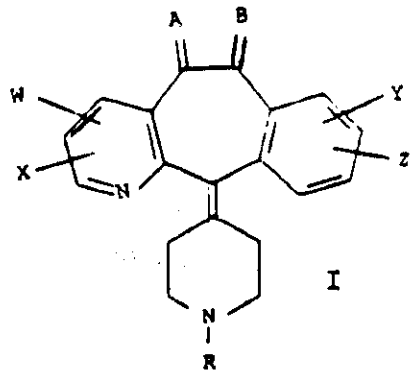
CHEMICAL ABSTRACTS, vol. 106, no. 13, 30th March 1987, page 636, abstract no. 102062w, Columbus, Ohio, US; W. HALCZENKO et al.: "Benzocycloheptapyridines. Analogs of azatadine"

Description

The present invention relates to certain 6,11-dihydro-11-(4-piperidylidene)-5H-benzo [5,6]cyclohepta [1,2-b]pyridines and to pharmaceutical compositions and methods of using such compounds.

United States Patents 3,326,924, 3,717,647 and 4,282,233, European published Application No. 0042544 and Villani et al., Journal of Medicinal Chemistry, Vol. 15, No. 7, pp 750-754 (1972) and Villani et al. Arzneim-Forsch Drug Res., Vol. 36, p. 1311 (1986) describe certain 11-(4-piperidylidene)-5H-benzo[5,6] cyclohepta[1,2-b]pyridines as antihistamines. U.S. Patent 4,355,036 describes certain N-substituted piperidylidene compounds.

This invention is a compound having the structural formula I:



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R represents H or alkyl, such that

(1) when R represents alkyl,

at least one of A and B represents a substituent group selected from H and OR^1, H and $OC(O)R^1$, $=NOR^1$ or $-O-(CH_2)_n-O-$, and the other may represent H_2 or one of the above listed substituent groups;

W, X, Y and Z may be the same or different and each independently represents H, halo, alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ or $-N(R^1)_2$;

R^1 is H, alkyl or aryl and in $N(R^1)_2$, R^1 can be alkanediyl, and n is 2, 3 or 4, and

(2) when R represents H,

A or B may be the same or different and each independently represents H_2, H and OR^1, H and $OC(O)R^1$, =O, $=NOR^1$ or $-O-(CH_2)_n-O-$;

W, X, Y and Z may be the same or different and each independently represents H, halo, alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ or $-N(R^1)_2$, with the provisos that when A and B both represent H_2, W is OH, and when A or B represents =O, at least one of W, X, Y and Z represents halo, alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ or $-N(R^1)_2$, and

R^1 and n are as defined above.

Preferred identities for R, R^1, A, B, W, X, Y and Z are as follows:

Substituent	Preferred Identity
R	straight, branched or cyclic C_{1-6} alkyl
R^1	H
A,B	one of A and B is H_2 and the other of A and B represents H- and $OC(O)R^1$, =O, $=NOR^1$ or $-O-(CH_2)_nO-$.
W,X,Y,Z	H, halo, alkyl, $-CF_3$, $-SR^1$, $-OR^1$ or $N(R^1)_2$.

Particularly preferred class of compounds include:

.... compounds wherein at least one of A and B represents H and OR^1.

.... compounds wherein A and B represent H_2, and W represents OR^1.

.... compounds wherein R^1 represents H

.... compounds wherein at least one of Y and Z represents halo

.... compounds wherein W represents OR^1 at position 3

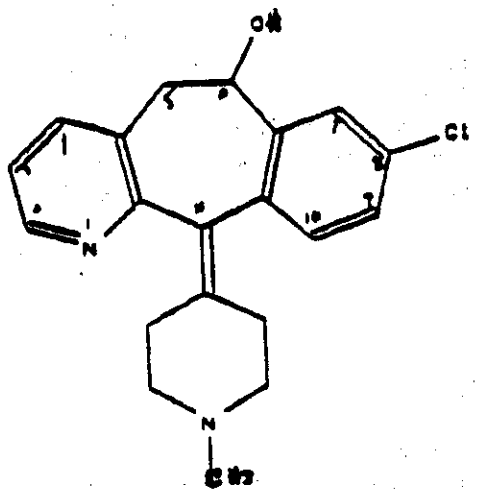
In a preferred embodiment of the invention, R represents -H or lower alkyl. More preferably, R

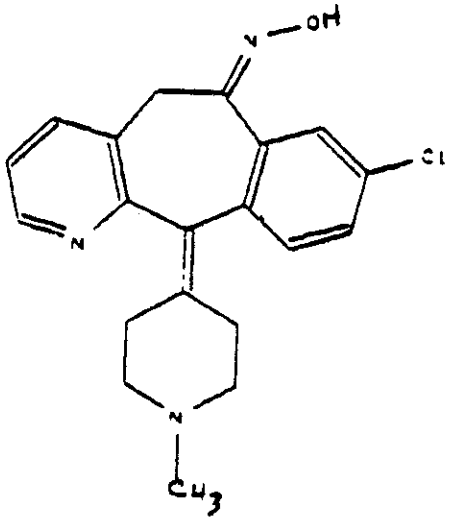
represents alkyl having from 1-3 carbon atoms.

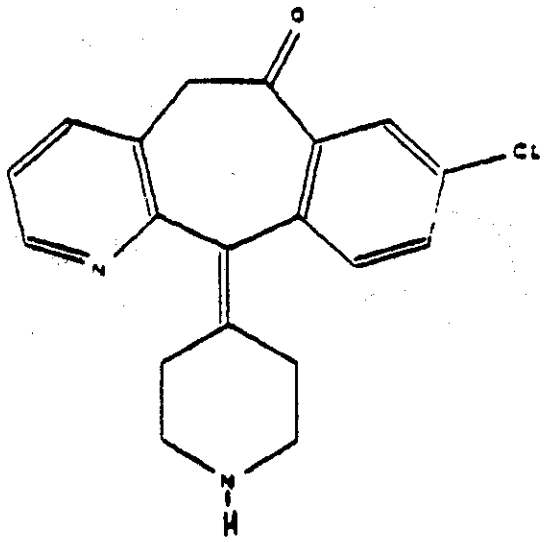
The preferred embodiments of the invention further include those where A or B represent -OH, =O, OH or =N=OR^1, wherein R^1 is as previously defined.

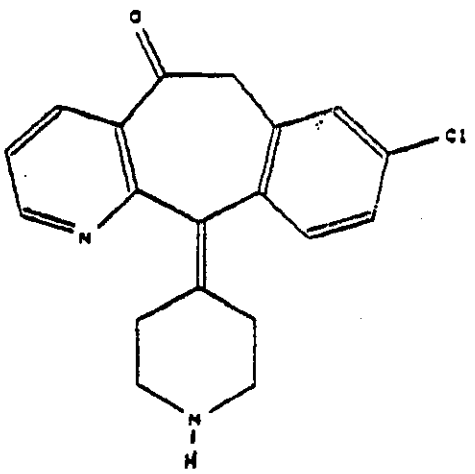
Preferred W, X, Y, and Z groups include -H, -OH, and halo, and the most preferred values for W, X, and Y are -H. The most preferred value for Z is halo, and in particular -Cl.

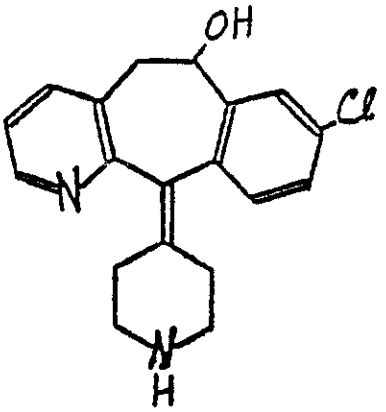
Preferred compounds of the invention include:

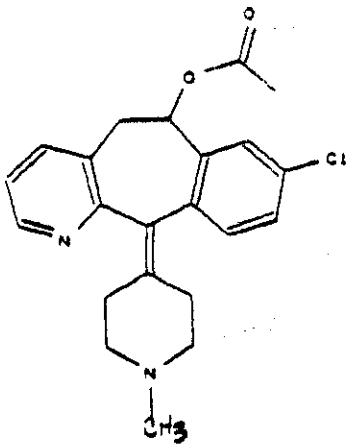


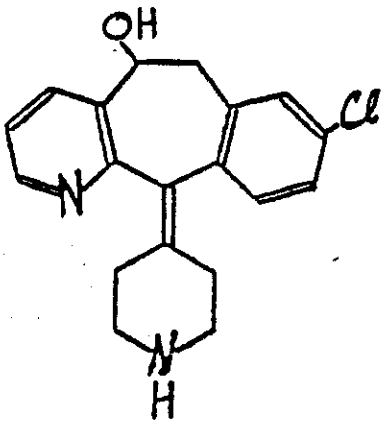


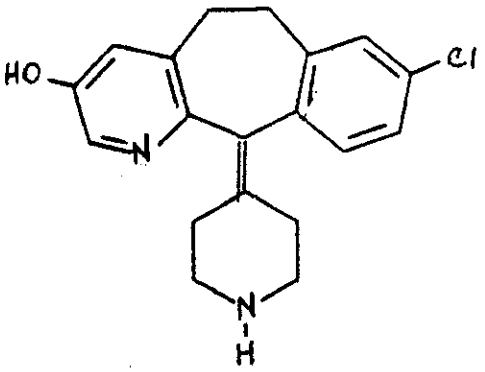












The invention includes a composition which comprises a compound of formula I as defined above in combination with a pharmaceutically acceptable carrier.

As used herein, the following terms are used as defined below unless otherwise indicated:

alkyl - (including the alkyl portion of substituted alkyl, the divalent alkyl moiety of alkanediyl and dialkylamino) straight, branched or cyclic carbon chains containing from 1 to 20 carbons;

lower alkyl - straight or branched carbon chain of from 1 to 6 carbon atoms;

aryl - (including the aryl portion of substituted aryl, arylthio and aryloxy) - represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is a phenyl ring), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of

attachment; and
halo - represents fluoro, chloro, bromo and iodo.

Certain compounds of the invention may exist in isomeric forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures.

The compounds of the invention of formula I can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemihydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

As noted above, the pyridine and benzene ring structures of formula I may contain one or more substituents W, X, Y and Z. In compounds where there is more than one such substituent, they may be the same or different. Thus compounds having combinations of such substituents are within the scope of the invention. Also, the lines drawn into the rings from the W, X, Y and Z groups indicate that such groups may be attached at any of the available positions. For example, the W and X groups may be attached at the 2, 3 or 4 positions while the Y and Z groups may be attached at any of the 7, 8, 9 or 10 positions.

Carbon atoms 5 and 6 of formula I are referred to as the "bridgehead carbons", and may each contain one or more substituents. Carbon atom 5 may be substituted with group A and carbon atom 6 may be substituted with group B. Where more than one group is attached, they may be the same or different.

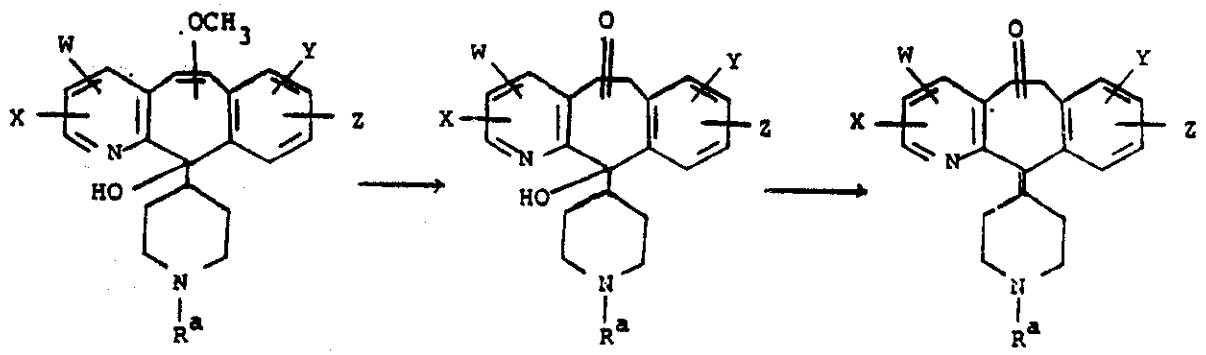
Certain compounds of the invention will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic compounds of the invention also form pharmaceutically acceptable salts, e.g., acid addition salts for example, the piperidino or pyridino nitrogen can form salts with strong acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

All such acid, base and quaternary salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

The following process may be employed to produce compounds of structural formula I. For the compounds II through XIII which are substituted at one bridgehead carbon atom, the substitution group shown may have a bond drawn into the cycloheptane ring through the bridgehead, rather than to a specific bridgehead carbon atom. This is used to indicate that attachment of the substitution group to a particular bridgehead carbon atom is a function of the starting compound. For example, if the methoxy group of compound II below is attached to bridgehead carbon 5, the carbonyl group on the bridgehead of compound III will be positioned at carbon 5 also. However, both isomers are contemplated as being within the scope of the invention.

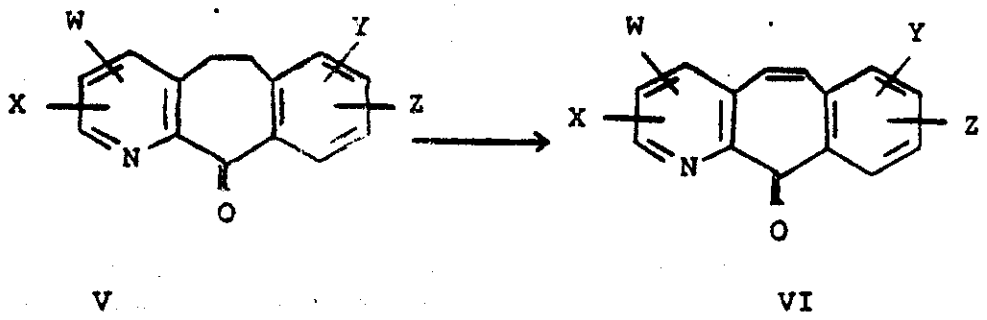
By substituting an isomer of the precursor compound, a compound can be synthesized having the substitution on the bridgehead carbon atoms different from that disclosed in the drawing.



II III IV

A compound of formula II wherein R^a is alkyl may be hydrolyzed with any strong, aqueous acid, for example, 80-95% H_2SO_4 or HCl, having a pH less than 1, at a temperature not higher than room temperature for not generally longer than one hour to produce an intermediate compound of formula III.

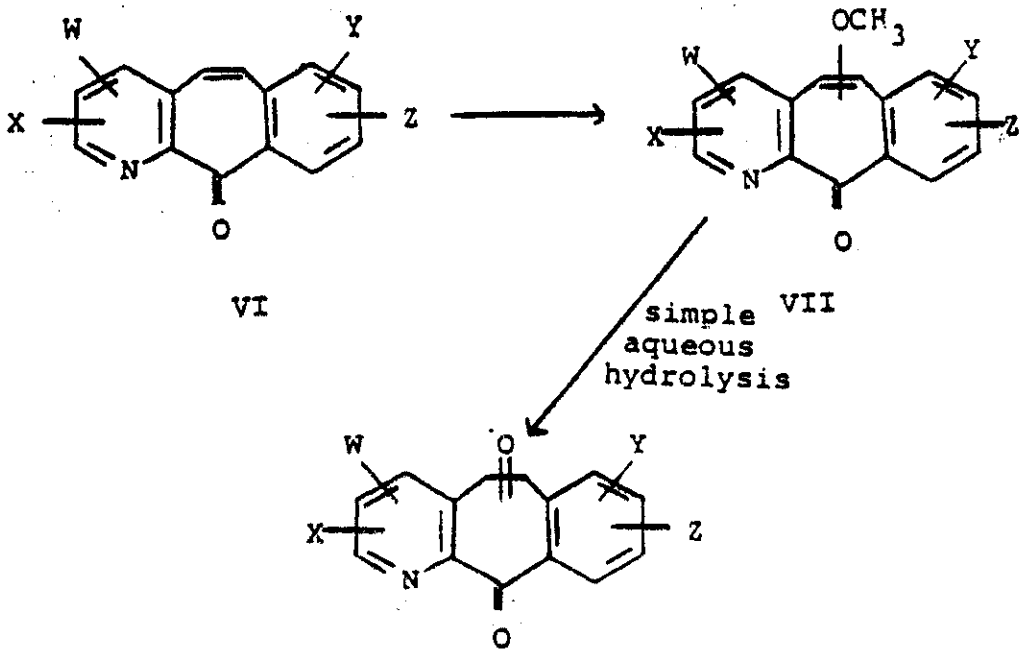
After complete hydrolysis, compound III may be dehydrated with CF_3SO_3H (triflic acid) or a similar acid to yield compound IV which is a compound of the invention, falling within the scope of compound I. Examples of other acids for dehydrating compound III at carbon atom 11 include, for example, HF/BF_3, CH_3SO_3H/BF_3, etc. The reaction can be performed in the absence of or with an inert co-solvent such as CH_2Cl_2. The temperature and time of the reaction vary with the acid employed. When triflic acid is used as the super acid system, the temperature may be controlled to minimize side reactions. For example, Compound III having a carbonyl at carbon atom 5 is best dehydrated when the temperature is maintained in the range of from about 40°C to about 80°C, preferably about 75°C. Alternatively, dehydration of a compound having a carbonyl at carbon atom 6 is best accomplished at elevated temperatures, such as from about 100°C to 130°C.



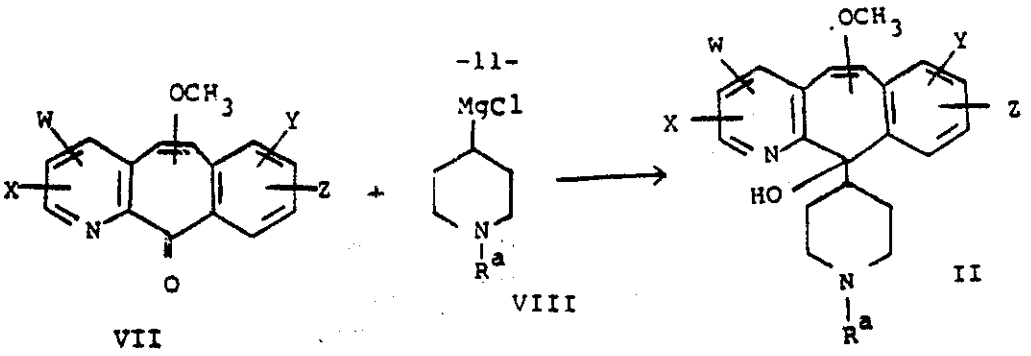
V VI

The alkoxy compound of formula II may be prepared from a starting material of formula V, which is disclosed in U.S. Patent 3,326,924. The bridgehead of Compound V is first brominated with an appropriate brominating agent, such as N-bromosuccinimide (NBS) in the presence of an initiator, such as azobisisobutyryl nitrile (ABIN), benzoyl peroxide or the like in an inert solvent, such as CCl_4, benzene or a similar solvent. Heat or light may be required to initiate the reaction. The bromine on the bridgehead may then be eliminated with base to form the olefinic Compound VI. Examples of suitable bases for elimination include diazabicycloundecane (DBU), diazabicyclononane (DBN) and diazabicyclooctane (DABCO). Elimination is typically performed in an inert solvent at reflux temperature. Examples of suitable inert solvents include CH_2Cl_2, CCl_4, toluene, tetrahydrofuran (THF), dioxane, and $CHCl_3$, with $CHCl_3$ being preferred.

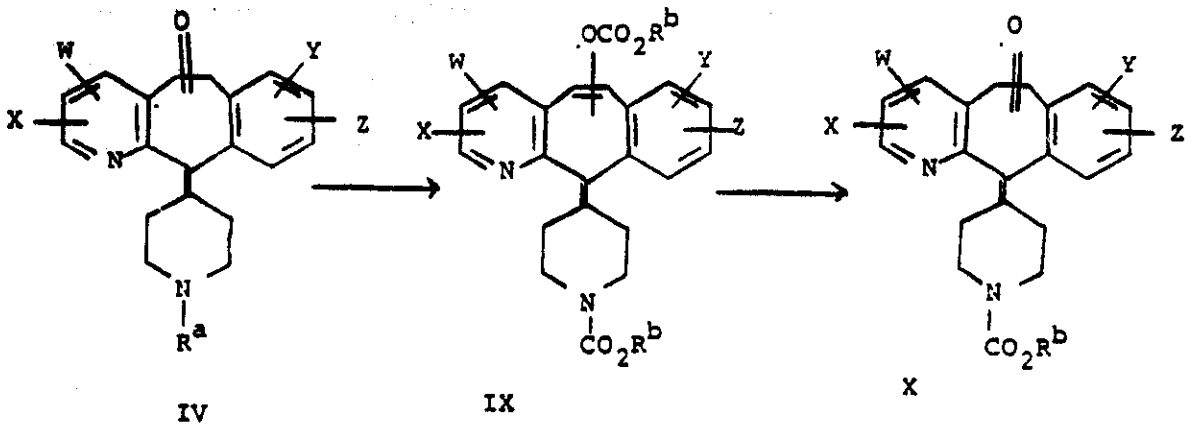
Alternatively, Compound V may be refluxed in the presence of an oxidizing agent to yield compound VI. Representative examples of oxidizing agents suitable for oxidizing compound V include 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) and SeO_2.



Compound VI may be converted to Compound VII by adding excess powdered $AgNO_3$ in methanol, followed by the addition of excess Br_2, which bromoetherificates the unsubstituted bridgehead carbon atom. The bridgehead bromine is then eliminated with excess base, such as DBU to provide a compound of formula VII. The reaction may be run in an inert solvent such as $CHCl_3$ at reflux temperature. The resultant isomeric mixture may be separated by column chromatography or any other appropriate method.



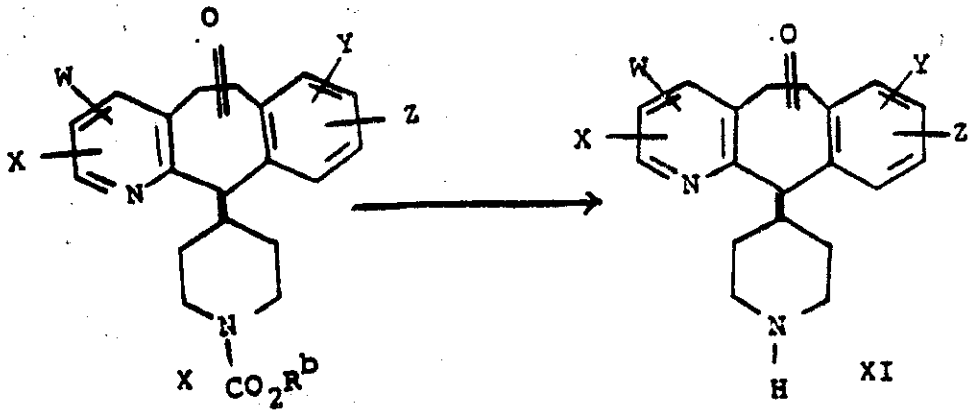
A compound of formula II is prepared by treating the 5-substituted or 6-substituted isomer represented by compound VII with a Grignard reagent VIII in an inert solvent, such as ether, benzene, or tetrahydrofuran (THF). Compound VIII where R^a equals alkyl is prepared in a known manner from magnesium and the 4-chloro N-substituted piperidine. The reaction may be refluxed if necessary, after which it may be quenched with NH_4Cl to form compound II.



IV IX X

Compound IX may be prepared by reacting the bridgehead carbonyl compound of formula IV with an appropriate chloroformate, e.g., phenyl chloroformate, alkyl chloroformate, etc. to generate the enol carbonate on the bridgehead and the appropriate carbamate on the piperidylidene ring. For example, R^b in phenylchloroformate is phenyl; R^b in 2,2,2-trichloroethylchloroformate is 2,2,2-trichloroethyl, etc. Reactions may be run at temperatures ranging from about 70 °C to about 100 °C, in an inert solvent, such as toluene. Furthermore, an organic base, such as triethylamine may be added.

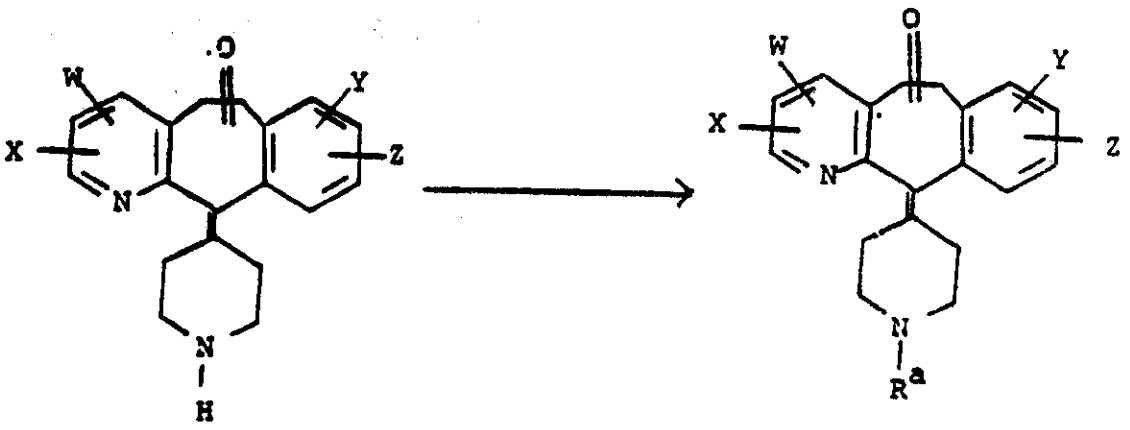
The bridgehead carbonate moiety of Compound IX may be removed via mild aqueous base hydrolysis, for example with NaOH, K_2CO_3, etc., preferably at room temperature to yield compound X. The progress of the reaction may be monitored by thin layer chromatography to prevent removal of the carbamate group.



XI

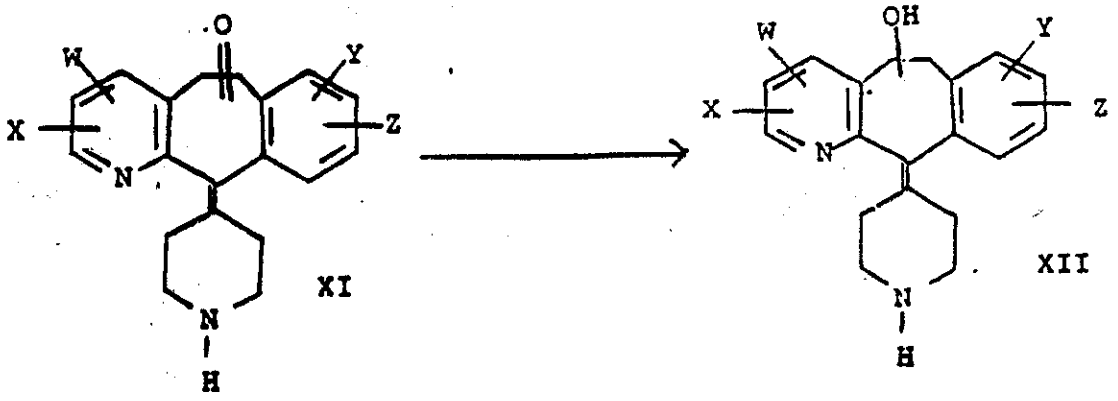
Compound X may be treated with aqueous acid (e.g., HCl) or base (e.g., KOH) with heating, usually at about 100 °C, to form the unsubstituted piperidylidene amine (R is hydrogen) Compound XI.

Alternatively, depending upon the nature of R^b, as determined by one of skill in the art, compound X may be treated with an organometallic reagent (e.g., CH_3Li), a reducing agent (e.g., Zn in acid), or hydrogen with an appropriate catalyst to form compound XI.

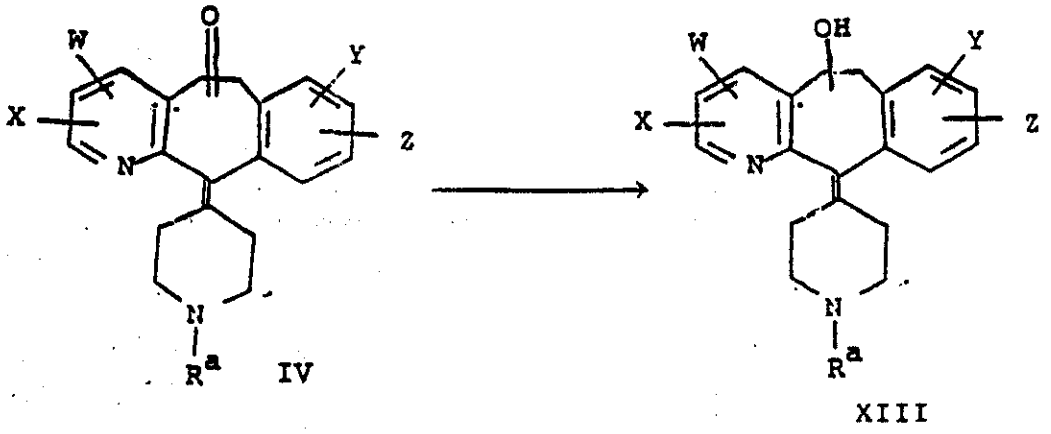


XI IV

Compound IV above may be formed by reacting compound XI with the appropriate alkyl halide (R^aX) in an inert solvent, such as THF, diethyl ether, toluene, DMF or acetonitrile in the presence of base, such as triethylamine.

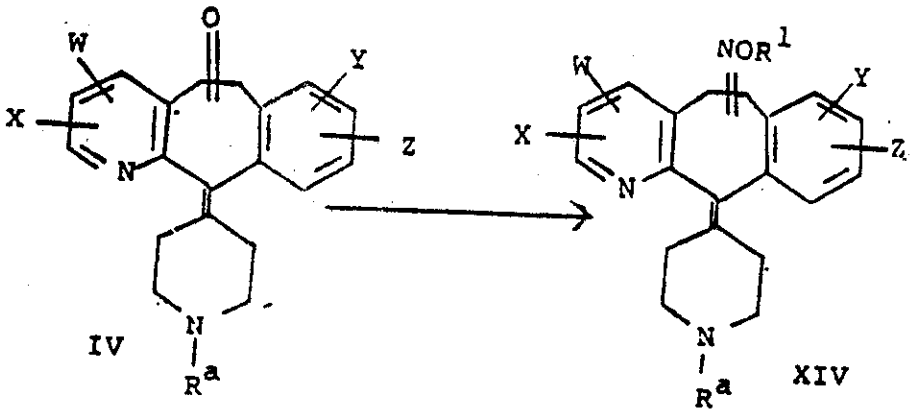


XI XII



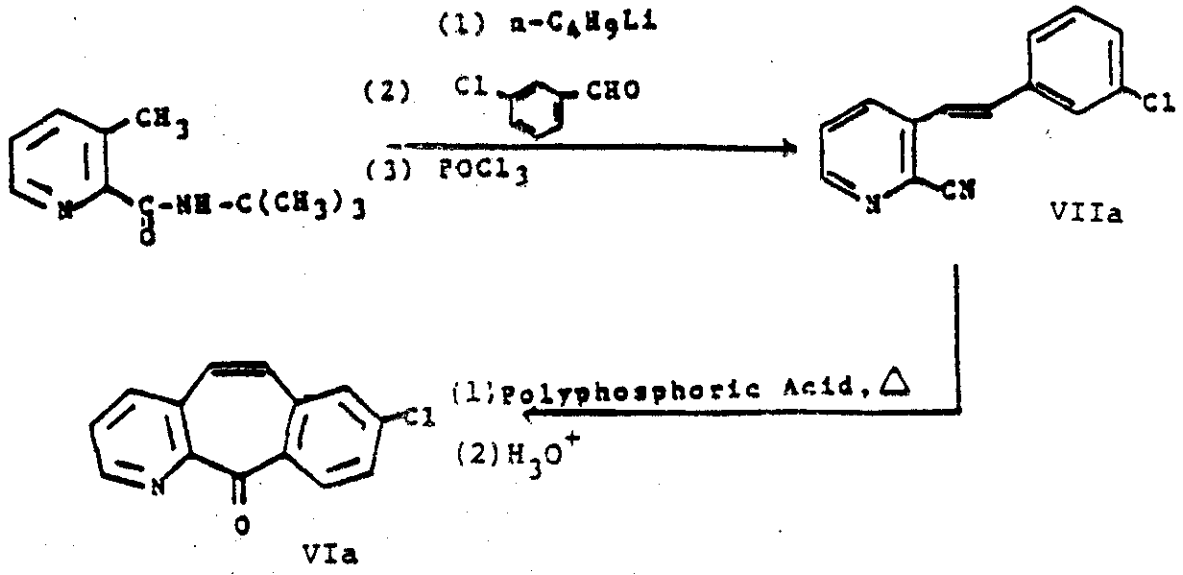
IV XIII

The bridgehead carbonyl of compound XI or IV may be reduced to an hydroxy group by treating compound XI or IV with an appropriate reducing agent, such as $NaBH_4$ in CH_3OH or $LiAlH_4$ in ether to produce a compound of formula XII or XIII respectively.



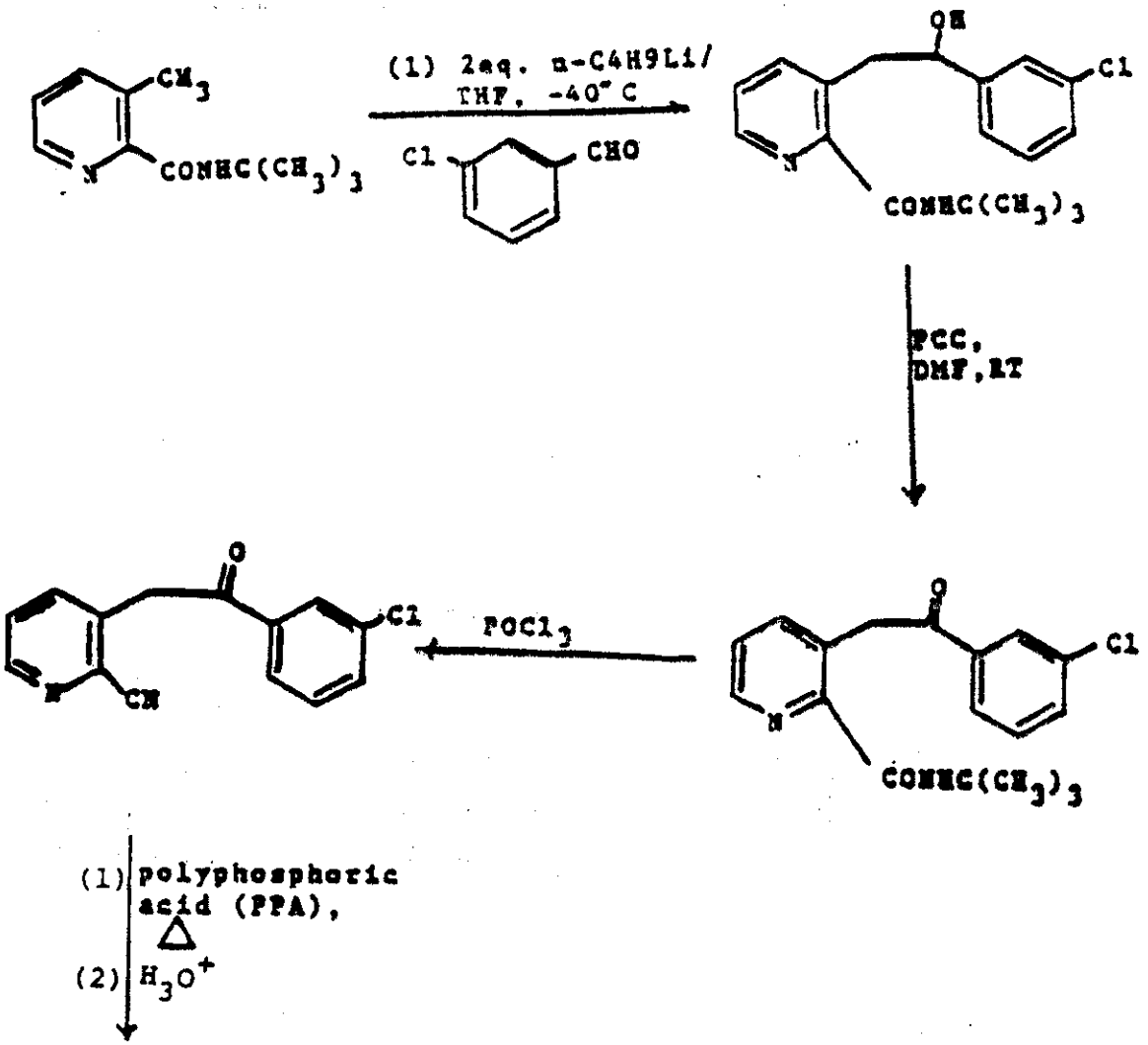
A compound of formula IV may be treated with an appropriate amine in a protic solvent under anhydrous conditions to produce a compound of formula XIV. A representative example of an amine useful herein is hydroxylamine, which reacts with compound IV at room temperature.

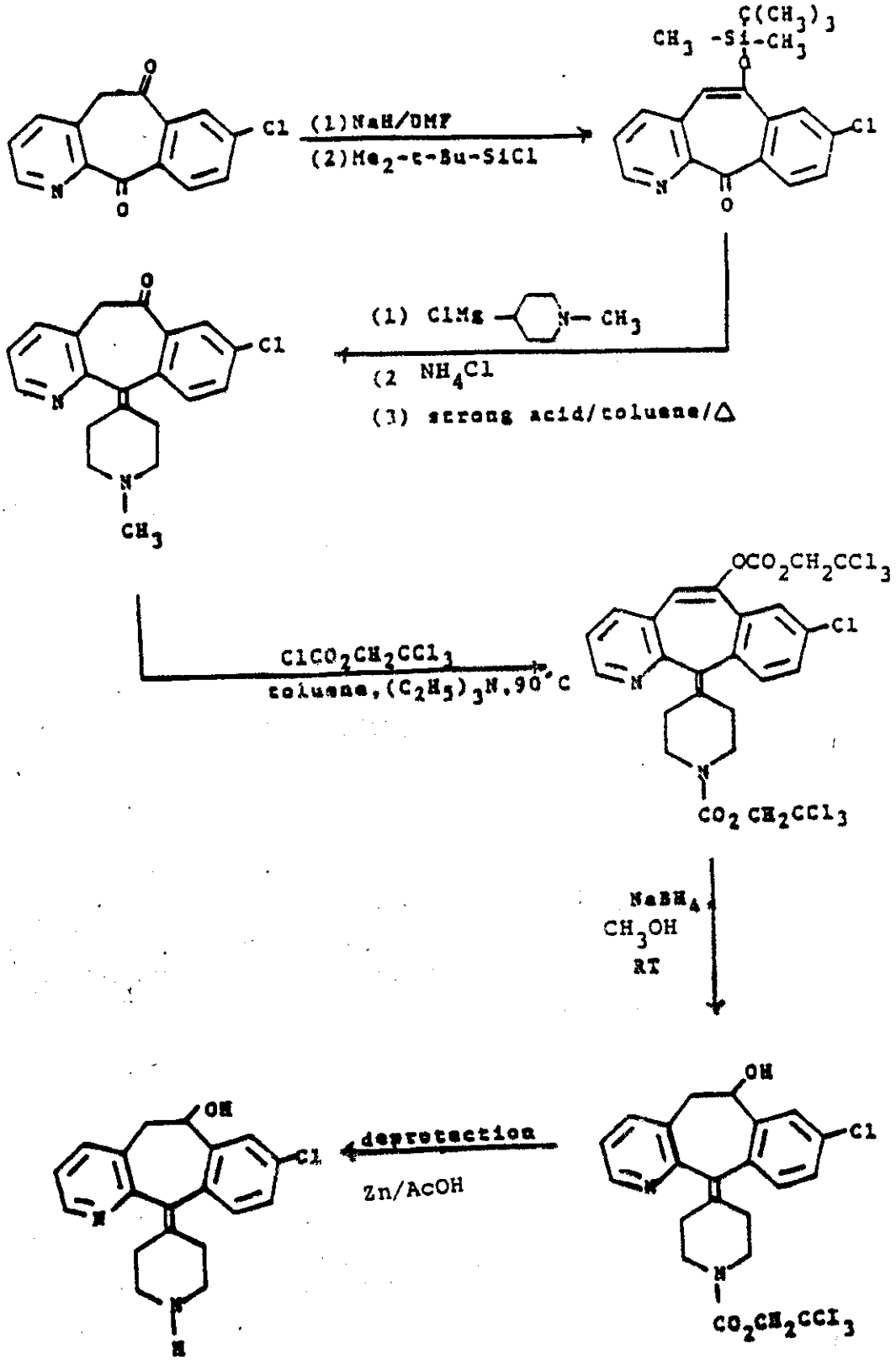
Alternatively, the unsaturated ketone compound VIa which is a chloro substituted compound of VI may be produced via cyclization of the unsaturated nitrile compound VIIa with polyphosphoric acid in the reaction scheme set forth below:



Although the unsaturated nitrile VIIa may be predominantly the trans isomer, the strongly acidic conditions of the cyclization will isomerize the trans to the cis isomer which can then close to the unsaturated aza ketone VIa.

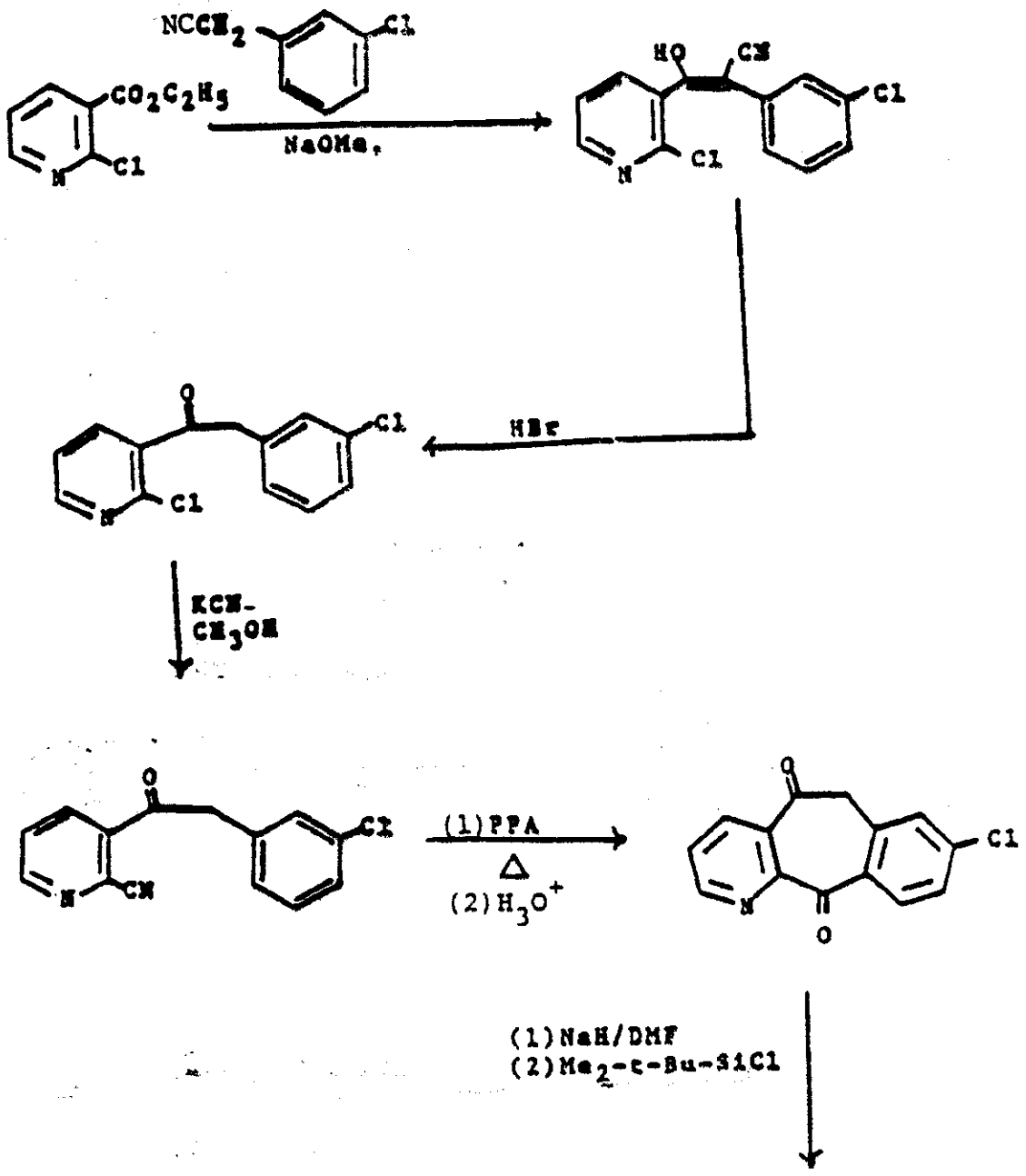
The 6-hydroxy substituted compounds of the invention may also be prepared by the following reaction scheme using known techniques:

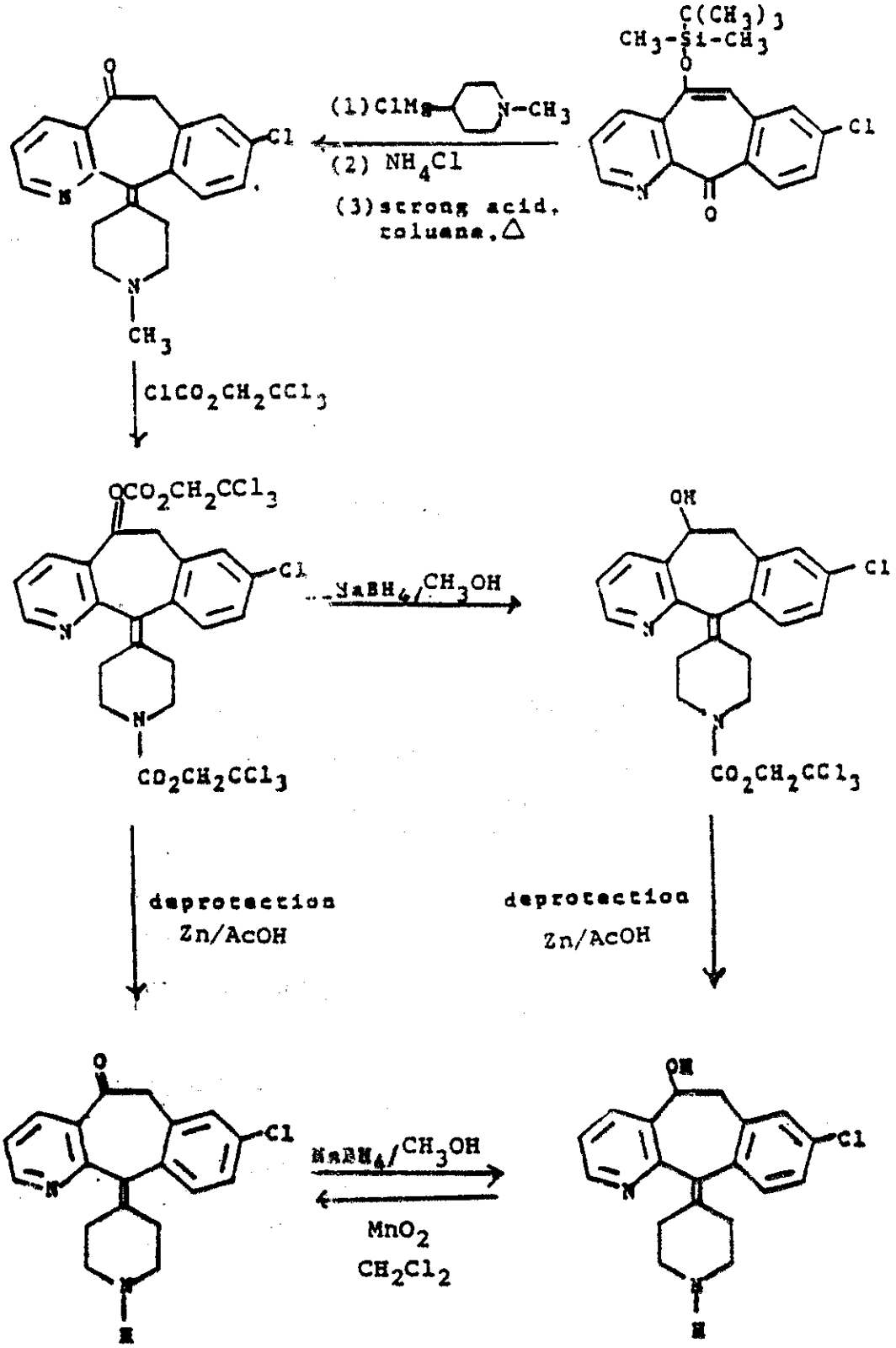

CH3
CONHC(CH3)3
(1) 2eq. n-C4H9Li/
THF, -40° C
Cl
CHO
OH
Cl
CONHC(CH3)3
PCC,
DMF, RT
O
Cl
POCl3
O
Cl
CH
CONHC(CH3)3
(1) polyphosphoric
acid (PPA),
(2) H3O+



The strong acid in the above scheme can be, for example, sulfuric acid at about 60 °C. The deprotection step may be accomplished, for example, by use of Zn and CH_3COOH.

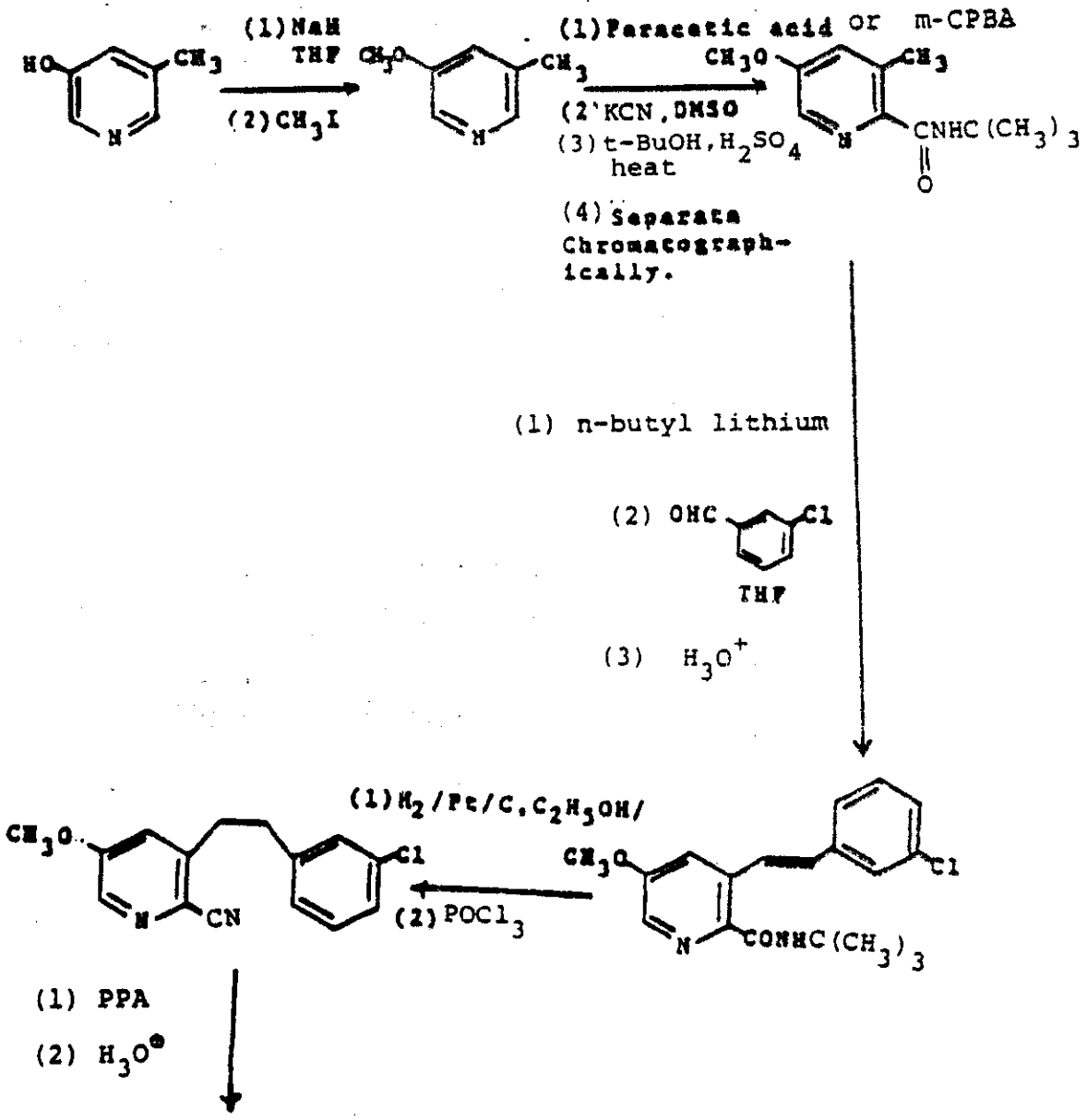
Likewise, the 5-hydroxy substituted compounds of the invention may be prepared using known techniques by the following reaction scheme:

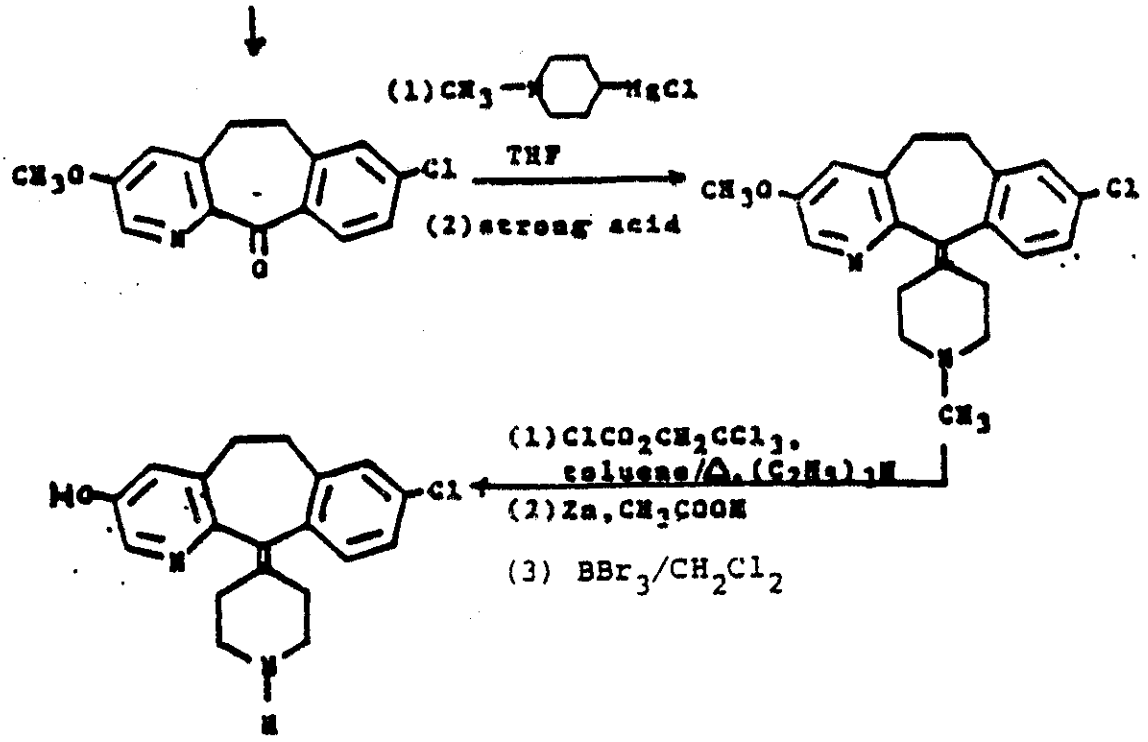

NCCH2
Cl
CO2C2H5
Cl
NaOMe,
HO
CN
Cl
Cl
HBr
O
Cl
Cl
KCN-
CH3OH
O
Cl
CN
(1)PPA
Δ
(2)H3O+
O
Cl
O
(1)NaH/DMF
(2)Me2-t-Bu-SiCl



The 5- and 6-keto substituted compounds of the invention can be prepared from the corresponding 5-or 6-hydroxy substituted compounds by, for example, oxidation with MnO_2 in CH_2Cl_2.

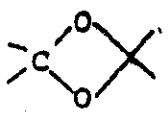
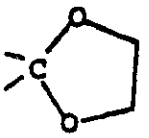
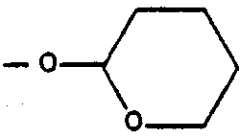
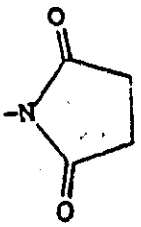
The 3-hydroxy substituted compounds of the invention may be prepared by the reaction scheme described below.


(1) NaH
THF
(2) CH_3I
(1) Peracetic acid or m-CPBA
(2) KCN, DMSO
(3) t-BuOH, H_2SO_4
heat
(4) Separate Chromatographically.
(1) n-butyl lithium
(2) OHC
Cl
THF
(3) H_3O^+
(1) H_2/Pt/C, C_2H_5OH/
(2) $POCl_3$
(1) PPA
(2) $H_3O^{\oplus}$



The compounds of the invention may alternatively be prepared and isolated from human and monkey urine after oral dosing with 8-chloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo[5,6]-cyclohepta[1,2-b]pyridine. Extraction of the urine samples with CH_2Cl_2 and purification by HPLC using reverse phase columns provided a mixture containing about 50% by weight of the compound 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-5-ol and about 32% by weight of the compound 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2]-b]pyridin-6-ol and also separately the compound 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-3-ol. The yield of the metabolities may be increased by treatment of the urine with glucuronidase prior to extraction with CH_2Cl_2.

In the above processes it is sometimes desirable and/or necessary to protect certain A, B, W, X, Y, Z or R groups during the reactions. Conventional protecting groups are operable. For example, the groups listed in column 1 of the following table may be protected as indicated in column 2 of the table:

1. Group to be Protected	2. Protected Group
-COOH	-COOalkyl, -COObenzyl, -COOphenyl
>NH	N-CO_2alkyl, N-CO_2benzyl, N-$CO_2CH_2CCl_3$
>C=O	 
-OH	
$-NH_2$	

Of course, other protecting groups well known in the art may be used. After the reaction or reactions, the protecting groups may be removed by standard procedures.

The compounds of the invention possess antihistaminic properties which may be assessed by test procedure A below. Test procedure A. "Prevention of histaminic-induced lethality" demonstrates basic antihistaminic activity of representative compounds of structural formula I. Greater protection against histamine lethality is indicative of strong antihistaminic properties.

Test procedures B, C and D demonstrate the extent of CNS activity induced by the compounds of the invention. The presence of strong CNS activity indicates a high probability of sedation caused by the compounds, a typically undesirable side effect of antihistamines. Consequently, a low level of CNS activity is preferred in most circumstances.

Antihistamine Activity Assay

A. Prevention of histamine-induced lethality in guinea pigs.

The compounds shown below in Table A were evaluated for antihistamine activity by their ability to protect female albino guinea pigs (250-350 g) against death induced by the intravenous injection of histamine dihydrochloride at 1.1 mg/kg, which is approximately twice the LD_{99}. Doses of the antagonists were administered orally to separate groups of fasted animals 1 hour prior to the challenge with histamine and protection from death recorded for 30 minutes after histamine. ED_{50} values were determined for each drug by probit analysis.

CNS Activity Assays

B. Antagonism of Physostigmine Lethality.

The physostigmine-induced lethality test is indicative of CNS activity and the test described is a modification of the technique reported by COLLIER et al., Br. J. Pharmac., 32, 295-310 (1968). Physostigmine salicylate (1.0 mg/kg s.c.) produces 100% lethality when administered to mice grouped 10 per plastic cage (11 × 26 × 13 cm). Test agents were administered orally 30 minutes prior to physostigmine. The number of survivors were counted 20 minutes after physostigmine administration.

C. Antagonism of Acetic Acid Writhing.

The acetic acid writhing test is a second test useful for determining CNS activity, and is essentially that described by HENDERSHOT and FORSAITH, J. Pharmac. Exp. Ther., 125, 237-240 (1959), except that acetic acid rather than phenylquinone was used to elicit writhing. Mice were injected with 0.6% aqueous acetic acid at 10 mg/kg i.p. 15 minutes after oral administration of the test drug. The number of writhes for each animal was counted during a 10 minute period starting 3 minutes after acetic acid treatment. A writhe was defined as a sequence of arching of the back, pelvic rotation and hind limb extension.

D. Antagonism of Electro-Convulsive Shock (ECS).

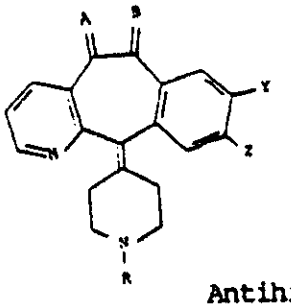
The ECS test is a third test useful for determining CNS activity. For the ECS test, a modification of the method of TOMAN et al., J. Neurophysiol., 9, 231-239 (1946), was used. One hour after oral administration of the test drug or vehicle, mice were administered a 13 mA, 60 cycle a.c. electro-convulsant shock (ECS) for 0.2 seconds via corneal electrodes. This shock intensity produces tonic convulsions, defined as extension of the hind limbs, in at least 95% of vehicle-treated mice.

Of the above test procedures for measuring CNS activity, the physostigmine-induced lethality test is believed to be a major index of non-sedating characteristics, since it reflects mainly central anticholinergic potency which is believed to contribute to sedative activity.

Representative results of test procedure A with compounds of the invention are presented below in Table A.

Table A

Compound



A	B	Y	Z	R	Antihistamine Activity Dose mg/kg	% Survival
H,H	=O	-Cl	-H	-H	1 PO	40%
=O	H,H	-Cl	-H	-H	1 PO	100%
H,OH	H,H	-Cl	-H	-H	5 PO	80%
H,H	H,OH	-Cl	-H	$-CH_3$	1 PO	80%
H,H	=NOH	-Cl	-H	$-CH_3$	1 PO	100%
H,H	$H,OC(O)CH_3$	-Cl	-H	$-CH_3$	1 PO	100%

As seen from the data of Table A, the compounds of structural formula I exhibit antihistaminic properties to varying degrees. Consequently, it is within the scope of this invention to use each of these compounds when clinically appropriate. For example, if strong antihistaminic activity is necessary, such a compound could be chosen by the clinician. Alternatively, if weak antihistaminic activity is required, a different compound of the invention would be utilized by the clinician.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active compound. In the tablet the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Liquid preparations can also be formulated in solution in polyethylene glycol and/or polypropylene glycol, which may contain water.

Aqueous solutions suitable for oral use can be prepared by adding the active component in water and adding suitable colorants, flavors, stabilizing, sweetening, solubilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose and other well-known suspending agents.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas. Inhalation aerosols may be packaged in a pressure resistant container, which may have a metered dose feature suitable for administration into the oral cavity for inhalation, or into the nasal passageways, thereby delivering a precise amount of aerosol per use.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit. Alternately, sufficient solid may be provided so that after conversion to liquid form, multiple individual liquid doses may be obtained by measuring predetermined volumes of the liquid form preparation as with a syringe, teaspoon or other volumetric container. When multiple liquid doses are so prepared, it is preferred to maintain the unused portion of said liquid doses at low temperature (i.e., under refrigeration) in order to retard possible decomposition. The solid form preparations intended to be converted to liquid form may contain, in addition to the active material, flavorants, colorants, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents and the like. The solvent utilized for preparing the liquid form prepara-tion may be water, isotonic water, ethanol, glycerine, propylene glycol and the like as well as mixtures thereof. Naturally, the solvent utilized will be chosen with regard to the route of administration, for example, liquid preparations containing large amounts of ethanol are not suitable for parenteral use.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, for example, packeted tablets, capsules and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet or tablet itself or it can be the appropriate number of any of these packaged form. The compositions can, if desired, also contain other therapeutic agents.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 100 mg, according to the particular application. The appropriate dosage can be determined by comparing the activity of the compound with the activity of a known antihistaminic compound such as 8-chloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, which compound is disclosed in U.S. Patent No. 4,282,233.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgement of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptom being treated. A typical recommended dosage regimen is oral administration of from 0.25 to 100 mg/day, preferably 10 to 20 mg/day, in two to four divided doses to achieve relief of the symptoms.

The following examples are intended to illustrate, but not to limit, the present invention.

PREPARATIVE EXAMPLE 1

8-Chloro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one

Reflux a mixture of 8-chloro-5,6-dihydro-1H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one (25.99 g, 0.107

mol.), recrystallized N-bromosuccinimide (21.35 g, 0.120 mol) and 167 mg (.102 mmol) of azobisisobutyrylnitrile in 400 mL of carbontetrachloride under an argon atmosphere for 1.25 hours. Cool the solution slowly to 50 °C and filter off the resultant precipitate.

Reflux the precipitate with 1,8-diazabicyclo [5.4.0]undec-7-ene ("DBU") (20 mL, 0.134 mol) in CH_2Cl_2 - (400 mL) for 1 hour. Wash with water (3X), dry over magnesium sulfate, filter and concentrate in vacuo. Recrystallize the crude product from CH_2Cl_2/toluene to give the title compound as colorless needles (8.93 g, yield 35%).

ALTERNATIVE PREPARATIVE EXAMPLE 1

8-Chloro-11-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one

Reflux a mixture of 10.23 gm (44.5 mmol) of 8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]-pyridine-11-one and 20.96 gm (92.3 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone(DDQ) in 100 mL of dioxane under an atmosphere of nitrogen for 5 days. Add additional amounts (10.06 gm and 8.02 gm) of DDQ after 3 and 4 days, respectively. Cool the mixture to room temperature and pour into 200 mL of ether. Extract the mixture two times with 5% aqueous HCl. Combine the aqueous portions and wash three times with ether, each time filtering mixture. Basify the mixture with solid sodium hydroxide and filter off and dry the precipitate. Recrystallize the solid from hot toluene/hexane to provide the title compound (3.62g - 36% yield).

PREPARATIVE EXAMPLE 2

A. 5-Methoxy-8-chloro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one

B. 6-Methoxy-8-chloro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one

Add Br_2 (5.10 mL, 99 mmol) to a mixture of the title compound of Preparative Example 1 (8.15 g, 33.7 mmol) and powdered $AgNO_3$ (23.19 g, 137 mmol) in 300 mL of dry methanol at room temperature under an argon atmosphere. After 8 hours, add additional $AgNO_3$ (5.90 g, 34.7 mmol) followed by additional Br_2 (1.7 mL, 33.0 mmol). After 0.5 hours pour the mixture into water and extract (4X) with CH_2Cl_2. Combine the organic phases, dry over magnesium sulfate, filter and concentrate in vacuo to give a mixture of the crude bromo ethers, title compounds A and B above.

Dissolve the crude product in CH_2Cl_2 (200 mL) at room temperature and place under an argon atmosphere. Add DBU (20 mL, 134 mmol) and reflux for 1.3 hours. Add additional DBU (10 mL, 67 mmol) and reflux the mixture for an additional hour. Pour the mixture into water and extract (3X) with CH_2Cl_2. Combine the organic phases, wash with water and dry over magnesium sulfate. Filter and concentrate in vacuo. The two isomeric vinyl ethers title compounds A and B are separated and purified via flash chromatography [40% - 75% ethyl acetate in hexanes] and recrystallize from ethyl acetate hexanes to give title compound A (1.51 g, 14.3%, mp 156 to 158 °C) and title compound B (3.68 g, 35%, mp 161 to 162 °C).

PREPARATIVE EXAMPLE 3A

6-Methoxy-8-chloro-11-(1-methyl-4-piperidinyl)benzo[5,6]cyclohepta[1,2-b]pyridin-11-ol

Add a 1.5 M Grignard solution of N-methyl 4-chloropiperidine in tetrahydrofuran (THF) dropwise over a 10 minute period (17.2 mL, 26.6 mmol) to the title compound of Preparative Example 2A (6.0 g, 22.1 mmol) in THF (80 mL) at 0 °C under an Argon atmosphere. Quench the reaction after 1 hour with water and extract (3X) with ethyl acetate. Combine the organic portions, wash with brine, dry over sodium sulfate, filter and concentrate in vacuo. Chromatograph on silica gel (5% CH_3OH in CH_2Cl_2) to give the title compound (5.01 g, 61%) which may be recrystallized from isopropyl ether to give a solid in the form of white needles (mp 159-160 °C).

PREPARATIVE EXAMPLE 3B

5 Methoxy-8-chloro-11-(1-methyl-4-piperidinyl)benzo[5,6]cyclohepta[1,2-b]pyridin-11-ol

Add a 1.5 M Grignard solution of N-methyl 4-chloropiperidine (150 mL, 22.5 mmol) in THF dropwise over a 7 minute period to title compound B of Preparative Example 2 (5.00 g, 18.4 mmol) in THF (70 mL) at 0 °C under an argon atmosphere. Quench the reaction after 30 minutes with a saturated solution of NH_4Cl (pH 8) and extract (3X) with $CHCl_3$. Combine the organic portions, wash with brine, dry over sodium sulfate, filter and concentrate in vacuo. Purify with flash chromatography (CH_3OH 5% in CH_2Cl_2) to give the title compound (3.60 g, 53%) as a solid. The solid may be recrystallized from isopropyl ether to give a white powder (mp 168-170 °C).

PREPARATIVE EXAMPLE 4A

8-Chloro-11-(1-methyl-4-piperidylidene)-5,11-dihydro-6H-benzo[5,6]cyclohepta[1,2-b]pyridin-6-one

Mix the title compound of Preparative Example 3A (2.00 g, 5.39 mmol) slowly in 95% aqueous H_2SO_4 - (30 ml). Stir at room temperature under an argon atmosphere for 30 minutes and add trifluoromethyl sulfonic acid (30 mL). Heat the mixture to 115 °C and maintain for one hour. Cool the mixture to room temperature, pour onto ice, basify with 25% aqueous NaOH and extract (2X) with CH_2Cl_2. Combine the organic portions and wash with brine. Dry over sodium sulfate, filter, and concentrate in vacuo to give the title compound (1.41 g, 77%). Recrystallize the material from ethyl acetate/isopropyl ether to give the title compound as a granular solid (1.12 g, 61%, mp 181-183 °C).

PREPARATIVE EXAMPLE 4B

8-Chloro-11-(1-methyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-5-one

Dissolve the title compound of Preparative Example 3B (4.26 g) in CH_3OH (6 mL) at 0 °C under an argon atmosphere. Add slowly a cooled solution of 92% aqueous H_2SO_4 (54 mL). Allow the mixture to warm to room temperature for 35 minutes. Pour the solution onto ice, basify with aqueous NaOH (25%), and extract with methylene chloride (3X). Combine the organic portions, wash with brine and dry over sodium sulfate. Filter and concentrate in vacuo. Triturate the residue with ispropyl ether to give an intermediate, 8-chloro-11-hydroxy-11-(1-methyl-4-piperidinyl)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-5-one as a white solid (3.58 g., 92%, m.p. 170 to 174 °C as HCl salt).

Dissolve the intermediate compound (3.58 g, 10.0 mmol) in trifluoromethane sulfonic acid (50 mL) and heat to 45 °C under an argon atmosphere for 3 hours. Pour the mixture onto ice, basify with aqueous NaOH (25% w/v), and extract with $CHCl_3$ (3X). Combine the organic portions, wash with brine and dry over sodium sulfate. Filter and concentrate in vacuo. Chromatograph on silica gel (5% CH_3OH in CH_2Cl_2) to give the title compound as an off white solid (1.703 g, 50%, 58% based on recovered starting material). An analytical sample was prepared by recrystallization of the product with ethyl acetate/isopropyl ether (mp 162-163 °C).

PREPARATIVE EXAMPLE 5

Ethyl 4-(8-chloro-6-ethoxycarbonyloxy-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine carboxylate

Add dropwise a mixture of ethyl chloroformate (1.34 mL, 14.0 mmol) in toluene (12 mL) to a solution of the title compound of Preparative Example 4A (952 mg, 2.81 mmol) and in triethylamine (590 mL, 4.23 mmol) at 80 °C under an argon atmosphere. After 30 minutes cool the mixture to room temperature, filter and concentrate in vacuo. Purify the crude product via flash chromatography [5% CH_3OH in CH_2Cl_2] to yield the title compound as a glass (1.11 g., 84%).

PREPARATIVE EXAMPLE 6

Ethyl 4-(8-chloro-5-ethoxycarbonyloxy-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine carboxylate

Dissolve the title compound of Preparative Example 4B (617 mg, 1.82 mmol) and triethylamine (0.50 mL, 3.58 mmol) in toluene (12 mL) at 80 °C under an argon atmosphere. Add dropwise over 2 minutes ethyl chloroformate (0.87 mL, 9.10 mmol). After 25 minutes cool the mixture to room temperature, filter, and concentrate in vacuo. Purify the crude product via flash chromatography (1% CH_3OH in CH_2Cl_2) to yield

the title compound as a glass (834 mg, 98%).

EXAMPLE 1

8-Chloro-11-(4-piperidylidene)-5,11-dihydro-6H-benzo[5,6]cyclohepta[1,2-b]pyridin-6-one

Mix the title compound of Preparative Example 5 (1.40 g., 2.99 mmol) and aqueous KOH (20 mL, 13% w/v) in ethanol (15 mL) and reflux under an argon atmosphere for 42 hours. Pour the mixture into water and extract (4X) with CH_2Cl_2. Combine the organic portions, wash with brine, dry over sodium sulfate, filter and concentrate in vacuo. Purify the residue via flash chromatography (10 - 20% CH_3OH in CH_2Cl_2) and recrystallize from CH_2Cl_2/pentane to give the title compound as a yellowish solid (6.55 mg, 67% mp 207-209 °C (dec)).

EXAMPLE 2

6-Hydroxy-8-chloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

Mix the title compound of Example 1, (0.29 g, 0.893 mmol) in CH_3OH (14 mL) at 0 °C under an argon atmosphere. Add $NaBH_4$ (165 mg, 4.36 mmol) in 3 portions. After 30 minutes, pour the mixture into water and extract (3X) with CH_2Cl_2. Combine the organic portions, wash once with brine, dry over sodium sulfate, filter and concentrate in vacuo to give a crude product. Purifiy via flash chromatography [5 - 10% CH_3OH saturated with NH_3 in CH_2Cl_2] to give the title compound, which can be triturated with isopropyl ether/pentane to give an off-white solid (249 mg, 85%).

EXAMPLE 3

8-Chloro-6-hydroxyimino-11-[1-methyl-4-piperidylidene]-6H-benzo[5,6]cyclohepta[1,2-b]pyridine

Add the title compound of Preparative Example 4A (369 mg, 1.1 mmol) to a solution of $NH_2OH \cdot HCl$ (190 mg, 2.7 mmol), dry pyridine (0.245 mL, 3.0 mmol), water (1.0 mL) and absolute ethanol (20 mL). Stir the reaction for 17 hours at room temperature, and quench with water. Basify the reaction to pH 10 with dilute NaOH. Extract the solution with CH_2Cl_2 (3X), combine the organic phases and dry over sodium sulfate. Filter the organic phase and concentrate to a yellowish oil. Triturate the oil with pentane and isopropyl ether to yield the title compound as a white powder (387 mg, 98%, m.p. 172-175 °C).

EXAMPLE 4

8-Chloro-11-(1-methyl-4-piperidylidene)-5,11-dihydro-6H-benzo[5,6]cyclohepta[1,2-b]pyridin-6-ol

Add $NaBH_4$ (155.7 mg, 4.1 mmol) to an ice-bath cooled solution of the title compound of Preparative Example 4A (277 mg, 0.87 mmol) in CH_3OH (14 mL) under an argon atmosphere. Stir the reaction while warming to room temperature (1 hour). Extract with CH_2Cl_2 (2 x 150 mL) and wash with brine. Dry the organic phase over sodium sulfate, filter and concentrate in vacuo to give a yellowish foam-solid. Recrystallize from ethyl acetate and diethyl ether to give the title compound (270 mg, 97%, mp 222-225 °C).

EXAMPLE 5

6-Acetoxy-8-Chloro-11-(1-methyl-4-piperidylidene)-5,11-dihydro-6H-benzo[5,6]cyclohepta[1,2-b]pyridine

Dissolve the title compound of Example 4 (286 mg, 0.84 mmol) in CH_2Cl_2 (8.5 mL) and add pyridine (1.26 mL, 15.6 mmol) under an argon atmosphere. Add acetic anhydride (0.84 mL, 8.9 mmol), and warm to 35 °C (oil bath temperature) for 6 hours. Cool to room temperature and quench with water. Extract the product with CH_2Cl_2 (2 x 150 mL) and wash with brine. Dry the organic phase over sodium sulfate, filter and concentrate in vacuo. Azeotrope with toluene to give the title compound, a white solid, as the hydrochloride hemihydrate (350 mg, 97%). An analytical sample was prepared by recrystallization from ethylacetate (mp 252-254 °C (dec)).

EXAMPLE 6

8-Chloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-5-one

Mix the title compound of Preparative Example 6 (897 mg, 1.91 mmol) and aqueous KOH (20 mL, 13% w/v) in ethanol (15 mL) and reflux under an argon atmosphere for 25 hours. Pour the mixture into water and extract with $CHCl_3$ (3X). Combine the organic portions, wash with brine, dry over sodium sulfate, filter, and concentrate in vacuo. Purify the residue via flash chromatography (2% CH_3OH saturated with NH_3 in CH_2Cl_2) and triturate with isopropyl ether to give the title compound as a white solid (417 mg, 67%, mp 194-196 °C (dec)).

EXAMPLE 7

5-Hydroxy-8-chloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

Mix the title compound of Example 6 (400 mg, 1.23 mmol) in CH_3OH (20 mL) at 0 °C under an argon atmosphere, and add in 3 portions $NaBH_4$ (total 231 mg, 6.10 mmol). After 30 minutes, pour the mixture into water and extract (3X) with ethyl acetate. Combine the organic portions, wash with brine, dry over sodium sulfate, filter and concentrate in vacuo. Triturate the solid with isopropyl ether/ethyl acetate to give the title compound as a white solid (351 mg, 87%).

The following formulations exemplify some of the dosage forms of the compositions of this invention. In each, the term "active compound" designates for purposes of the formulation the compound, 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine-5-ol, or a pharmaceutically acceptable salt or solvate thereof. However, any other compound falling within the scope of formula I can be used.

Pharmaceutical Dosage Form Examples

Example A

Tablets

No.	Ingredient	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4") if needed. Dry the damp granules. Screen the dried granules if needed and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

Example B
Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	4	7
	Total	250	700

Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

Example C
Parenteral

Ingredient	mg/vial	mg/vial
Active Compound Sterile Powder	100	500

Add sterile water for injection or bacteriostatic water for injection, for reconstitution.

Example D
Injectable

Ingredient	mg/vial	mg/vial
Active Compound	100	500
Methyl p-hydroxybenzoate	1.8	1.8
Propyl p-hydroxybenzoate	0.2	0.2
Sodium Bisulfite	3.2	3.2
Disodium Edetate	0.1	0.1
Sodium Sulfate	2.6	2.6
Water for Injection q.s. ad	1.0 ml	1.0 ml

Method of Manufacture

1. Dissolve parabens in a portion (85% of the final volume) of the water for injection at 65-70° C.

2. Cool to 25-35°C. Charge and dissolve the sodium bisulfite, disodium edetate and sodium sulfate.
3. Charge and dissolve drug.
4. Bring the solution to final volume by added water for injection.
5. Filter the solution through 0.22 membrane and fill into appropriate containers.
6. Terminally sterilize the units by autoclaving.

Example E
Nasal Spray

		mg/ml
Active Compound		10.0
Phenyl Mercuric Acetate		0.02
Aminoacetic Acid USP		3.7
Sorbitol Solution, USP		57.0
Benzalkonium Chloride Solution		0.2
Sodium Hydroxide 1N Solution to adjust pH		-----
Water Purified USP	to make	1.0 ml

Example F
Ointment

Formula	mg/g
Active Compound	1.0-20.0
Benzyl Alcohol, NF	20.0
Mineral Oil, USP	50.0
White Petrolatum, USP to make	1.0 g

Method of Manufacture

Disperse active compound in a portion of the mineral oil. Mix and heat to 65°C, a weighed quantity of white petrolatum, the remaining mineral oil and benzyl alcohol, and cool to 50°-55°C. with stirring. Add the dispersed active compound to the above mixture with stirring. Cool to room temperature.

Example G

Cream

Formula	mg/g
Active Compound	1.0-20.0
Stearic Acid, USP	60.0
Glyceryl Monostearate	100.0
Propylene Glycol, USP	50.0
Polyethylene Sorbitan Monopalmitate	50.0
Sorbitol Solution, USP	30.0
Benzyl Alcohol, NF	10.0
Purified Water, USP to make	1.0 g

Method of Manufacture

Heat the stearic acid, glyceryl monostearate and polyethylene sorbitan monopalmitate to 70°C. In a separate vessel, dissolve sorbital solution, benzyl alcohol, water, and half quantity of propylene glycol and heat to 70°C. Add the aqueous phase to oil phase with high speed stirring. Dissolve the active compound in remaining quantity of propylene glycol and add to the above emulsion when the temperature of emulsion is 37°-40°C. Mix uniformly with stirring and cool to room temperature.

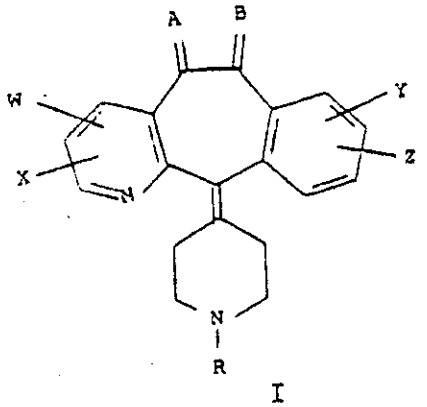
The relevant teachings of all published references cited herein are incorporated by reference.

While the present invention has been described in connection with the certain specific embodiments thereof, it will be evident to one of ordinary skill in the art that many alternatives, modifications and variations may be made. All such alternatives, modifications and variations are intended to be included within the spirit and scope of the invention.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB,.IT, LI, LU, NL, SE

1. A compound represented by structural Formula I:



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R represents H or straight, branched or cyclic C_{1-20} alkyl, such that

(1) when R represents straight, branched or cyclic C_{1-20} alkyl, at least one of A and B represents a

substituent group selected from H and OR^1, H and $OC(O)R^1$, $=NOR^1$ or $-O-(CH_2)_n-O-$, and the other may represent H_2 or one of the above listed substituent groups;

W, X, Y and Z may be the same or different and each independently represents H, fluoro, chloro, bromo or iodo, straight, branched or cyclic C_{1-20} alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ or $-N(R^1)_2$;

R^1 is H, straight, branched or cyclic C_{1-20} alkyl or C_{6-15} aryl and in $N(R^1)_2$, R^1 can be straight, branched or cyclic C_{1-20} alkanediyl, and n is 2, 3 or 4, and

(2) when R represents H,

A or B may be the same or different and each independently represents H_2, H and OR^1, H and $OC(O)R^1$, =O, $=NOR^1$ or $-O-(CH_2)_n-O-$;

W, X, Y and Z may be the same or different and each independently represents H, fluoro, chloro, bromo or iodo, straight, branched or cyclic C_{1-20} alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$ or $-CO_2R^1$ or $-N(R^1)2$, with the provisos that when A and B both represent H_2, W is OR^1 and R^1 is H, and when A or B represents =O, at least one of W, X, Y and Z represents fluoro, chloro, bromo or iodo, straight, branched or cyclic C_{1-20} alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ or $-N(R^1)_2$; and

R^1 and n are as defined above,

with the proviso that said compound of Formula I is not 8-chloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6] cyclohepta[1,2-b]pyridin-5-one or 5-hydroxy-8-chloro-11-(4-piperidylidine)-6,11-dihydro-5H-benzo-[5, 6]cyclohepta[1,2-b]pyridine.

2. A compound is defined in claim 1 wherein R represents straight, branched or cyclic C_{1-20} alkyl; at least one of A and B represents a substituent group selected from H and OR^1, H and $OC(O)R_1$, $=NOR^1$ or $-O-(CH_2)_n-O-$, and the other may represent H_2 or one of the above listed substituent groups;

W, X, Y and Z may be the same or different and each independently represents H, fluoro, chloro, bromo or iodo, straight, branched or cyclic C_{1-20} alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-CO_2R^1$ or $-N(R^1)_2$;

R^1 is H, C_1-C_{20} alkyl or C_6-C_{15} aryl and n is 2, 3 or 4.

3. A compound as defined in Claim 1 wherein R represents H;

A or B may be the same or different and each independently represents H_2, H and OR^1, H and $OC(O)R^1$, =O, $=NOR^1$ or $-O-(CH_2)_n-O-$;

W, X, Y and Z may be the same or different and each independently represents H, fluoro, chloro, bromo or iodo, straight, branched or cyclic C_{1-20} alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, or $-CO_2R^1$ or $-N(R^1)_2$ with the provisos that when A and B both represent H_2, W is -OH, and when A or B represents =O, at least one of W, X, Y and Z represents fluoro, chloro, bromo or iodo, straight, branched or cyclic C_{1-20} alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ or $-N(R^1)_2$, and

R^1 and n are as previously defined.

4. A compound as defined in Claim 2 wherein R represents straight branched or cyclic C_{1-6} alkyl.

5. A compound as defined in any of claims 1-4 above wherein one of A and B is H_2 and the other of A and B represents H- and $OC(O)R^1$, =O, $=NOR^1$ or $-O-(CH_2)_nO-$.

6. A compound as defined in any of claims 1-5 above wherein at least one of A and B represents H and OR^1.

7. A compound as defined in any of claims 1-6 above wherein A and B represent H_2, and W represents OR^1.

8. A compound as defined in any of claims 1-7 above wherein R^1 represents H.

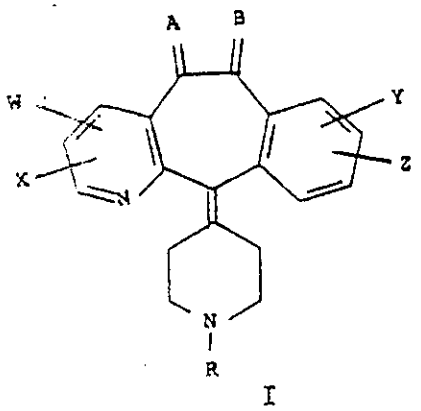
9. A compound as defined in any of claims 1-8 above wherein W, X, Y and Z independently represent H, fluoro, chloro, bromo or iodo alkyl, $-CF_3$, $-SR^1$, $-OR^1$ or $N(R^1)_2$.

10. A compound as defined in any of claims 1-9 above wherein at least one of Y and Z represents fluoro, chloro, bromo or iodo.

11. A compound as defined in any of claims 1-10 above wherein -W represents OR^1 at position 3.

12. A compound as defined in claim 1 having the following name:
8-chloro-11-[4-piperidylidene]-5,11-dihydro-6H-benzo[5,6]cyclohepta[1,2-b]pyridin-6-one;
6-hydroxy-8-chloro-11-[4-piperidylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine;
8-chloro-6-hydroxyimino-11-[1-methyl-4-piperidylidine]-6H-benzo[5,6]cyclohepta[1,2-b]pyridine;
8-chloro-11-[1-methyl-4-piperidylidene]-5,11-dihydro-6H-benzo[5,6]-cyclohepta[1,2-b]pyridin-6-ol;
6-acetoxy-8-chloro-11-[1-methyl-4-piperidylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]-pyridine;
3-hydroxy-8-chloro-11-[4-piperidylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

13. A pharmaceutical composition which comprises a compound represented by structural Formula I:



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:
R represents H or straight, branched or cyclic C_{1-20} alkyl, such that
(1) when R represents straight, branched or cyclic C_{1-20} alkyl, at least one of A and B represents a substituent group selected from H and OR^1, H and $OC(O)R^1$, $=NOR^1$ or $-O-(CH_2)_n-O-$, and the other may represent H_2 or one of the above listed substituent groups;
W, X, Y and Z may be the same or different and each independently represents H, fluoro, chloro, bromo or iodo, straight, branched or cyclic C_{1-20} alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ or $-N(R^1)_2$;
R^1 is H, straight, branched or cyclic C_{1-20} alkyl or C_{6-15} aryl and in $N(R^1)_2$, R^1 can be straight, branched or cyclic C_{1-20} alkanediyl, and n is 2, 3 or 4, and
(2) when R represents H,
A or B may be the same or different and each independently represents H_2, H and OR^1, H and $OC(O)R^1$, =O, $=NOR^1$ or $-O-(CH_2)_n-O-$;
W, X, Y and Z may be the same or different and each independently represents H, fluoro, chloro, bromo or iodo, straight, branched or cyclic C_{1-20} alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$ or $-CO_2R^1$ or -N(R¹)2, with the provisos that when A and B both represent H_2, W is OR^1 and R^1 is H, and when A or B represents =O, at least one of W, X, Y and Z represents fluoro, chloro, bromo or iodo, straight, branched or cyclic C_{1-20} alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ or $-N(R^1)_2$; and
R^1 and n are as defined above.

14. A pharmaceutical composition according to Claim 13 wherein said compound of Formula I is as defined in any one of Claims 2 to 12.

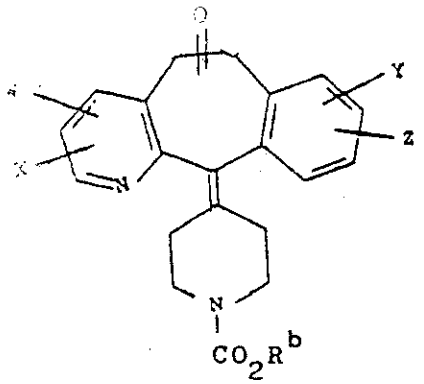
15. A pharmaceutical composition according to Claim 13 wherein said compound of Formula I is
8-chloro-11-[4-piperidylidene]-6,11-dihydro-5H-benzo[5,6] cyclohepta[1,2-b]pyridin-5-one; or
5-hydroxy-8-chloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

16. A method of making a pharmaceutical composition comprising mixing a compound of Formula I as defined in Claim 13 with a pharmaceutically acceptable carrier.

17. The use of a compound as defined in Claim 13 for the preparation of a pharmaceutical composition for anti-allergy application.

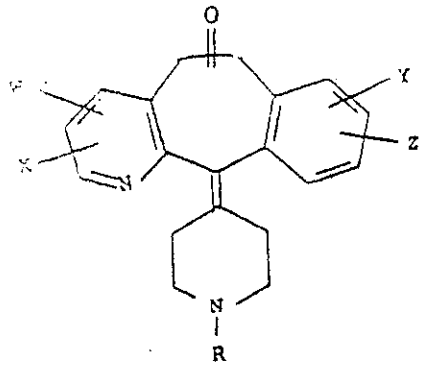
18. A process for producing a compound having structural Formula I as defined in Claim 13 characterised by:

a) decarboxylating a compound of the structure



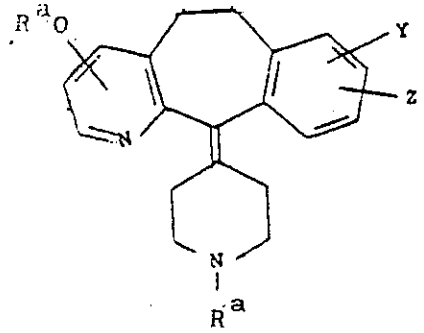
where R_b is straight, branched or cyclic C_{1-20} alkyl, or C_{6-15} aryl, with the proviso that said compound of formula I is other than 8-chloro-11-[4-piperidylidene]-6,11-dihydro-5H-benzo-[5,6]-cyclohepta[1,2-b]pyridin-5-one; or

b) reducing the keto compound



at the keto group, with the proviso that said compound of formula I is other than 5-hydroxy-8-chloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

c) dealkylating a compound of the structure



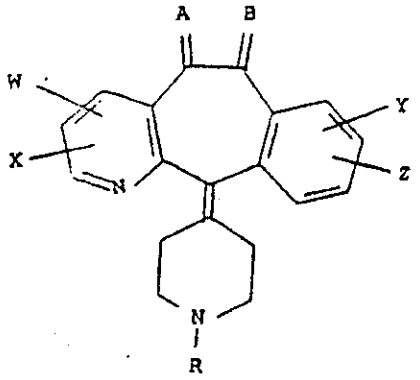
where R^a is straight, branched or cyclic C_{1-20} alkyl; or

(d) oral dosing a human and/or monkey with 8-chloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b] pyridine and isolating from the respective human and/or monkey urine;

which processes may further comprise the step of converting one functional group of a compound of Formula I into another functional group of Formula I.

Claims for the following Contracting States : ES, GR

1. A process for producing a compound having structural Formula I



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R represents H or straight, branched or cyclic C_{1-20} alkyl, such that

(1) when R represents straight, branched or cyclic C_{1-20} alkyl, at least one of A and B represents a substituent group selected from H and OR^1, H and $OC(O)R^1$, $=NOR^1$ or $-O-(CH_2)_n-O-$, and the other may represent H_2 or one of the above listed substituent groups;

W, X, Y and Z may be the same or different and each independently represents H, fluoro, chloro, bromo or iodo, straight, branched or cyclic C_{1-20} alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ or $-N(R^1)_2$;

R^1 is H, straight, branched or cyclic C_{1-20} alkyl or C_{6-15} aryl and in $N(R^1)_2$, R^1 can be straight, branched or cyclic C_{1-20} alkanediyl, and n is 2, 3 or 4, and

(2) when R represents H,

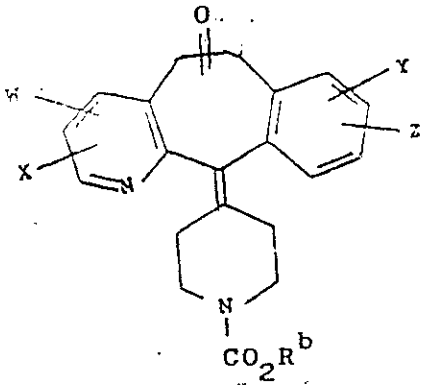
A or B may be the same or different and each independently represents H_2, H and OR^1, H and $OC(O)R^1$, $=O$, $=NOR^1$ or $-O-(CH_2)_n-O-$;

W, X, Y and Z may be the same or different and each independently represents H, fluoro, chloro, bromo or iodo, straight, branched or cyclic C_{1-20} alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$ or $-CO_2R^1$ or $-N(R^1)2$, with the provisos that when A and B both represent H_2, W is OR^1 and R^1 is H, and when A or B represents $=O$, at least one of W, X, Y and Z represents fluoro, chloro, bromo or iodo, straight, branched or cyclic C_{1-20} alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ or $-N(R^1)_2$; and

R^1 and n are as defined above.

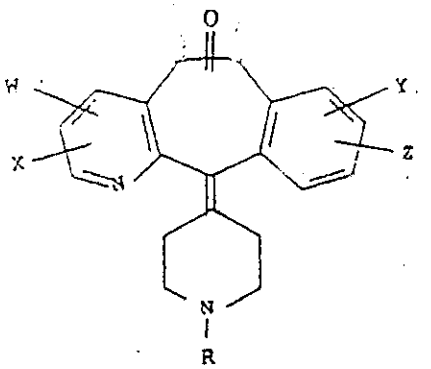
characterised by:

a) decarboxylating a compound of the structure



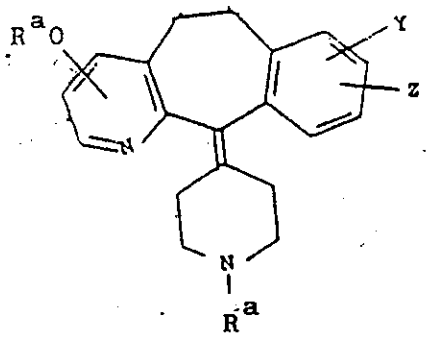
where R_b is straight, branched or cyclic C_{1-20} alkyl, or C_{6-15} aryl, with the proviso that said compound of formula I is other than 8-chloro-11-[4-piperidylidene]-6,11-dihydro-5H-benzo-[5,6]-cyclohepta[1,2-b]pyridin-5-one; or

b) reducing the keto compound



at the keto group, with the proviso that said compound of formula I is other than 5-hydroxy-8-chloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

c) dealkylating a compound of the structure



where R^a is straight, branched or cyclic C_{1-20} alkyl; or

(d) oral dosing a human and/or monkey with 8-chloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b] pyridine and isolating from the respective human and/or monkey urine;

which processes may further comprise the step of converting one functional group of a compound of Formula I into another functional group of Formula I.

2. A process as claimed in claim 1 wherein R represents straight, branched or cyclic C_{1-20} alkyl; at least one of A and B represents a substituent group selected from H and OR^1, H and $OC(O)R_1$, $=NOR^1$ or $-O-(CH_2)_n-O-$, and the other may represent H_2 or one of the above listed substituent groups;

W, X, Y and Z may be the same or different and each independently represents H, fluoro, chloro, bromo or iodo, straight, branched or cyclic C_{1-20} alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-CO_2R^1$ or $-N(R^1)_2$;

R^1 is H, C_{1-20} alkyl or C_{6-15} aryl and n is 2, 3 or 4.

3. A process as claimed in Claim 1 wherein R represents H;

A or B may be the same or different and each independently represents H_2, H and OR^1, H and $OC(O)R^1$, =O, $=NOR^1$ or $-O-(CH_2)_n-O-$;

W, X, Y and Z may be the same or different and each independently represents H, fluoro, chloro, bromo or iodo, straight, branched or cyclic C_{1-20} alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, or $-CO_2R^1$ or $-N(R^1)_2$ with the provisos that when A and B both represent H_2, W is -OH, and when A or B represents =O, at least one of W, X, Y and Z represents fluoro, chloro, bromo or iodo, straight, branched or cyclic C_{1-20} alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ or $-N(R^1)_2$, and

R^1 and n are as previously defined.

4. A process as claimed in Claim 2 wherein R represents straight branched or cyclic C_{1-6} alkyl.

5. A process as claimed in any of claims 1-4 above wherein one of A and B is H_2 and the other of A and B represents H- and $OC(O)R^1$, =O, $=NOR^1$ or $-O-(CH_2)_nO-$.

6. A process as claimed in any of claims 1-5 above wherein at least one of A and B represents H and OR^1.

7. A process as claimed in any of claims 1-6 above wherein A and B represent H_2, and W represents OR^1.

8. A process as claimed in any of claims 1-7 above wherein R^1 represents H.

9. A process as claimed in any of claims 1-8 above wherein W, X, Y and Z independently represent H, fluoro, chloro, bromo, iodo, alkyl, $-CF_3$, $-SR^1$, $-OR^1$ or $N(R^1)_2$.

10. A process as claimed in any of claims 1-9 above wherein at least one of Y and Z represents fluoro, chloro, bromo or iodo.

11. A process as claimed in any of claims 1-10 above wherein W represents OR^1 at position 3.

12. A process as claimed in claim 1 wherein said produced compound has the following name:

8-chloro-11-[4-piperidylidene]-5,11-dihydro-6H-benzo [5,6]cyclohepta[1,2-b]pyridin-6-one;
6-hydroxy-8-chloro-11-[4-piperidylidene]6,11-dihydro-5H-benzo [5,6]cyclohepta[1,2-b]pyridine;
8-chloro-6-hydroxyimino-11-[1-methyl-4-piperidylidine]-6H-benzo[5,6]cyclohepta[1,2-b]pyridine;
8-chloro-11-[1-methyl-4-piperidylidene]-5,11-dihydro-6H-benzo[5,6]-cyclohepta[1,2-b]pyridin-6-ol;
6-acetoxy-8-chloro-11-[1-methyl-4-piperidylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]-pyridine;
3-hydroxy-8-chloro-11-[4-piperidylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine;
8-chloro-11-[4-piperidylidene]-6,11-dihydro-5H-benzo[5,6] cyclohepta[1,2-b]pyridin-5-one; or
5-hydroxy-8-chloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

13. A process for producing a pharmaceutical composition which comprises admixing a compound represented by structural Formula I as defined in Claim 1 with a pharmaceutically acceptable carrier.

14. A process according to Claim 13 wherein said compound of Formula I is as defined in any one of Claims 2 to 12.

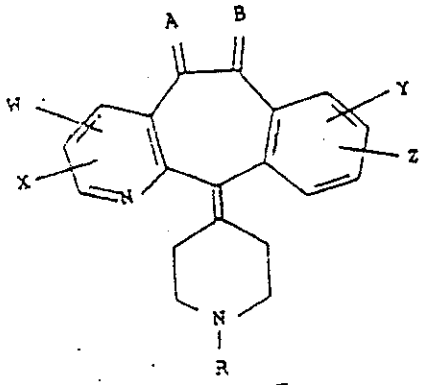
15. A process according to Claim 13 wherein said compound of Formula I is one of the compounds specified in Claim 12.

16. The use of a compound as defined in Claim 13 for the preparation of a pharmaceutical composition for anti-allergy application.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung, dargestellt durch Strukturformel I



I

oder deren pharmazeutisch annehmbares Salz oder Solvat, worin

R H oder geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl in der Weise bedeutet, daß,

(1) wenn R geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl bedeutet, wenigstens eines von A und B eine aus H und OR^1, H und $OC(O)R^1$, $=NOR^1$ oder $-O-(CH_2)_n-O-$ ausgewählte Substituenten-Gruppe bedeutet, und die andere H_2 oder eine der voranstehend aufgezählten Substituenten-Gruppen bedeuten kann;

W, X, Y und Z gleich oder verschieden sein können und jeweils unabhängig H, Fluor, Chlor, Brom oder Iod, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ oder $-N(R^1)_2$ bedeuten;

R^1 H, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl oder C_{6-15} Aryl ist und R^1 in $-N(R^1)_2$ geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkandiyl sein kann, und n 2, 3 oder 4 ist, und

(2) wenn R H bedeutet, A und B gleich oder verschieden sein können und jeweils unabhängig H_2, H und OR^1, H und $OC(O)R^1$, =O, $=NOR^1$ oder $-O-(CH_2)_n-O-$ bedeuten;

W, X, Y und Z gleich oder verschieden sein können und jeweils unabhängig H, Fluor, Chlor, Brom oder Iod, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$ oder $-CO_2R^1$ oder $-N(R^1)_2$ bedeuten, mit den Maßgaben, daß, wenn A und B beide H_2 bedeuten, W OR^1 ist und R^1 H ist, und wenn A oder B =O bedeuten, wenigstens eines von W, X, Y und Z Fluor, Chlor, Brom oder Iod, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl, $-CF_3$, $-NO_2$, $-OC(O)-R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ oder $-N(R^1)_2$ bedeutet; und

R^1 und n wie voranstehend definiert sind, mit der Maßgabe, daß die Verbindung der Formel I nicht 8-Chlor-11-(4-piperidyliden)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-5-on oder 5-Hydroxy-8-chlor-11-(4-piperidyliden)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin ist.

2. Verbindung wie in Anspruch 1 definiert, worin R geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl bedeutet, wenigstens eines von A und B eine aus H und OR^1, H und $OC(O)R^1$, $=NOR^1$ oder $-O-(CH_2)_n-O-$ ausgewählte Substituenten-Gruppe bedeutet, und das andere H_2 oder eine der voranstehend aufgezählten Substituenten-Gruppen bedeuten kann;

W, X, Y und Z gleich oder verschieden sein können und jeweils unabhängig H, Fluor, Chlor, Brom oder Iod, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-CO_2R^1$ oder $-N(R^1)_2$ bedeuten;

R^1 H, C_{1-20} Alkyl oder C_{6-15} Aryl ist und n 2, 3 oder 4 ist.

3. Verbindung wie in Anspruch 1 beansprucht, worin R H bedeutet, A oder B gleich oder verschieden sein können und jeweils unabhängig H_2, H und OR^1, H und $OC(O)R^1$, =O, $=NOR^1$ oder $-O-(CH_2)_n-O-$ bedeuten;

W, X, Y und Z gleich oder verschieden sein können und jeweils unabhängig H, Fluor, Chlor, Brom oder Iod, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$ oder $-CO_2R^1$ oder $-N(R^1)_2$ bedeuten, mit den Maßgaben, daß, wenn A und B beide H_2 bedeuten, W -OH ist, und wenn A oder B =O bedeuten, wenigstens eines von W, X, Y und Z Fluor, Chlor, Brom oder Iod, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ oder $-N(R^1)_2$ bedeutet; und
R^1 und n wie voranstehend definiert sind.

4. Verbindung wie in Anspruch 2 definiert, worin R geradkettiges, verzweigtes oder cyclisches C_{1-6} Alkyl bedeutet.

5. Verbindung wie in einem der voranstehenden Ansprüche 1-4 definiert, worin eines von A und B H_2 ist und das andere von A und B H- und $OC(O)R^1$, =O, $=NOR^1$ oder $-O-(CH_2)_n-O-$ bedeutet.

6. Verbindung wie in einem der voranstehenden Ansprüche 1-5 definiert, worin wenigstens eines von A und B H und OR^1 bedeutet.

7. Verbindung wie in einem der voranstehenden Ansprüche 1-6 definiert, worin A und B H_2 bedeuten und W OR^1 bedeutet.

8. Verbindung wie in einem der voranstehenden Ansprüche 1-7 definiert, worin R^1 H bedeutet.

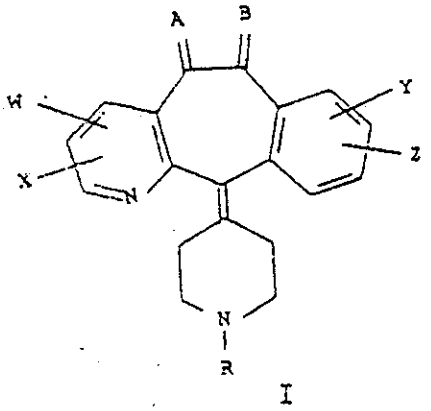
9. Verbindung wie in einem der voranstehenden Ansprüche 1-8 definiert, worin W, X, Y und Z unabhängig H, Fluor, Chlor, Brom oder Iod, Alkyl, $-CF_3$, $-SR^1$, $-OR^1$ oder $N(R^1)_2$ bedeuten.

10. Verbindung wie in einem der voranstehenden Ansprüche 1-9 definiert, worin wenigstens eines von Y und Z Fluor, Chlor, Brom oder Iod bedeutet.

11. Verbindung wie in einem der voranstehenden Ansprüche 1-10 definiert, worin W OR^1 in Position 3 bedeutet.

12. Verbindung wie in Anspruch 1 definiert, welche den folgenden Namen besitzt:
8-Chlor-11-[4-piperidyliden]-5,11-dihydro-6H-benzo[5,6]cyclohepta[1,2-b]pyridin-6-on,
6-Hydroxy-8-chlor-11-[4-piperidyliden]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin,
8-Chlor-6-hydroxyimino-11-[1-methyl-4-piperidyliden]-6H-benzo[5,6]cyclohepta[1,2-b]pyridin,
8-Chlor-11-[1-methyl-4-piperidyliden]-5,11-dihydro-6H-benzo[5,6]cyclohepta[1,2-b]pyridin-6-ol,
6-Acetoxy-8-chlor-11-[1-methyl-4-piperidyliden]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin,
3-Hydroxy-8-chlor-11-[4-piperidyliden]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin.

13. Pharmazeutische Zusammensetzung, welche eine durch die Strukturformel I



I

dargestellte Verbindung oder deren pharmazeutisch annehmbares Salz oder Solvat umfaßt, worin R H oder geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl in der Weise bedeutet, daß,

(1) wenn R geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl bedeutet, wenigstens eines von A und B eine aus H und OR^1, H und $OC(O)R^1$, $=NOR^1$ oder $-O-(CH_2)_n-O-$ ausgewählte Substituenten- Gruppe bedeutet, und das andere H_2 oder eine der voranstehend aufgezählten Substituenten-Gruppen bedeuten kann;
W, X, Y und Z gleich oder verschieden sein können und jeweils unabhängig H, Fluor, Chlor, Brom oder Iod, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ oder $-N(R^1)_2$ bedeuten;
R^1 H, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl oder C_{6-15} Aryl ist und R^1 in $-N(R^1)_2$ geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkandiyl sein kann, und n 2, 3 oder 4 ist, und
(2) wenn R H bedeutet, A und B gleich oder verschieden sein können und jeweils H_2, H und OR^1, H und $OC(O)R^1$, =O, $=NOR^1$ oder $-O-(CH_2)_n-O-$ bedeuten;
W, X, Y und Z gleich oder verschieden sein können und jeweils unabhängig H, Fluor, Chlor, Brom oder Iod, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ oder $-N(R^1)_2$ bedeuten, mit den Maßgaben, daß, wenn A und B beide H_2 bedeuten, W OR^1 ist und R^1 H ist, und wenn A oder B =O bedeuten, wenigstens eines von W, X, Y und Z Fluor, Chlor, Brom oder Iod, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl, $-CF_3$, $-NO_2$, $-OC(O)-R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ oder $-N(R^1)_2$ bedeutet; und
R^1 und n wie voranstehend definiert sind.

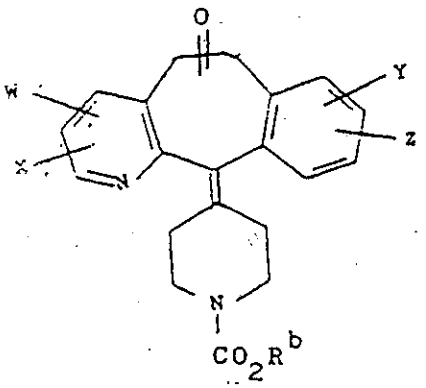
14. Pharmazeutische Zusammensetzung gemäß Anspruch 13, worin die Verbindung der Formel I wie in einem der Ansprüche 2 bis 12 definiert ist.

15. Pharmazeutische Zusammensetzung gemäß Anspruch 13, worin die Verbindung der Formel I 8-Chlor-11-[4-piperidyliden]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-5-on oder 5-Hydroxy-8-chlor-11-(4-piperidyliden)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin ist.

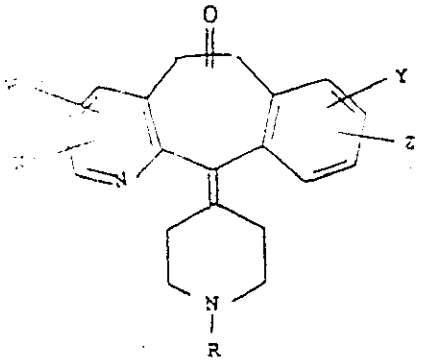
16. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend das Vermischen einer Verbindung der wie in Anspruch 13 definierten Formel I mit einem pharmazeutisch annehmbaren Träger.

17. Verwendung einer wie in Anspruch 13 definierten Verbindung zur Herstellung einer pharmazeutischen Zusammensetzung zur antiallergischen Anwendung.

18. Verfahren zur Herstellung einer Verbindung mit der wie in Anspruch 13 definierten Strukturformel I, gekennzeichnet durch
a) Decarboxylieren einer Verbindung der Struktur

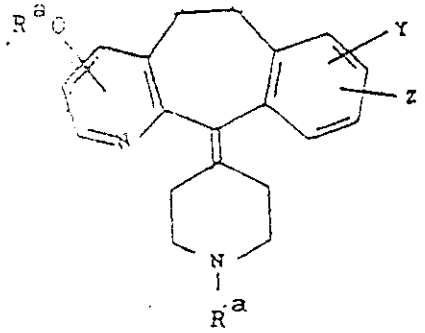


worin R_b geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl oder C_{6-15} Aryl ist, mit der Maßgabe, daß die Verbindung der Formel I eine andere als 8-Chlor-11-[4-piperidyliden]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-5-on ist, oder
b) Reduzieren der Keto-Verbindung



an der Keto-Gruppe, mit der Maßgabe, daß die Verbindung der Formel I eine andere als 5-Hydroxy-8-chlor-11-(4-piperidyliden)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin ist,

c) Entalkylieren einer Verbindung der Struktur



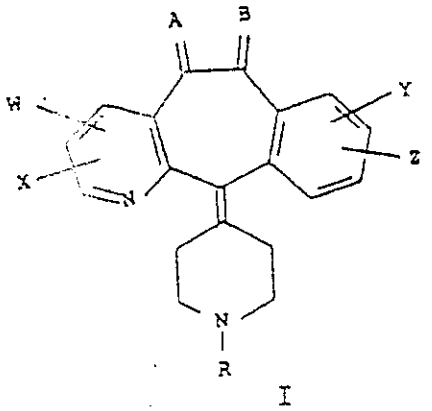
worin R^a geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl ist, oder

d) orale Verabreichung von 8-Chlor-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidyliden)-5H-benzo-[5,6]cyclohepta[1,2-b]pyridin an einen Menschen und/oder Affen und Isolieren aus dem jeweiligen Menschen- und/oder Affenurin,

wobei diese Verfahren weiterhin die Stufe der Überführung einer funktionellen Gruppe einer Verbindung der Formel I in eine andere funktionelle Gruppe der Formel I umfassen.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer Verbindung mit der Strukturformel I



I

oder deren pharmazeutisch annehmbares Salz oder Solvat, worin

R H oder geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl in der Weise bedeutet, daß,

(1) wenn R geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl bedeutet, wenigstens eines von A und B eine aus H und OR^1, H und $OC(O)R^1$, $=NOR^1$ oder $-O-(CH_2)_n-O-$ ausgewählte Substituenten-Gruppe bedeutet, und die andere H_2 oder eine der voranstehend aufgezählten Substituenten-Gruppen bedeuten kann;

W, X, Y und Z gleich oder verschieden sein können und jeweils unabhängig H, Fluor, Chlor, Brom oder Iod, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ oder $-N(R^1)_2$ bedeuten;

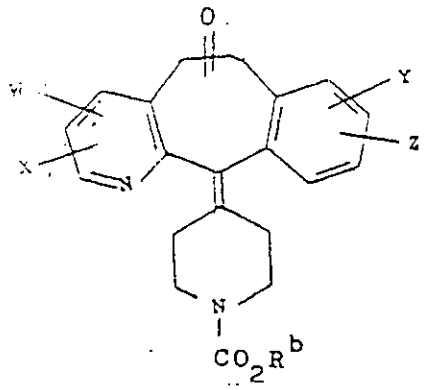
R^1 H, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl oder C_{6-15} Aryl ist und R^1 in $-N(R^1)_2$ geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkandiyl sein kann, und n 2, 3 oder 4 ist, und

(2) wenn R H bedeutet, A und B gleich oder verschieden sein können und jeweils unabhängig H_2, H und OR^1, H und $OC(O)R^1$, =O, $=NOR^1$ oder $-O-(CH_2)_n-O-$ bedeuten;

W, X, Y und Z gleich oder verschieden sein können und jeweils unabhängig H, Fluor, Chlor, Brom oder Iod, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$ oder $-CO_2R^1$ oder $-N(R^1)_2$ bedeuten, mit den Maßgaben, daß, wenn A und B beide H_2 bedeuten, W OR^1 ist und R^1 H ist, und wenn A oder B =O bedeuten, wenigstens eines von W, X, Y und Z Fluor, Chlor, Brom oder Iod, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl, $-CF_3$, $-NO_2$, $-OC(O)-R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ oder $-N(R^1)_2$ bedeutet; und

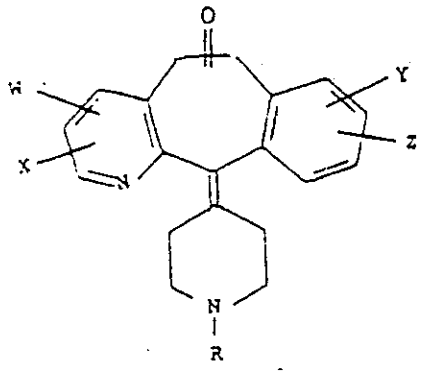
R^1 und n wie voranstehend definiert sind, gekennzeichnet durch

a) Decarboxylieren einer Verbindung der Struktur



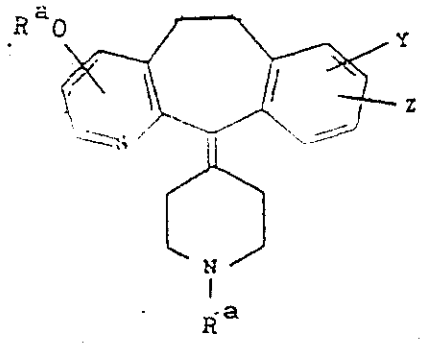
worin R_b geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl oder C_{6-15} Aryl ist, mit der Maßgabe, daß die Verbindung der Formel I eine andere als 8-Chlor-11-[4-piperidyliden]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-5-on ist, oder

b) Reduzieren der Keto-Verbindung



an der Keto-Gruppe, mit der Maßgabe, daß die Verbindung der Formel I eine andere als 5-Hydroxy-8-chlor-11-(4-piperidyli-den)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin ist,

c) Entalkylieren einer Verbindung der Struktur



worin R^a geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl ist, oder

d) orale Verabreichung von 8-Chlor-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidyliden)-5H-benzo-[5,6]cyclohepta[1,2-b]pyridin an einen Menschen und/oder Affen und Isolieren aus dem jeweiligen Menschen- und/oder Affenurin,

wobei diese Verfahren weiterhin die Stufe der Überführung einer funktionellen Gruppe einer Verbindung der Formel I in eine andere funktionelle Gruppe der Formel I umfassen können.

2. Verfahren wie in Anspruch 1 beansprucht, wobei R geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl bedeutet, wenigstens eines von A und B eine aus H und OR^1, H und $OC(O)R^1$, $=NOR^1$ oder $-O-(CH_2)_n-O-$ ausgewählte Substituenten-Gruppe bedeutet, und das andere H_2 oder eine der voranstehend aufgezählten Substituenten-Gruppen bedeuten kann;
W, X, Y und Z gleich oder verschieden sein können und jeweils unabhängig H, Fluor, Chlor, Brom oder Iod, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-CO_2R^1$ oder $-N(R^1)_2$ bedeuten;
R^1 H, C_{1-20} Alkyl oder C_{6-15} Aryl ist und n 2, 3 oder 4 ist.

3. Verfahren wie in Anspruch 1 beansprucht, worin R H bedeutet, A oder B gleich oder verschieden sein können und jeweils unabhängig H_2, H und OR^1, H und $OC(O)R^1$, $=O$, $=NOR^1$ oder $-O-(CH_2)_n-O-$ bedeuten;
W, X, Y und Z gleich oder verschieden sein können und jeweils unabhängig H, Fluor, Chlor, Brom oder Iod, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$ oder $-CO_2R^1$ oder $-N(R^1)_2$ bedeuten, mit den Maßgaben, daß, wenn A und B beide H_2 bedeuten, W -OH ist, und wenn A oder B $=O$ bedeuten, wenigstens eines von W, X, Y und Z Fluor, Chlor, Brom oder Iod, geradkettiges, verzweigtes oder cyclisches C_{1-20} Alkyl, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ oder $-N(R^1)_2$ bedeutet; und
R^1 und n wie voranstehend definiert sind.

4. Verfahren wie in Anspruch 2 definiert, worin R geradkettiges, verzweigtes oder cyclisches C_{1-6} Alkyl bedeutet.

5. Verfahren wie in einem der voranstehenden Ansprüche 1-4 definiert, worin eines von A und B H_2 ist und das andere von A und B H- und $OC(O)R^1$, $=O$, $=NOR^1$ oder $-O-(CH_2)_n-O-$ bedeutet.

6. Verfahren wie in einem der voranstehenden Ansprüche 1-5 definiert, worin wenigstens eines von A und B H und OR^1 bedeutet.

7. Verfahren wie in einem der voranstehenden Ansprüche 1-6 definiert, worin A und B H_2 bedeuten und W OR^1 bedeutet.

8. Verfahren wie in einem der voranstehenden Ansprüche 1-7 definiert, worin R^1 H bedeutet.

9. Verfahren wie in einem der voranstehenden Ansprüche 1-8 definiert, worin W, X, Y und Z unabhängig H, Fluor, Chlor, Brom oder Iod, Alkyl, $-CF_3$, $-SR^1$, $-OR^1$ oder $N(R^1)_2$ bedeuten.

10. Verfahren wie in einem der voranstehenden Ansprüche 1-9 definiert, worin wenigstens eines von Y und

Z Fluor, Chlor, Brom oder Iod bedeutet.

11. Verfahren wie in einem der voranstehenden Ansprüche 1-10 definiert, worin W OR^1 in Position 3 bedeutet.

12. Verfahren wie in Anspruch 1 definiert, worin die hergestellte Verbindung den folgenden Namen besitzt:
8-Chlor-11-[4-piperidyliden]-5,11-dihydro-6H-benzo[5,6]cyclohepta[1,2-b]pyridin-6-on,
6-Hydroxy-8-chlor-11-[4-piperidyliden]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin,
8-Chlor-6-hydroxyimino-11-[1-methyl-4-piperidyliden]-6H-benzo[5,6]cyclohepta[1,2-b]pyridin,
8-Chlor-11-[1-methyl-4-piperidyliden]-5,11-dihydro-6H-benzo[5,6]cyclohepta[1,2-b]pyridin-6-ol,
6-Acetoxy-8-chlor-11-[1-methyl-4-piperidyliden]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin,
3-Hydroxy-8-chlor-11-[4-piperidyliden]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin,
8-Chlor-11-[4-piperidyliden]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-5-on oder
5-Hydroxy-8-chlor-11-(4-piperidyliden)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin.

13. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, welches das Vermischen einer Verbindung der wie in Anspruch 1 definierten Formel I mit einem pharmazeutisch annehmbaren Träger umfaßt.

14. Verfahren gemäß Anspruch 13, wobei die Verbindung der Formel I wie in einem der Ansprüche 2 bis 12 definiert ist.

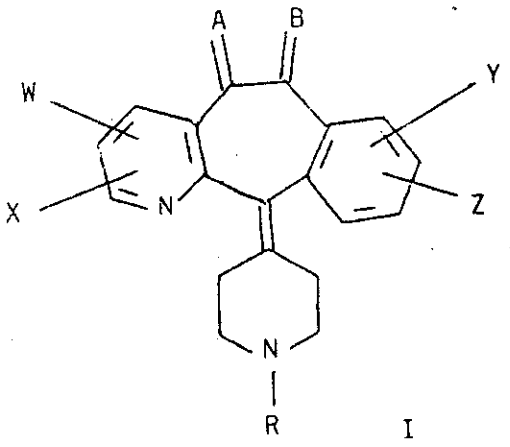
15. Verfahren gemäß Anspruch 13, wobei die Verbindung der Formel I eine der in Anspruch 12 bezeichneten Verbindungen ist.

16. Verwendung einer wie in Anspruch 13 definierten Verbindung zur Herstellung einer pharmazeutischen Zusammensetzung zur antiallergischen Anwendung.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé représenté par la formule de structure I



I

ou son sel ou solvat acceptable en pharmacie, où :

R représente H ou un alkyle C_{1-20} droit, ramifié ou cyclique, de façon que

(1) quand R représente un alkyle C_{1-20} droit, ramifié ou cyclique, au moins l'un de A et B représente un groupe substituant choisi parmi H et OR^1, H et $OC(O)R^1$, $=NOR^1$ ou $-O-(CH_2)_n-O-$ et l'autre peut représenter H_2 ou l'un des groupes substituants dont la liste est donnée ci-dessus ;

W, X, Y et Z peuvent être identiques ou différents et chacun représente indépendamment H, fluoro, chloro, bromo ou iodo, alkyle C_{1-20} droit, ramifié ou cyclique, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ ou $-N(R^1)_2$;

R^1 est H, alkyle C_{1-20} droit, ramifié ou cyclique ou aryle C_{6-15} et dans $N(R^1)_2$, R^1 peut être alcanediyle C_{1-20}, droit, ramifié ou cyclique et n est 2, 3 ou 4, et

(2) quand R représente H,

A ou B peut être identique ou différent et chacun représente indépendamment H_2, H et OR^1, H et $OC(O)R^1$, =O, $=NOR^1$ ou $-O-(CH_2)_n-O-$;

W, X, Y et Z peuvent être identiques ou différents et chacun représente indépendamment H, fluoro, chloro, bromo ou iodo, alkyle C_{1-20} droit, ramifié ou cyclique, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$ ou $-CO_2R^1$ ou $-N(R^1)_2$ à condition que quand A et B représentent tous deux H_2, W soit OR^1 et R^1 soit H et quand A ou B représente =O, au moins l'un de W, X, Y et Z représente fluoro, chloro, bromo ou iodo, alkyle C_{1-20} droit, ramifié ou cyclique, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ ou $-N(R^1)_2$; et

R^1 et n sont tels que définis ci-dessus,

à condition que ledit composé de Formule I ne soit pas 8-chloro-11-(4-pipéridylidène)-6,11-dihydro-5H-benzo[5,6]-cyclohepta[1,2-b]pyridin-5-one ni 5-hydroxy-8-chloro-11-(4-pipéridylidine)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

2. Composé tel que défini à la revendication 1, où R représente alkyle C_{1-20} droit, ramifié ou cyclique ; au moins l'un de A et B représente un groupe substituant choisi parmi H et OR^1, H et $OC(O)R^1$, $=NOR^1$ ou $-O-(CH_2)_n-O-$, l'autre pouvant représenter H_2 ou l'un des groupes substituants dont la liste est donnée ci-dessus ;

W, X, Y et Z peuvent être identiques ou différents et chacun représente indépendamment H, fluoro, chloro, bromo ou iodo, alkyle C_{1-20} droit, ramifié ou cyclique, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-CO_2R^1$ ou $-N(R^1)_2$;

R^1 est H, alkyle C_{1-20} ou aryle C_{6-15} et n est 2, 3 ou 4.

3. Composé selon la revendication 1, où R représente H ;

A ou B peuvent être identiques ou différents et chacun représente indépendamment H_2, H et OR^1, H et $OC(O)R^1$, =O, $=NOR^1$ ou $-O-(CH_2)_n-O-$;

W, X, Y et Z peuvent être identiques ou différents et chacun représente indépendamment H, fluoro, chloro, bromo ou iodo, alkyle C_{1-20} droit, ramifié ou cyclique, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, OR^1 ou $-CO_2R^1$ ou $-N(R^1)_2$ aux conditions que quand A et a représentent tous deux H_2, W soit -OH, et quand A et B représentent =O, au moins l'un de W, X, Y et Z représente fluoro, chloro, bromo ou iodo, alkyle C_{1-20} droit, ramifié ou cyclique, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ ou $-N(R^1)_2$ et

R^1 et n sont tels que précédemment définis.

4. Composé selon la revendication 2, où R représente alkyle C_{1-6} droit, ramifié ou cyclique.

5. Composé selon l'une quelconque des revendications 1-4 ci-dessus, où l'un de A et B est H_2 et l'autre de A et B représente H- et $OC(O)R^1$, =O, $=NOR^1$ ou $-O-(CH_2)_nO-$.

6. Composé selon l'une quelconque des revendications 1-5 ci-dessus, où au moins l'un de A et B représente H et OR^1.

7. Composé selon l'une quelconque des revendications 1-6 ci-dessus, où A et B représentent H_2 et W représente OR^1.

8. Composé selon l'une quelconque des revendications 1-7 ci-dessus, où R^1 représente H.

9. Composé selon l'une quelconque des revendications 1-8 ci-dessus, où W, X, Y et Z représentent indépendamment H, fluoro, chloro, bromo ou iodo, alkyle, $-CF_3$, $-SR^1$, $-OR^1$ ou $N(R^1)_2$.

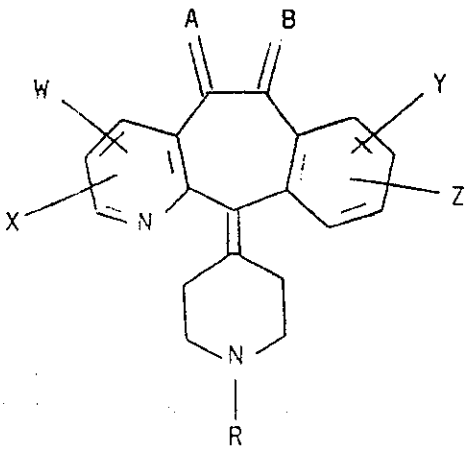
10. Composé selon l'une quelconque des revendications 1-9 ci-dessus, où au moins l'un de Y et Z représente fluoro, chloro, bromo ou iodo.

11. Composé selon l'une quelconque des revendications 1-10 ci-dessus, où W représente OR^1 à la position 3.

12. Composé selon la revendication 1 ayant le nom suivant :

8-chloro-11-[4-pipéridylidène]-5,11-dihydro-6H-benzo[5,6]cyclohepta[1,2-b]pyridin-6-one ;
6-hydroxy-8-chloro-11-[4-pipéridylidène]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine ;
8-chloro-6-hydroxyimino-11-[1-méthyl-4-pipéridylidine]-6H-benzo[5,6]cyclohepta[1,2-b]pyridine ;
8-chloro-11-[1-méthyl-4-pipéridylidène]-5,11-dihydro-6H-benzo[5,6]-cyclohepta[1,2-b]pyridin-6-ol ;
6-acétoxy-8-chloro-11-[1-méthyl-4-pipéridylidène]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]-pyridine ;
3-hydroxy-8-chloro-11-[4-pipéridylidène]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

13. Composition pharmaceutique qui contient un composé représenté par la formule de structure I :



I

ou son sel ou solvat acceptable en pharmacie, où :

R représente H ou un alkyle C_{1-20} droit, ramifié ou cyclique, de façon que

(1) quand R représente un alkyle C_{1-20} droit, ramifié ou cyclique, au moins l'un de A et B représente un groupe substituant choisi parmi H et OR^1, H et $OC(O)R^1$, $=NOR^1$ ou $-O-(CH_2)_n-O-$ et l'autre peut représenter H_2 ou l'un des groupes substituants dont la liste est donnée ci-dessus ;

W, X, Y et Z peuvent être identiques ou différents et chacun représente indépendamment H, fluoro, chloro, bromo ou iodo, alkyle C_{1-20} droit , ramifié ou cyclique, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ ou $-N(R^1)_2$;

R^1 est H, alkyle C_{1-20} droit, ramifié ou cyclique ou aryle C_{6-15} et dans $N(R^1)_2$, R^1 peut être alcanediyle C_{1-20}, droit, ramifié ou cyclique et n est 2, 3 ou 4, et

(2) quand R représente H,

A ou B peuvent être identiques ou différents et chacun représente indépendamment H_2, H et OR^1, H et $OC(O)R^1$, $=O$, NOR^1 ou $-O-(CH_2)_n-O-$;

W, X, Y et Z peuvent être identiques ou différents et chacun représente indépendamment H, fluoro, chloro, bromo ou iodo, alkyle C_{1-20} droit, ramifié ou cyclique, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, ou $-CO_2R^1$ ou $-N(R^1)_2$, à condition que quand A et B représentent tous deux H, W soit OR^1 et R^1 soit H et quand A ou B représente $=O$, au moins l'un de W, X, Y et Z représente fluoro, chloro, bromo ou iodo, alkyle C_{1-20} droit, ramifié ou cyclique, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ ou $-N(R^1)_2$; et

R^1 et n sont tels que définis ci-dessus.

14. Composition pharmaceutique selon la revendication 13, où ledit composé de Formule I est tel que défini selon l'une quelconque des revendications 2 à 12.

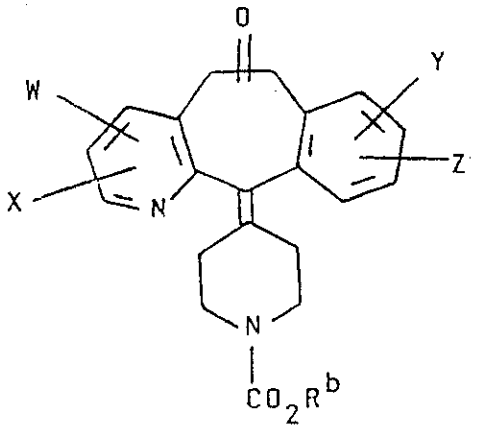
15. Composition pharmaceutique selon la revendication 13, où ledit composé de Formule I est
8-chloro-11-[4-pipéridylidène]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-5-one ; ou
5-hydroxy-8-chloro-11-(4-pipéridylidène)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

16. Méthode de production d'une composition pharmaceutique comprenant le mélange d'un composé de Formule I tel que défini à la revendication 13 avec un support acceptable en pharmacie.

17. Utilisation d'un composé tel que défini à la revendication 13, pour la préparation d'une composition pharmaceutique pour application anti-allergie.

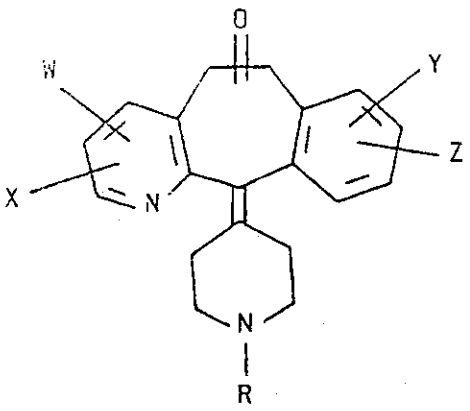
18. Procédé de production d'un composé ayant la Formule de structure I tel que défini à la revendication 13, caractérisé par :

a) la décarboxylation d'un composé de la structure



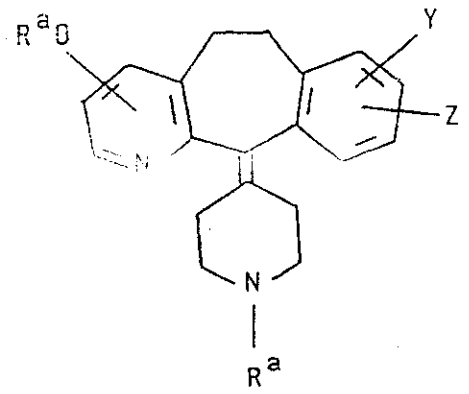
où R_b est alkyle C_{1-20} droit, ramifié ou cyclique ou bien aryle C_{6-15} à condition que ledit composé de Formule I soit autre que 8-chloro-11-[4-pipéridylidène]-6,11-dihydro-5H-benzo[5,6]-cyclohepta[1,2-b]pyridin-5-one; ou

b) la réduction du composé céto



au groupe céto, à condition que ledit composé de formule I soit autre que 5-hydroxy-8-chloro-11-[4-pipéridylidène]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]-pyridine.

c) la désalkylation d'un composé de la structure



où R^a est alkyle C_{1-20} droit, ramifié ou cyclique ;

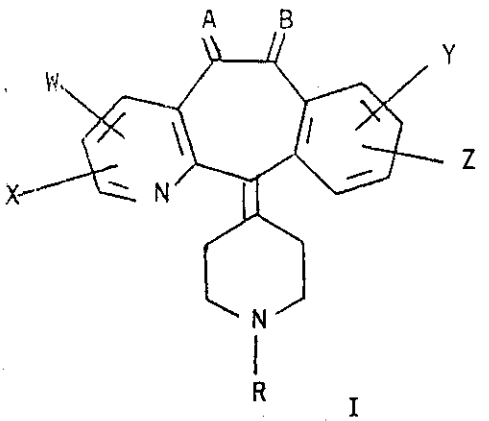
ou

d) le dosage oral pour un être humain et/ou un singe d'une 8-chloro-6,11-dihydro-11-(1-éthoxycarbonyl-4-pipéridylidène)-5H-benzo[5,6]cyclophepta[1,2-b]pyridine et isolement de l'urine respective de l'être humain et/ou du singe ;

lesquels procédés peuvent de plus comprendre l'étape de conversion d'un groupe fonctionnel d'un composé de Formule I en un autre groupe fonctionnel de Formule I.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de production d'un composé ayant la formule de structure I



I

ou son sel ou solvat acceptable en pharmacie, où

R représente H ou un alkyle C_{1-20} droit, ramifié ou cyclique, de façon que

(1) quand R représente un alkyle C_1-C_{20} droit, ramifié ou cyclique, au moins l'un de A et B représente un groupe substituant choisi parmi H et OR^1, H et $OC(O)R_1$, $=NOR^1$ ou $-O-(CH_2)_n-O-$ et l'autre peut représenter H_2 ou l'un des groupes substituants dont la liste est donnée ci-dessus ;

W, X, Y et Z peuvent être identiques ou différents et chacun représente indépendamment H, fluoro, chloro, bromo ou iodo, alkyle C_{1-20} droit, ramifié ou cyclique, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ ou $-N(R^1)_2$;

R^1 est H, alkyle C_{1-20} droit, ramifié ou cyclique ou aryle C_{6-15} et dans $N(R^1)_2$, R^1 peut être alcanediyle C_{1-20} droit, ramifié ou cyclique et n est 2, 3 ou 4 et

(2) quand R représente H,

A ou B peut être identique ou différent et chacun représente indépendamment H_2, H et OR^1, H et $OC(O)R^1$, $=O$, $=NOR^1$ ou $-O-(CH_2)_n-O-$;

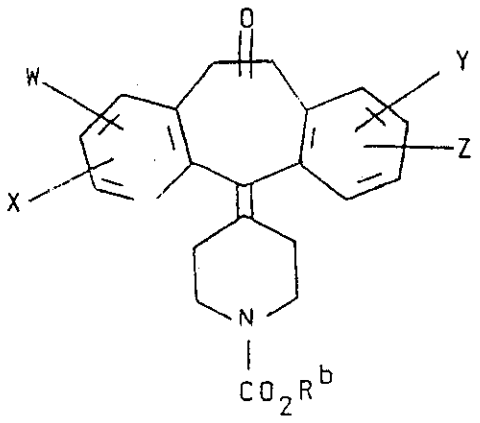
W, X, Y et Z peuvent être identiques ou différents et chacun représente indépendamment H, fluoro, chloro, bromo ou iodo, alkyle C_{1-20} droit, ramifié ou cyclique, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$ ou $-CO_2R^1$ ou $-N(R^1)_2$ à condition que quand A et B représentent tous deux H, W soit OR^1 et R^1 soit H

et quand A ou B représente =O, au moins l'un de W, X, Y et Z représente fluoro, chloro; bromo ou iodo, alkyle C_{1-20} droit, ramifié ou cyclique, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ ou $-N(R^1)_2$; et

R^1 et n sont tels que définis ci-dessus,

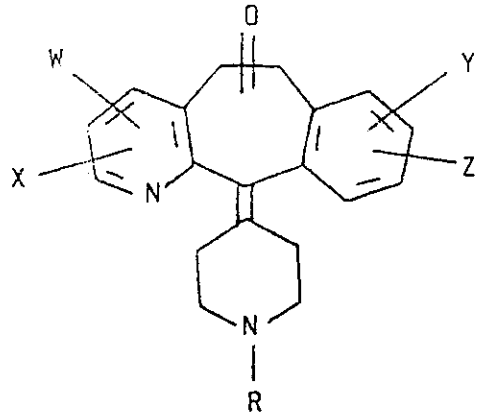
caractérisé par

a) la décarboxylation d'un composé de la structure



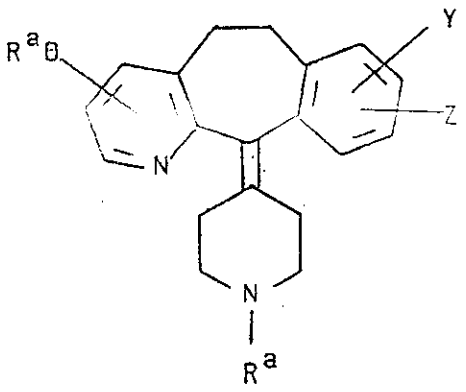
où R_b est alkyle C_{1-20} droit, ramifié ou cyclique ou bien aryle C_6-C_{15}, à condition que ledit composé de Formule I soit autre que 8-chloro-11-[4-pipéridylidène]-6,11-dihydro-5H-benzo[5,6]-cyclohepta[1,2-b]pyridin-5-one; ou

b) la réduction du composé céto



au groupe céto, à condition que ledit composé de formule I soit autre que 5-hydroxy-8-chloro-11-(4-pipéridylidène)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

c) la désalkylation d'un composé de la structure



où R^a est alkyle C_{1-20} droit, ramifié ou cyclique ;
ou
d) le dosage oral pour un être humain et/ou un singe d'une 8-chloro-6,11-dihydro-11-(1-éthoxycarbonyl-4-pipéridylidène)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine et isolement de l'urine respective de l'être humain et/ou du singe ;
lesquels procédés peuvent de plus comprendre l'étape de conversion d'un groupe fonctionnel d'un composé de la Formule I en un autre groupe fonctionnel de Formule I.

2. Procédé tel que défini à la revendication 1, où R représenté alkyle C_{1-20} droit, ramifié ou cyclique ; au moins l'un de A et B représente un groupe substituant choisi parmi H et OR^1, M et $OC(O)R^1$, $=NOR^1$ ou $-O-(CH_2)_n-O-$, l'autre pouvant représenter H_2 ou l'un des groupes substituants dont la liste est donnée ci-dessus ;
W, X, Y et Z peuvent être identiques ou différents et chacun représente indépendamment H, fluoro, chloro, bromo ou iodo, alkyle C_{1-20} droit, ramifié ou cyclique, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-CO_2R^1$ ou $-N(R^1)_2$;
R^1 est H, alkyle C_{1-20} ou aryle C_{6-15} et n est 2, 3 ou 4.

3. Procédé selon la revendication 1, où R représente H ;
A ou B peuvent être identiques ou différents et chacun représente indépendamment H_2, H et OR^1, H et $OC(O)R^1$, $=O$, $=NOR^1$ ou $-O-(CH_2)_n-O-$;
W, X, Y et Z peuvent être identiques ou différents et chacun représente indépendamment H , fluoro, chloro, bromo ou iodo, alkyle C_{1-20} droit, ramifié ou cyclique, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, ou $-CO_2R^1$ ou $-N(R^1)_2$; aux conditions que quand A et B représentent tous deux H_2, W soit -OH, et quand A et B représentent $=O$, au moins l'un de W, X, Y et Z représente fluoro, chloro, bromo ou iodo, alkyle C_{1-20} droit, ramifié ou cyclique, $-CF_3$, $-NO_2$, $-OC(O)R^1$, $-SR^1$, $-OR^1$, $-CO_2R^1$ ou $-N(R^1)_2$ et
R^1 et n sont tels que précédemment définis.

4. Procédé selon la revendication 2, où R représente alkyle C_{1-6} droit, ramifié ou cyclique.

5. Procédé selon l'une quelconque des revendications 1-4 ci-dessus, où l'un de A et B est H_2 et l'autre de A et B représente H- et $OC(O)R^1$, $=O$, $=NOR^1$ ou $-O-(CH_2)_nO-$.

6. Procédé selon l'une quelconque des revendications 1-5 ci-dessus, où au moins l'un de A et B représente H et OR^1.

7. Procédé selon l'une quelconque des revendications 1-6 ci-dessus, où A et B représentent H_2 et W représente OR^1.

8. Procédé selon l'une quelconque des revendications 1-7 ci-dessus, où R^1 représente H.

9. Procédé selon l'une quelconque des revendications 1-8 ci-dessus, où W, X, Y et Z représentent indépendamment H, fluoro, chloro, bromo , iodo, alkyle, $-CF_3$, $-SR^1$, $-OR^1$ ou $N(R^1)_2$.

10. Procédé selon l'une quelqonque des revendications 1-9 ci-dessus, où au moins l'un de Y et Z représente fluoro, chloro, bromo ou iodo.

11. Procédé selon l'une quelconque des revendications 1-10 ci-dessus, où W représente OR^1 à la position 3.

12. Composé selon la revendication 1, où ledit composé produit a le nom suivant :
8-chloro-11-[4-pipéridylidène]-5,11-dihydro-6H-benzo[5,6]cyclohepta[1,2-b]pyridin-6-one ;
6-hydroxy-8-chloro-11-[4-pipéridylidène]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine ;
8-chloro-6-hydroxyimino-11-[1-méthyl-4-pipéridylidine]-6H-benzo[5,6]cyclohepta[1,2-b]pyridine ;
8-chloro-11-[1-méthyl-4-pipéridylidène]-5,11-dihydro-6H-benzo[5,6]cyclohepta[1,2-b]pyridin-6-ol ;
6-acétoxy-8-chloro-11-[1-méthyl-4-pipéridylidène]-6,11-dihydro-5H-benzo[5,7]cyclohepta[1,2-b]pyridine ;
3-hydroxy-8-chloro-11-[4-pipéridylidène]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine ;
8-chloro-11-[4-pipéridylidène]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-5-one ; ou
5-hydroxy-8-chloro-11-[4-pipéridylidène]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

13. Procédé de production d'une composition pharmaceutique qui comprend le mélange d'un composé représenté par la formule de structure I selon la revendication 1 avec un support acceptable en pharmacie.

14. Procédé selon la revendication 13, où ledit composé de Formule I est tel que défini selon l'une quelconque des revendications 2 à 12.

15. Procédé selon la revendication 13, où ledit composé de Formule I est l'un des composés spécifiés à la revendication 12.

16. Utilisation d'un composé selon la revendication 13 pour la préparation d'une composition pharmaceutique pour une application anti-allergie.

REGISTER ENTRY FOR EP0288640

European Application No EP87309349.6 filing date 22.10.1987

Priority claimed:
28.04.1987 in United States of America - doc: 43409

Designated States BE CH DE ES FR GB GR IT LI LU NL SE AT

Title
6,11-DIHYDRO-11-(4-PIPERIDYLIDENE)-5H-BENZO[5,6]CYCLOHEPTA-[1,2-B]PYRIDINE
S AND COMPOSITIONS AND METHODS OF USE

Applicant/Proprietor
SCHERING CORPORATION, 2000 Galloping Hill Road, Kenilworth, New Jersey 07033, United States of America [ADP No. 50348622002]

Inventors
JOHN J. PIWINSKY, 19 Pitman Road, Parsippany,New Jersey 07054, United States of America [ADP No. 56083975001]

MICHAEL JOHN GREEN, 43 Meadow Run Drive, Skillman New Jersey 08558, United States of America [ADP No. 56083983001]

ASHIT KUMAR GANGULY, 96 Cooper Avenue, Upper Montclair New Jersey 07043, United States of America [ADP No. 56083991001]

JESSE KWOK-KEUNG WONG, 547 Andress Terrace, Union New Jersey 07083, United States of America [ADP No. 56084007001]

BERNARD KATCHEN, 18 Chestnut Street, Livingston New Jersey 07039, United States of America [ADP No. 56084015001]

JEFFREY ABBOTT CRAMER, 246 Maryland Street, Westfield New Jersey 07090, United States of America [ADP No. 56084023001]

Classified to
C07D A61K

Address for Service
MATHYS & SQUIRE, 10 Fleet Street, London, EC4Y 1AY, United Kingdom [ADP No. 00001081001]

EPO Representative
STEPHEN DAVID RITTER, Mathys & Squire 10 Fleet Street, London EC4Y 1AY, United Kingdom [ADP No. 50530237001]

Publication No EP0288640 dated 02.11.1988
Publication in English

Examination requested 22.10.1987

Patent Granted with effect from 09.09.1992 (Section 25(1)) with title
6,11-DIHYDRO-11-(4-PIPERIDYLIDENE)-5H-BENZO[5,6]CYCLOHEPTA-[1,2-B]PYRIDINE
S AND COMPOSITIONS AND METHODS OF USE.

05.02.1992 MATHYS & SQUIRE, 10 Fleet Street, London, EC4Y 1AY, United Kingdom
[ADP No. 00001081001]
registered as address for service
Entry Type 8.11 Staff ID. SW1 Auth ID. AA

10.08.1992 Notification from EPO of change of Applicant/Proprietor details from
SCHERING CORPORATION, 2000 Galloping Hill Road, Kenilworth, New Jersey 07033, United States of America [ADP No. 50348622002]
to
SCHERING CORPORATION, 2000 Galloping Hill Road, Kenilworth New Jersey 07033, United States of America [ADP No. 50348622002]
Entry Type 25.14 Staff ID. RD06 Auth ID. EPT

10.08.1992 Notification from EPO of change of Inventor details from
JOHN J. PIWINSKY, 19 Pitman Road, Parsippany,New Jersey 07054, United States of America [ADP No. 56083975001]

MICHAEL JOHN GREEN, 43 Meadow Run Drive, Skillman New Jersey 08558, United States of America [ADP No. 56083983001]

ASHIT KUMAR GANGULY, 96 Cooper Avenue, Upper Montclair New Jersey 07043, United States of America [ADP No. 56083991001]

JESSE KWOK-KEUNG WONG, 547 Andress Terrace, Union New Jersey 07083, United States of America [ADP No. 56084007001]

BERNARD KATCHEN, 18 Chestnut Street, Livingston New Jersey 07039, United States of America [ADP No. 56084015001]

JEFFREY ABBOTT CRAMER, 246 Maryland Street, Westfield New Jersey 07090, United States of America [ADP No. 56084023001]
to
JOHN J. PIWINSKY, 19 Pitman Road, Parsippany,New Jersey 07054, United States of America [ADP No. 56083975001]

MICHAEL JOHN GREEN, 43 Meadow Run Drive, Skillman, New Jersey 08558, United States of America [ADP No. 60089687001]

ASHIT KUMAR GANGULY, 96 Cooper Avenue, Upper Montclair, New Jersey 07043, United States of America [ADP No. 60089695001]

JESSE KWOK-KEUNG WONG, 547 Andress Terrace, Union, New Jersey 07083, United States of America [ADP No. 60089703001]

BERNARD KATCHEN, 18 Chestnut Street, Livingston, New Jersey 07039, United States of America [ADP No. 60089711001]

JEFFREY ABBOTT CRAMER, 246 Maryland Street, Westfield, New Jersey 07090, United States of America [ADP No. 60089729001]
Entry Type 25.14 Staff ID. RD06 Auth ID. EPT

05.01.1995 Notification of change of Address For Service address of
MATHYS & SQUIRE, 10 Fleet Street, London, EC4Y 1AY, United Kingdom
[ADP No. 00001081001]
to
MATHYS & SQUIRE, 100 Grays Inn Road, LONDON, WC1X 8AL, United Kingdom [ADP No. 00001081001]
dated 12.12.1994. Written notification filed on GB2278511
Entry Type 7.3 Staff ID. AS1 Auth ID. EO

**** END OF REGISTER ENTRY ****

RENEWAL DETAILS

PUBLICATION NUMBER EP0288640

PROPRIETOR(S)

SCHERING CORPORATION, 2000 Galloping Hill Road, Kenilworth New Jersey 07033, United States of America

DATE FILED 22.10.1987

DATE GRANTED 09.09.1992

DATE NEXT RENEWAL DUE 22.10.1995

DATE NOT IN FORCE

DATE OF LAST RENEWAL 14.09.1994

YEAR OF LAST RENEWAL 08

STATUS PATENT IN FORCE

**** END OF REPORT ****