

PATENT SPECIFICATION

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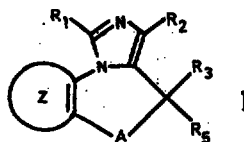
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(54) DIAZEPINE DERIVATIVES

(71) We, F. HOFFMANN-LA ROCHE & CO. AKTIENGESELLSCHAFT, a Swiss Company, organised under the laws of Switzerland, of 124-184 Grenzecherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the pharmacologically active imidazo[1,5-a][1,4]diazepine compounds series. The chemical structure of these compounds may be depicted by the following formula



- 10 wherein A represents $-\text{C}(\text{R}_6)=\text{N}-$; R_1 represents hydrogen, lower alkyl, hydroxy
 lower alkyl, acyloxy lower alkyl, phenyl, alkoxy lower alkyl, halo lower alkyl, amino
 lower alkyl, substituted amino lower alkyl, substituted phenyl, pyridyl, aralkyl or the
 15 group $-\text{COR}_{10}$ (wherein R_{10} represents hydrogen or lower alkyl) or $-\text{COOR}$ (where-
 in R represents lower alkyl); R_2 represents chloro, bromo, iodo, hydroxy lower alkyl,
 acyloxy lower alkyl, alkoxy lower alkyl, halo lower alkyl, amino lower alkyl, cyano,
 cyano lower alkyl, acylamino, lower alkoxy carbonylamino, aralkyloxy carbonylamino,
 substituted amino lower alkyl, the group $-\text{COOR}_{10}$ (wherein R_{10} represents hydrogen
 or lower alkyl), the group $-\text{COR}_{10}$ (wherein R_{10} represents hydrogen or lower alkyl)
 20 or a derivative thereof, i.e., a) the group $-\text{C}(\text{R}_{10})=\text{N}-\text{R}_{11}$, wherein R_{11} represents
 hydrogen, lower alkyl, hydroxy, alkoxy, amino, mono or di-alkylamino or arylamino
 and R_{10} represents hydrogen or lower alkyl; b) the group $-\text{CONR}_{12}\text{R}_{13}$, wherein R_{12}
 and R_{13} represent individually hydrogen, lower alkyl, hydroxy lower alkyl, lower alkenyl,
 aryl or the group $-(\text{CH}_2)_n\text{NR}_{14}\text{R}_{15}$ (wherein R_{14} and R_{15} represent individually

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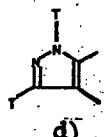
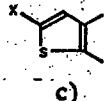
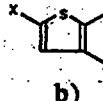
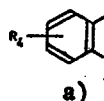
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hydrogen, lower alkyl, hydroxy lower alkyl or lower alkenyl, or R_{14} and R_{15} together form a part of a heterocyclic ring, and n is 1 to 4) or R_{12} and R_{13} together form a part of a heterocyclic ring; or c) the group $-\text{CON}(R_{16})\text{N}(R_{17}, R_{18})$, wherein one of R_{16} , R_{17} and R_{18} represents hydrogen, or lower alkyl or the group $-(\text{CH}_2)_n\text{N}(R_{14}, R_{15})$ (wherein n is 1 to 4 and R_{14} and R_{15} represent individually hydrogen, lower alkyl, hydroxy lower alkyl or lower alkenyl of R_{14} and R_{15} together form a part of a heterocyclic ring) and the remaining R_{16} , R_{17} and R_{18} represent hydrogen or lower alkyl; and R_2 represents additionally hydrogen or lower alkyl in the case where R_1 represents hydroxy lower alkyl, acyloxy lower alkyl, halo lower alkyl, amino lower alkyl, substituted amino lower alkyl, the group $-\text{COR}_{10}$ (wherein R_{10} represents hydrogen or lower alkyl) or $-\text{COOR}$ (wherein R represents lower alkyl); R_3 represents hydrogen or lower alkyl; R_4 represents phenyl, mono-substituted phenyl, di-substituted phenyl, pyridyl or mono-substituted pyridyl; and



represents the group



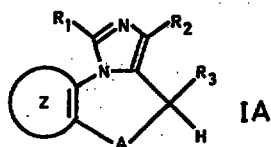
wherein X is hydrogen, chlorine, bromine or iodine, T is hydrogen or lower alkyl, R_4 represents hydrogen, halogen, nitro, cyano, trifluoromethyl, lower alkyl, substituted amino, amino, hydroxy lower alkyl or lower alkanoyl and R_5 represents hydrogen and additionally alkanoyloxy or hydroxy in the case where



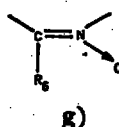
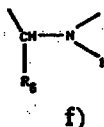
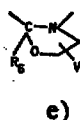
represents the group a), b) or c) above, and the pharmaceutically acceptable acid addition salts thereof.

Various analogous compounds derived from the above compounds are also considered to be within the scope of the invention and exhibit pharmacological activity per se.

Analog of the above compounds which form a part of this invention include compounds of the formula



wherein A represents the group



represents the formula a), b) and c) above, R_5 is hydrogen, R_1 , R_2 , R_3 and R_6 are as in formula I above and V represents hydrogen or lower alkyl, and the pharmaceutically acceptable acid addition salts thereof.

As used in this disclosure, the term "lower alkyl" or "alkyl" comprehends both

straight and branched chain (C_1-C_7) hydrocarbon radicals, preferably C_1-C_4 carbon-hydrogen radicals such as methyl, ethyl, propyl, isopropyl, butyl and the like. The term "lower alkyl" comprehends also cyclic hydrocarbon radicals, such as cyclopropyl.

By the term "lower alkanoyl" or "acyl" as utilized herein, an acyl moiety of a C_1-C_7 preferably a C_1-C_4 alkanoyl acid is intended, e.g., acetyl, propionyl, butyryl and the like, i.e., moieties of the formula $-COR_{20}$, wherein R_{20} is C_1-C_6 or hydrogen. Also as utilized herein, the term "lower alkanoyl" comprehends a protected ketone such as an acetal or ketal having 2 to 7 carbon atoms, e.g. an ethylenedioxy group. The ketal or aldehyde protecting group is utilized to prevent conversion of the contained ketone or aldehyde in oxidation, reduction and condensation reactions.

The term "halogen" is used to include all four forms thereof, i.e., chlorine, bromine, fluorine and iodine.

The terms "aromatic and aliphatic sulfonyl group" comprehends compounds of the formula SO_2X , wherein X is a branched or straight chain C_1-C_7 , preferably C_1-C_4 aliphatic group e.g., methyl or a substituted or unsubstituted aromatic group such as a phenyl or substituted phenyl derivative e.g., tolyl.

The R_8 phenyl moiety may be mono- or di-substituted provided that such di-substitution occurs in the 2,3; 2,5; or, most preferably, in the 2,6 position of the phenyl moiety. Suitable mono-substituents include halogen and nitro and preferably are substituted in the 2-position of the phenyl moiety. Suitable di-substituents are 2,6 or 2,5 di-halogen and 2,6 or 2,5 halogen-nitro. In the case of mono-substituted pyridyl, suitable substituents include halogen and nitro.

In the case of differently substituted R_8 and R_9 substituents, optical isomerism will occur and such optical antipodes and racemates are within the ambit of this invention.

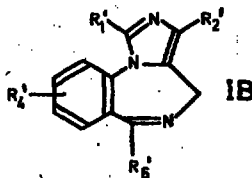
By the term "aryl" is meant a substituted or unsubstituted monocyclic aromatic moiety such as phenyl, chlorophenyl, tolyl, and the like. When various moieties are set herein to form a part of a heterocyclic ring, it is intended that the moieties, together with the nitrogen atom to which they are attached form, preferably, a 5 or 6 membered ring which contains at the most one additional hetero atom, preferably nitrogen or oxygen as the hetero atom. Thus, by the heterocyclic ring, there is intended such moieties as morpholino, piperazino, piperidino and pyrrolidino.

By the term "alkoxy" is meant straight or branched chain saturated hydrocarbon-oxy group containing from 1 to 7 carbon atoms, preferably from 1 to 4 carbon atoms, such as methoxy, ethoxy, propoxy and the like.

By the term "substituted amino" herein is meant an $-NH_2$ group which may be mono or disubstituted by lower alkyl, e.g. methylamino or dimethylamino groups, and an acyl amino group e.g., acetamino which may then be substituted on the nitrogen atom by a lower alkyl e.g., methyl, group.

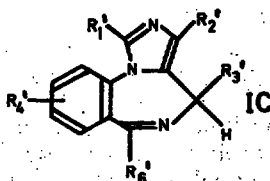
By the term "aralkyl" is meant a hydrocarbon group having both aromatic and aliphatic structures, that is, a hydrocarbon group in which a lower alkyl H atom is substituted by a monocyclic aryl group, e.g., phenyl, tolyl and the like.

Preferred compounds encompassed by the present invention are those of the general formula



wherein R_1' is hydrogen or lower alkyl, preferably methyl, R_4' is hydrogen, nitro or halogen, most preferably chlorine, and in a most preferred embodiment when positioned on the fused benzo portion of the imidazobenzodiazepine in the 8-position thereof, R_8' is phenyl or halo, nitro or lower alkyl-substituted phenyl, preferably halo, with fluorine being the preferred halogen and preferably positioned in the 2-position of the phenyl moiety, R_2' is hydroxy lower alkyl, e.g. hydroxy methyl, carboxylic acid hydrazide, such as $-CONHNH_2$, or carboxamide, i.e. a group of the formula $-CONH_2$.

Another preferred class of compounds falling within the scope of formula I are those of the general formula



wherein R_1' , R_2' , R_4' and R_6' are as in formula IB above and R_3' is lower alkyl, preferably methyl.

Compounds of formula IC and their pharmaceutically acceptable salts exhibit optical isomerism. Such a compound (IC wherein $R_3' = CH_3$) has been resolved into its optical enantiomers by a procedure similar to the one generally outlined in Advanced Organic Chemistry, L. Fieser and M. Fieser, 1961, pp. 85—88, Reinhold Publishing Co. Both the optical isomers and the racemic form of compound IC exhibit pharmacological activity. For example, in the case of the tartrate salt of compounds of formula IC the (+) isomer is considerably more active than the (−) isomer. The less active (−) isomer may, if desired, be converted to the active racemic form thereof such as by treatment with a non-aqueous base, e.g., sodium tertiary butoxide in the presence of an organic solvent in which the isomer is soluble.

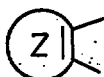
A further preferred group of compounds are those of formula I wherein



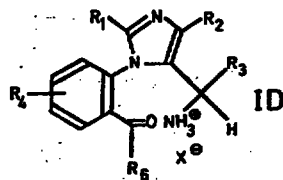
is an 8-chlorophenyl or an 8-chlorothieno[3,2-f] group, R_1 is hydrogen or methyl, R_2 is acetyl, carboxamido or dimethylcarboxamido, R_3 is 2'-fluoro- or 2'-chlorophenyl and R_4 and R_6 are hydrogen.

The pharmaceutically acceptable acid addition salts may be formed with both inorganic and organic pharmaceutically acceptable acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulfonic acid, para toluenesulfonic acid and the like. Such salts can be formed quite readily by those skilled in the art, with the prior art and the nature of the compound to be placed in salt form, in view.

Also within the ambit of the instant invention are compounds which are obtained by ring opening of formula I compounds, wherein



is R_4 -phenyl. Such compounds are of the formula

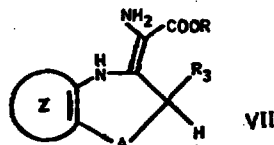


wherein X^- is the anion of an organic or inorganic acid, and R_1 , R_2 , R_3 , R_4 and R_6 are as in formula I.

It has been found that certain compounds of formula I in solution open to corresponding compounds of formula ID. Such open compounds exist in a pH-dependent equilibrium in solution with compounds of formula I, i.e., their corresponding ring closed compounds. The compounds of formula ID can be isolated as acid addition salts by treatment of their corresponding closed ring compounds with an aqueous mineral acid followed by evaporation of solvent. When isolated, these salts exhibit pharmacological activity comparable to their corresponding closed ring parents.

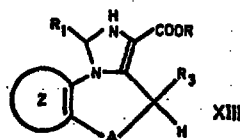
The invention also provides a process for the preparation of imidazo[1,5-a][1,4]-diazepine compounds of the general formula I above their analogs of formula IA above and the pharmaceutically acceptable acid addition salts thereof, which process comprises

a) reacting a compound of formula



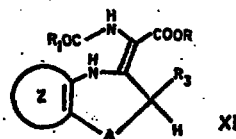
or an N-oxide thereof, with an alkanolic acid ortho ester of the formula $R_1C(OR)_2$, wherein R is lower alkyl and R_1 is hydrogen, lower alkyl, alkoxy lower alkyl or halo lower alkyl, or with a technical equivalent thereof to obtain directly a corresponding compound of formula I, any amino or alkylamino group being present in a protected form during this reaction, or

b) oxidizing a compound of formula



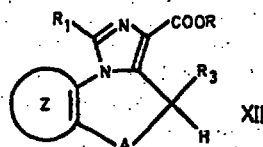
or an N-oxide thereof to a corresponding compound of formula I, or

c) dehydrating with concurrent cyclization a compound of formula



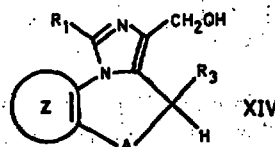
wherein R_1 is hydrogen, lower alkyl, phenyl, alkoxy lower alkyl, substituted phenyl, pyridyl or aralkyl, or an N-oxide thereof to a corresponding compound of formula I, or

d) hydrolyzing a compound of formula



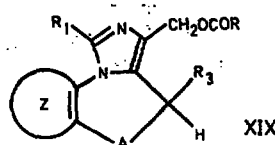
to the corresponding free acid, or

e) reducing a compound of formula XII to the corresponding compound of formula



or,

f) acylating a compound of formula XIV to a corresponding compound of formula



any substituent liable to undesirable acylation being present in protected form during this reaction, or

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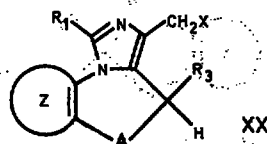
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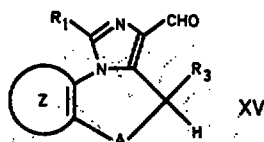
g) substituting the hydroxy group in the 3-substituent of a compound of formula XIV with a halogen, or

h) nucleophilically displacing the halogen in the 3-position substituent of a compound of formula



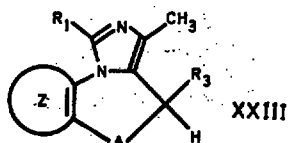
wherein X is halogen, by an amine, alkoxide or cyanide, any R_1 haloalkyl substituent being produced subsequent to the above nucleophilic reaction, and any hydroxy alkyl substituent being in a protected form during reaction with an alkoxide, or

i) reacting the 3-position aldehyde group of a compound of formula



with a lower alkyl, Grignard or lithium reagent, any R_1/R_4 hydroxy alkyl substituent being present in a protected form during this reaction, or

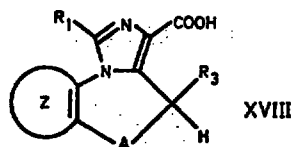
j) reductively dehalogenating the 3-position substituent of a compound of formula XX to the corresponding compound of formula



any nitro, cyano and R_1 haloalkyl substituent being formed subsequent to the production of compound of formula XXIII, or

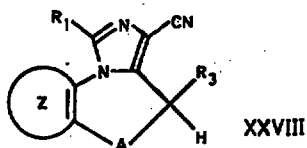
k) subjecting a compound of formula XII to ammonolysis with an amino compound of the formula H_2NR_{12} wherein R_{12} is hydrogen, lower alkyl, hydroxy lower alkyl, lower alkenyl, aryl or the group $-(CH_2)_nNR_{14}R_{15}$, wherein R_{14} and R_{15} are hydrogen, lower alkyl, hydroxy lower alkyl or lower alkenyl or taken together form a part of a heterocyclic ring and n is 1 to 4, any haloalkyl or ROOC-substituent being produced subsequent to the above ammonolysis, or

l) reacting an acid chloride of a compound of formula



with an amino compound of the formula $HNR_{12}R_{13}$, wherein R_{12} and R_{13} have the meaning indicated in formula I above, any haloalkyl or ROOC-substituent being produced subsequent to the above ammination, or

m) for the preparation of a nitrile of formula



dehydrating a corresponding $-CONH_2$ compound, or

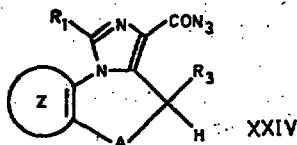
n) subjecting a compound of formula XII to direct hydrazinolysis with a hydrazine of the formula $HN(R_{16})NR_{17}R_{18}$, wherein R_{16} , R_{17} and R_{18} have the meaning indicated

in formula I above, any haloalkyl or ROOC-substituent being produced subsequent to the above hydrazinolysis, or

o) treating an acid chloride of a compound of formula XVIII with a hydrazine of the formula $\text{HN}(\text{R}_{16})\text{NR}_{17}\text{R}_{18}$, wherein R_{16} , R_{17} and R_{18} have the meaning indicated in formula I above, any haloalkyl or ROOC-substituent being produced subsequent to the above treatment with the hydrazine, or

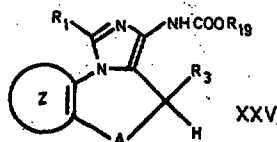
p) decarboxylating a compound of formula XVIII, or

q) heating a compound of formula



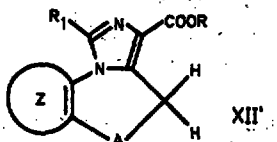
with an alkanol or an aralkanol, any haloalkyl substituent being formed subsequent to the Curtius type reaction, or

r) hydrogenating a compound of formula



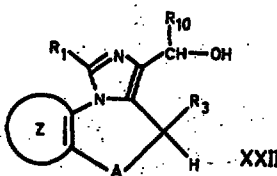
wherein R_{19} is benzyl, into the corresponding free amine and alkanoylating the compound thus obtained, any haloalkyl, nitro or cyano substituent being formed subsequent to the above hydrogenation, or

s) alkylating a compound of formula

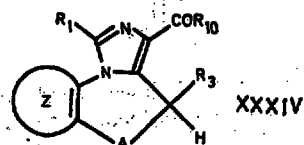


in the 4-position, no substituent with active hydrogen being present in case alkylation of such a substituent is undesirable and no haloalkyl substituent being present, or

t) oxidizing an alcohol of formula



wherein R_{10} is hydrogen or lower alkyl, to the corresponding acyl derivative of the formula



wherein R_{10} has the meaning as in formula XXII, any hydroxyalkyl substituent being present in a protected form during the above oxidation, or

u) treating a compound of formula XXXIV with a hydrazine of formula $\text{H}_2\text{NNR}_{20}$, wherein R_{20} is amino, mono- or dialkylamino or arylamino or with ammonia, hydroxyl amine, a lower alkylamino or a lower alkoxy amine, any R_1/R_4 acyl group

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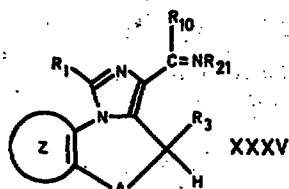
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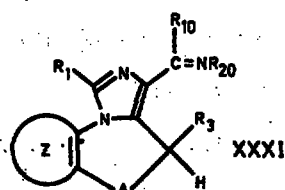
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being present in a protected form during the above reaction and any haloalkyl substituent being produced subsequent to the above reaction, or

v) reducing a compound of formula

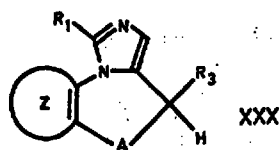


5 wherein R₂₁ is hydrogen, hydroxy, lower alkyl or lower alkoxy and R₁₀ is hydrogen or lower alkyl, or a compound of formula



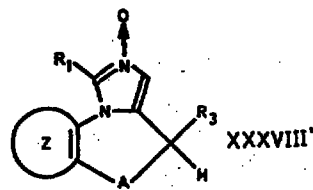
10 wherein R₂₀ is amino, mono- or dialkyl amino or arylamino and R₁₀ is hydrogen or lower alkyl, to the corresponding amino compound, any halo alkyl, nitro or cyano substituent being produced subsequent to the above reduction, or

w) introducing into the 3-position of a compound of formula



15 a chloro, bromo or iodo substituent, any hydroxyalkyl or aminoalkyl substituent being present in protected form during the above halogenation and any halogenated compound wherein R₁ is hydrogen being produced subsequent to the above halogenation step, or

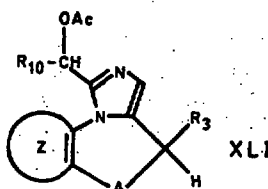
x) converting a compound of formula



wherein A is —C(R₆)=N— or —C(R₆)=N(→O)—,



is group a), b) or c) in formula I, R₁ is lower alkyl and R₆ is phenyl or mono- or disubstituted phenyl, into a corresponding compound of formula

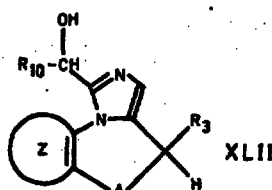


wherein R_{10} is hydrogen or lower alkyl and A,



and R_6 are as in formula XXXVIII', any R_6 -hydroxyalkyl substituent being present in protected form during the above conversion, or

5 y) converting a compound of formula XLI into a corresponding compound of formula

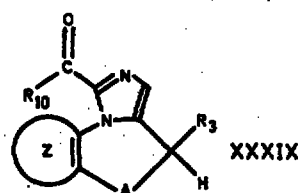


wherein A,



10 R_{10} and R_6 are as in formula XLI, or

aa) oxidizing a compound of formula XLII to a corresponding compound of formula



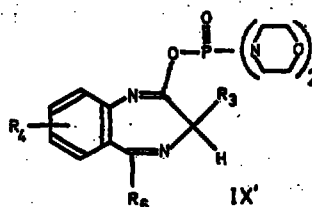
wherein A,



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R_{10} and R_6 are as in formula XLII, any hydroxyalkyl substituent being present in a protected form during the above oxidation, or

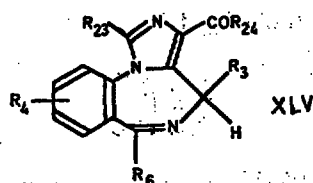
bb) reacting a compound of formula



20 with a nitron of the formula



wherein R_{23} is phenyl, substituted phenyl or pyridyl and R_{24} is lower alkoxy or dilower alkylamino, yielding a compound of formula



wherein R_{23} and R_{24} are as in formula XLVI, or

cc) homologating the R_2 substituent in the meaning of aminomethyl, substituted aminomethyl, cyanomethyl, halomethyl, methyl, acyloxymethyl or alkoxymethyl in compounds of formula I above to higher homologs, or

dd) preparing compounds of formula I above with an R_2 substituent being an isomer to α -hydroxy lower alkyl, or

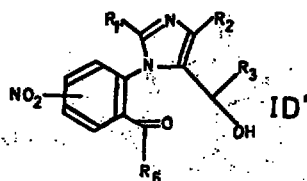
ee) reducing one compound of formula I to another compound of formula I, or

ff) converting an amino substituent present in a compound of formula I above or in an analog thereof corresponding to formula I but wherein A represents the group e), f) or g) above,



represents the group a), b) or c) above, R_5 is hydrogen and V represents hydrogen or lower alkyl, except that in formula I with A being structure f), R_4 is not nitro and R_5 is not nitro substituted, into the corresponding nitro, cyano, chloro or bromo substituent by means of a Sandmeyer reaction, or

gg) cyclizing a compound of formula



to a corresponding cyclized compound, or

hh) converting a compound of formula I above wherein



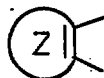
is group a), b) or c) above and R_5 is hydrogen, into the corresponding N-oxide thereof, or

ii) converting an N-oxide of a compound of formula I above wherein



is the group a), b) or c) above and R_5 is hydrogen into a corresponding compound of formula I wherein R_5 is alkanoyloxy, or

jj) converting a compound of formula I above, wherein



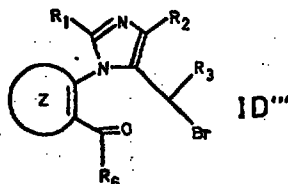
is the group a), b) or c) above and R_5 is alkanoyloxy into the corresponding compound of formula I above wherein R_5 is hydroxy, or

kk) converting a compound of formula I above, but wherein A is $-\text{CH}(\text{R}_6)-\text{N}(\text{R}_7)-$ in which R_7 is hydroxy, acyl or an aromatic or aliphatic sulfonyl group, into the corresponding compound of formula I above, or

ii) converting an analog of a compound of formula I above, wherein A is the group f) above into the corresponding compound of formula I above, or

mm) reacting a compound of formula I above with ethylene oxide or propylene oxide in the presence of a Lewis acid catalyst, or

nn) reacting a compound of the formula

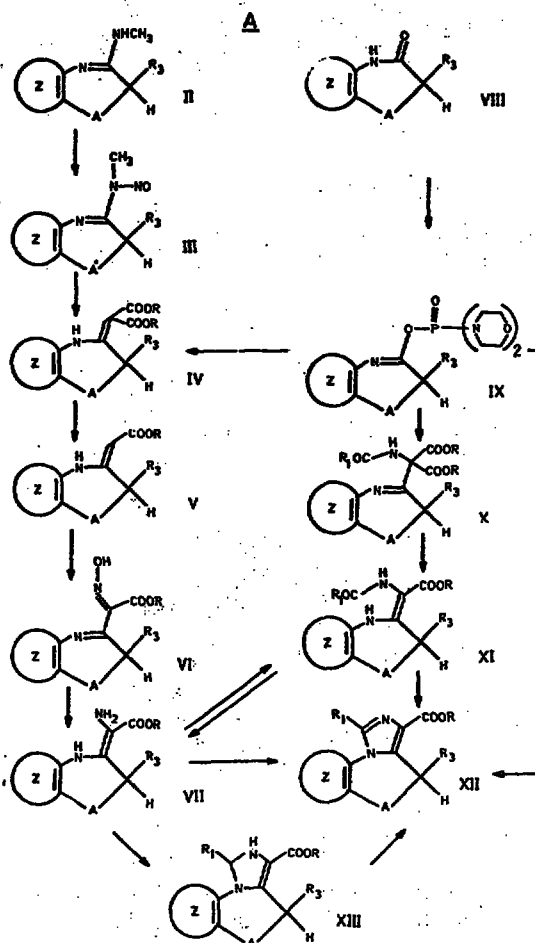


with ethanol-amine or a 1- or 2-alkyl substituted ethanolamine, or

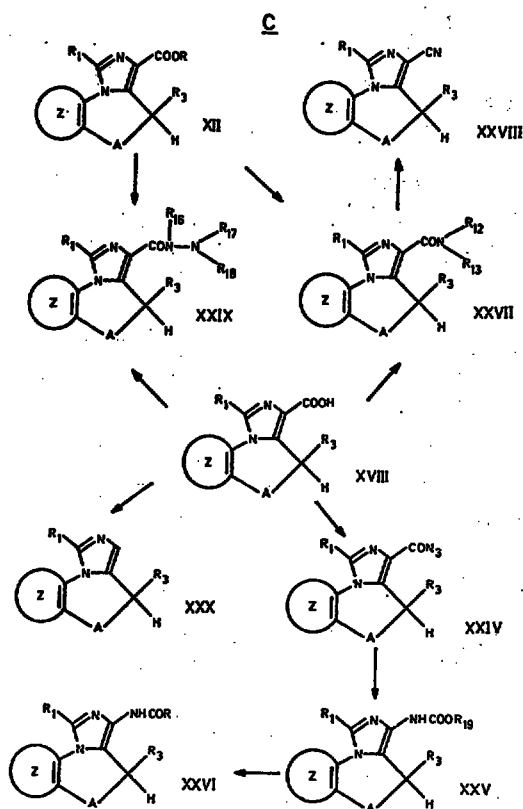
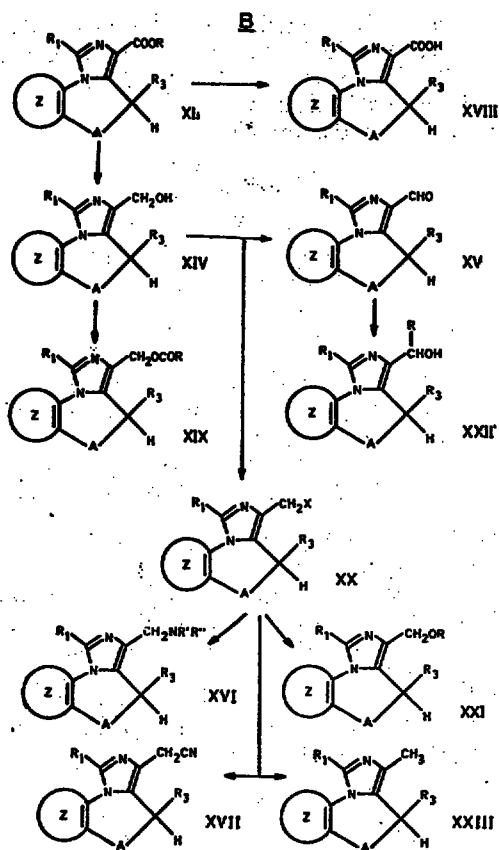
(oo) resolving a racemic compound of formula I above or an analog thereof as defined above into its optical enantiomers, or

pp) converting a compound of formula I above or an analog thereof as defined above into a pharmaceutically acceptable acid addition salt by reaction with a suitable acid, any R being lower alkyl.

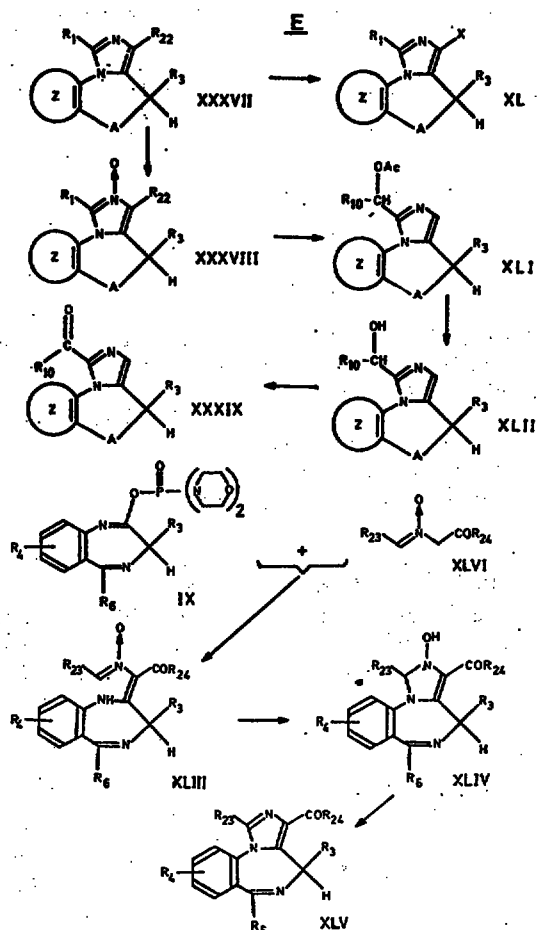
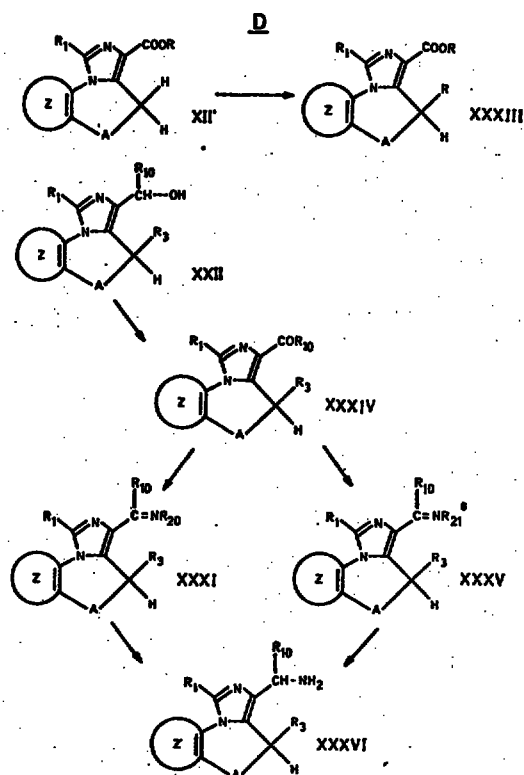
The general reaction schemes shown on the following five sheets A to E are illustrative of several of the reactions useful to produce compounds of the formula I. In these reaction schemes unless otherwise indicated R is lower alkyl and A, R₁, R₂, R₃ and R₄ are as in formula I. It is obvious to one skilled in the art that certain of the substituents may be attacked during the below reactions but such vulnerable groups may be modified before or after such reaction is carried out. The reactions shown on sheet A may also be performed with the corresponding N-oxides thereof [A=—C(R₆)=N(→O)—] but any N-oxide moiety present in compounds of formula VI will be removed during the conversion VI→VII.



19



20



Step II→III

Compounds of formula III are produced by the nitrosation of compounds of formula II. Such a nitrosation may be effected by "in situ formed" nitrous acid. Reagents which may be employed include (1) alkali metal nitrites, i.e., sodium nitrites, in the presence of organic or inorganic acids, i.e., glacial acetic acid, and aqueous or non-aqueous solvents; (2) alkyl nitrites, i.e., methyl nitrites, in the presence of an inert solvent such as an alcohol, chlorinated hydrocarbon or, for example, dimethylformamide, and (3) a nitrosyl chloride gaseous solution in an inert solvent and in the presence of an acid acceptor such as pyridine. Such a nitrosation reaction should be effected at around or below room temperature, i.e., in the range of -20°C to 25°C . An amino group or an alkylamino group present in the molecule may be protected during the nitrosation reaction, e.g. by means of acylation. Such protecting group can be removed at a convenient later stage of the reaction sequence.

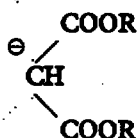
Step VIII→IX

Compounds of formula IX may be produced by the reaction of the compounds of formula VIII with dimorpholinophosphinic chloride. The reaction of formula VIII compounds with the phosphorylating agent to yield compounds of formula IX is accomplished by treatment of formula VIII compounds with a strong base sufficient to ionize the formula VIII compound to form the corresponding anion. Suitable bases include alkali metal alkoxides, such as potassium *tert*-butoxide or sodium methoxide, and alkali metal hydrides, such as sodium hydride, and alkyl lithium compounds, such as *n*-butyl lithium. The reaction temperature ranges from 0°C to 100°C and the reaction is carried out preferably in an aprotic polar inert solvent, i.e., one that would solubilize the ambient salts of the formula VIII compounds totally or at least partially. Preferred solvents are ethers, e.g., tetrahydrofuran or dioxane or tertiary amides, e.g., dimethylformamide.

It is evident that any amino or substituted amino group should be present is protected form in this reaction step the protective moiety can be removed afterwards at any convenient stage, e.g. subsequent to the formation of compound of formula XII.

Step III or IX→IV

Compounds of formula III or formula IX may be condensed with the anion generated from malonic ester of the formula



wherein R is lower alkyl, to produce compounds of formula IV. The anion is generated by deprotonating malonic ester with a suitable strong base such as alkali metal or alkaline earth metal alkoxides, hydrides or amides. The reaction of the formula III or IX compounds with the malonic ester anion is preferably effected in a solvent such as hydrocarbons, e.g., benzene, toluene, hexane, ethers e.g., dioxane, THF, diethyl ether, DMF, DMSO etc. at a temperature range of below room temperature to 150°C , preferably 0°C to 100°C , most preferably room temperature.

Step IV→V

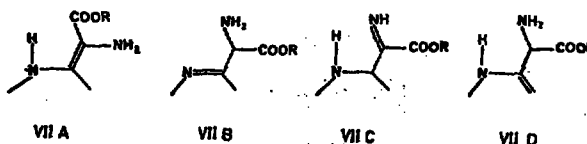
Compounds of the formula V are produced by the decarboxylation of compounds of the formula IV by reacting the formula IV compound with an alkali metal hydroxide such as NaOH or KOH in a suitable solvent such as alcohols, ethers or DMSO at a temperature range of room temperature to reflux temperature, preferably 60°C to 100°C .

Step V→VI

Compounds of formula VI are produced by the nitrosation of compounds of formula V by reacting same with nitrous acid generated from, for example, an alkali metal nitrite, alkyl nitrite or nitrosyl chloride, by reaction with organic or inorganic acid. Suitable solvents for the nitrosation reaction include ethers, alcohols, water, acids, e.g., acetic acid, DMF, DMSO and chlorinated hydrocarbons. The reaction may be carried out at about room temperature although such temperature is not critical.

Step VI→VII

Compounds of the formula VII are produced by the reduction of compounds of formula VI e.g. with Raney nickel and hydrogen or with zinc and acetic acid. This reduction results in the predominant production of compounds of formula VII with concurrent side production of small amounts of several possible isomers, i.e., compounds of the formulae



It should be noted that the above reductive step would reduce vulnerable groups, if present, as R_4 , such as a 7-position NO_2 or a 7-position CN . These groups may be replaced by methods known in the art and set forth herein.

Step VII→XII

Compounds of the formula XII are then formed by the reaction of formula VII compounds with an an alkanolic acid ortho ester of the formula

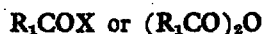


wherein R is lower alkyl and R_1 is hydrogen, lower alkyl, alkoxy lower alkyl or halo lower alkyl, optionally in the presence of an acid catalyst, e.g., an organic or inorganic acid; e.g., p-toluene sulfonic acid, phosphoric acid, etc., and at room temperature or above, i.e., 25°C to 150°C , in which instance the cyclization to compound XII occurs spontaneously. Technical equivalents of the above ortho ester include ortho amides, e.g. the dimethyl acetal of N,N -dimethyl formamide; N,N,N',N'',N''',N''' -hexamethylmethanetriamine; nitriles, e.g. acetonitrile; ester imidates, e.g. $\text{CH}_3-\text{C(=NH)}-\text{OC}_2\text{H}_5$.

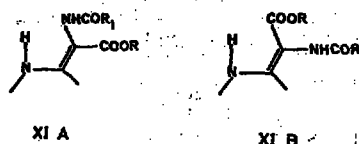
It is evident that any amino or alkylamino group present has to be protected during this reaction.

Step VII→XI

Compounds of formula XI may be formed by the acylation of formula VII compounds with a compound of the formula



wherein X is halo and R_1 is hydrogen, lower alkyl, phenyl, alkoxy lower alkyl, substituted phenyl, pyridyl or aralkyl. Solvents for the above process step include methylene chloride, ethers, chlorinated hydrocarbons, etc., preferably in combination with an acid acceptor such as an organic or inorganic base such as triethylamine, pyridine or an alkaline metal carbonate. The reaction may be effected at above or below room temperature but preferably is carried out at room temperature. Compounds of the formula XI are isomeric in nature, that is, may exhibit either of the following stereochemical structures

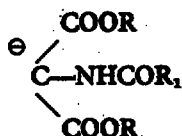
**Step XI→XII**

Compounds of the formula XII may also be formed by dehydration of formula XI compounds or isomers thereof with concurrent cyclization by heating. In this reaction step the meaning of the symbol R_1 in compounds of formulae XI and XII is restricted to hydrogen, lower alkyl, phenyl, alkoxy lower alkyl, substituted phenyl, pyridyl and aralkyl. This reaction step may be carried out with or without solvent, e.g., DMF, ethylene glycol, hexamethyl phosphoric triamide, at a temperature range of

100°C to 300°C, preferably at 150°C to 250°C, e.g., 200°C, with or without the presence of catalysts and water binding agents.

Step IX→X

Compounds of the formula X may be formed by the condensation reaction of a compound of the formula IX with the anion generated from acyl amino malonic ester of the formula



wherein R is lower alkyl and R₁ is hydrogen, lower alkyl, phenyl, alkoxy lower alkyl, substituted phenyl, pyridyl or aralkyl, to produce a compound of formula X. The anion is generated by deprotonating acylamino malonic ester with a suitable strong base such as alkali metal or alkaline earth metal alkoxides, hydrides or amides. The reaction of the formula IX compounds with the acyl amino malonic ester anion is preferably effected in a solvent such as hydrocarbons e.g., benzene, toluene, hexane, ethers e.g., dioxane, THF, diethyl ether, DMF, DMSO etc., at a temperature range of below room temperature to 150°C, preferably 0°C to 100°C, most preferably room temperature.

Step X→XI

Compounds of formula XI and isomers thereof are formed by the decarboxylation of formula X compounds with an alkali metal alkoxides in a solvent such as ethers, alcohols, DMSO, DMF, etc., at above or below room temperature, preferably at room temperature. Compounds of formula X and XI need not be isolated but can be converted in situ into compounds of formula XII.

Step VII→XIII

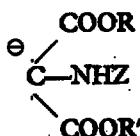
Compounds of the formula XIII are formed by the reaction of formula VII compounds with an aldehyde of the formula R₁CHO, wherein R₁ is as in formula I, but any amino or substituted amino group and preferably any RCO-group should be present in protected form. The protecting moiety can be removed afterwards, e.g. subsequent to the formation of compound of formula XII. Solvents suitable for this reaction step are hydrocarbons such as benzene, alcohols, ethers, chlorinated hydrocarbons, DMF, DMSO, etc., with or without the presence of water-binding agents, e.g. molecular sieves at above or below room temperature, preferably from room temperature to reflux temperature of the solvent.

Step XIII→XII

Compounds of the formula XIII may be converted to formula XII compounds by oxidation in situ by oxidizing agents such as manganese dioxide, air, oxygen, etc.

As indicated above, a final compound of formula XII wherein R₁ is amino can be converted into a corresponding compound wherein R₁ is nitro or cyano via a Sandmeyer reaction as set forth in this specification.

Another method for the preparation of compounds of formula XII wherein R₁ is nitro or cyano consists in preparing a corresponding compound of formula VII. The latter compound can be prepared by reacting a corresponding compound of formula IX with a protected amino malonic ester of the formula



wherein R is lower alkyl and Z is benzyloxycarbonyl, converting the compound of formula X, wherein R₁ is benzyloxy and R₂ is nitro or cyano, thus obtained to a corresponding compound of formula XI as described above for step X→XI and subjecting the compound thus obtained to a treatment with hydrogen bromide in glacial acetic acid yielding a compound of formula VII wherein R₁ is nitro or cyano. The inter-

mediates of formula X and XI need not be isolated. The compound of formula VII thus obtained is further converted to the final compound of formula XII via reacting steps VII→XIII and XIII→XII described above.

Step XII→XVIII

5 Formula XVIII compounds are formed by hydrolyzing formula XII compounds to the corresponding acids, preferably with alkali metal hydroxides, e.g., NaOH or KOH. This hydrolysis is conveniently effected in an inert solvent. Suitable solvents are alcohols, e.g. methanol, ethanol; ethers, e.g. dioxane, tetrahydrofuran; dimethylformamide, in combination with water. It is preferable to conduct this reaction step at a temperature between room temperature and the boiling point of the reaction mixture.

10 It is evident that during this reaction step an acyloxyalkyl group present will be hydrolyzed to the corresponding hydroxyalkyl group which in turn can be converted back to the acyloxyalkyl group at a convenient later stage. An R_1 -group in the meaning of $-\text{COOR}_1$ will also be hydrolyzed and decarboxylated to a corresponding compound wherein R_1 is hydrogen. The $-\text{COOR}_1$ moiety can be reintroduced from a formyl or hydroxymethyl group in known manner. A haloalkyl group present may be affected in this reaction step yielding a corresponding hydroxyalkyl compound which may also be converted back to the haloalkyl compound at a later stage in usual manner. Any compound of formula XII wherein R_4 is hydroxyalkyl should be protected during this halogenation reaction step, e.g. in form of the tetrahydropyranylether derivative thereof.

Step XII→XIV

25 Formula XIV compounds are formed by the reduction of formula XII compounds, preferably with lithium aluminum hydride or an equivalent reducing agent. This reduction is conveniently conducted in an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; ethers, e.g. diethylether, tetrahydrofuran, 2-dimethoxyethane; or mixtures thereof. It is preferable to perform this reduction at a temperature between about -50°C and the boiling point of the reaction mixture, most preferably between about -20°C and 0°C .

30 Nitro and cyano groups present may be affected during this reaction step. Such groups can be formed at a later stage of the synthesis.

Step XIV→XIX

35 Compounds of formula XIV can be converted to compounds of formula XIX by acylation with acid anhydrides or acid chlorides in presence or absence of an acid acceptor. This acylation is conveniently conducted in an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; chlorinated hydrocarbons, e.g. methylene chloride; ethers, e.g. tetrahydrofuran; dimethylformamide. Preferably this acylation is conducted at a temperature between about -50°C and 150°C , most preferably at room temperature. Acid acceptors that can be used in this reaction step are for instance pyridine, triethylamine, potassium carbonate.

40 It is evident that any substituent present as R_1 and/or R_4 and liable to being acylated during this reaction step should be protected in the usual manner in order to avoid any undesired acylation of such groups.

Step XIV→XV

45 Compounds of formula XV can be prepared by oxidation of formula XIV compounds by known oxidants such as chromium trioxide and manganese dioxide. This oxidation is conveniently conducted in an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; chlorinated hydrocarbons, e.g. methylene chloride; ketones, e.g. acetone; organic acids, e.g. acetic acid; pyridine, dimethylformamide, dimethylsulfoxide. The oxidation is preferably performed at a temperature between about -50°C and the boiling point of the reaction mixture, most preferably at about 0°C and room temperature.

50 It is evident that any substituent present as R_1 and/or R_4 in the meaning of hydroxyalkyl must be protected in the usual manner during this reaction step.

Step XIV→XX

55 Compounds of formula XX are prepared by substitution of hydroxy group in the 3-substituent of formula XIV compounds with a halogen. This reaction is preferably carried out by reagents such as a phosphorous halide, e.g. phosphorous trichloride, phosphorous tribromide or thionyl chloride. This reaction step is conveniently conducted

in an inert solvent or in the absence of a solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; chlorinated hydrocarbons, e.g. methylene chloride; ethers, e.g. tetrahydrofuran. The temperature at which this reaction step is performed is preferably situated between about -50°C and 100°C , most preferably between about 0°C and room temperature.

It is evident that any R_1/R , hydroxyalkyl group should be protected in case a conversion into the corresponding haloalkyl derivative is undesirable.

Step $\text{XX} \rightarrow \text{XVI}$; XXI , XVII

Compounds of formula XX can be reacted such that the halogen in the 3-substituent is nucleophilically displaced by other nucleophilic groups such as an amine (XVI , wherein R' is hydrogen or lower alkyl and R'' is hydrogen, lower alkyl or acyl), alkoxide (XXI) and cyanide (XVII).

In the reaction step $\text{XX} \rightarrow \text{XVI}$ a compound of formula XX is treated with ammonia or a mono- or dialkylamine. A compound obtained wherein R' and/or R'' is hydrogen can, if desired, be acylated with a suitable acylating agent. This reaction step can be effected in the absence or in the presence of an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; chlorinated hydrocarbons, e.g. methylene chloride, chlorobenzene; ethers, e.g. diethylether, tetrahydrofuran; dimethylformamide, dimethylsulfoxide. This reaction is preferably conducted at a temperature between about 0°C and the boiling point of the reaction mixture with or without applying pressure above atmospheric pressure.

It is evident that a compound of formula XVI wherein R_1 is haloalkyl has to be produced in a further step, e.g. using the corresponding hydroxyalkyl derivative as starting material, in known manner.

The reaction step $\text{XX} \rightarrow \text{XXI}$ is conveniently effected by treating a compound of formula XX with an alkali metal alkoxide, preferably in the presence of an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; ethers, e.g. tetrahydrofuran; dimethylformamide, dimethylsulfoxide, alcohols corresponding to the alkoxide used. Alternatively, a compound of formula XX is treated with an alkanol in the presence of an organic base, e.g. pyridine or triethylamine. The temperature to be applied for this reaction step is preferably situated between about -50°C and the boiling point of the reaction mixture, most preferably between room temperature and about 100°C , with or without using pressure above atmospheric pressure.

It is evident that a compound of formula XXI wherein R_1 is haloalkyl has to be produced in a further step as indicated above.

It is also evident that any hydroxyalkyl substituent present will have to be protected during this reaction step and deprotected at a later stage.

The reaction step $\text{XX} \rightarrow \text{XVII}$ is conveniently effected by treating a compound of formula XX with an alkali cyanide, preferably in an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; ethers, e.g. tetrahydrofuran; dimethylformamide, dimethylsulfoxide. The temperature for this reaction step is preferably situated between room temperature and the boiling point of the reaction mixture, most preferably between about 25°C and 160°C .

It is evident that also in this step a compound of formula XVII wherein R_1 is haloalkyl has to be produced in a further step as indicated above.

Step $\text{XX} \rightarrow \text{XXIII}$

Compounds of formula XXIII are formed by reduction of compounds of formula XX with hydrogen using a suitable catalyst, e.g. palladium or Raney nickel. This reaction step is conveniently effected in the presence of an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; ethers, e.g. tetrahydrofuran, dioxane. The reaction is preferably conducted at a temperature between about room temperature and the boiling point of the reaction mixture, most preferably at room temperature. If desired, pressure above atmospheric pressure can be applied.

It is evident that any nitro, cyano or additional haloalkyl substituent in a compound of formula XXIII has to be formed at a later stage of the synthesis.

Step $\text{XV} \rightarrow \text{XXII}'$

Compounds of formula XXII' are formed by reaction of formula XV 3-position aldehyde with an organometallic reagent such as a Grignard reagent or an alkyl lithium reagent. This reaction is conveniently effected in an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; chlorinated hydrocarbons, e.g. methylene chloride, ethers, e.g. diethylether, tetrahydrofuran, dimethoxyethane. The reaction is preferably

conducted at a temperature between about -100°C and 50°C , most preferably between about -20°C and room temperature.

It is evident that any carbonyl group in the substituents R_1 and R_4 has to be protected during this reaction step. Since an $R_{10}\text{OOC}$ -group would be affected in the step XV $\rightarrow$ XXII' such a group has to be formed after production of the compound of formula XXII', e.g. by using the corresponding aldehyde with protected α -hydroxyalkyl substituent in the 3-position as starting material. Any cyano substituent will have to be formed at a later stage of the synthesis.

Step XII or XVIII $\rightarrow$ XXVII

Compounds XXVII may be produced by direct aminolysis of compound of formula XII (with an amino compound of the formula H_2NR_{12}) or by conversion of XVIII to acid chloride, e.g. by treatment with phosphorous pentachloride and subsequent reaction with an amino compound of the formula $\text{HNR}_{12}\text{R}_{13}$. R_{12} and R_{13} have the meaning indicated in formula I.

The step XII $\rightarrow$ XXVII is conveniently effected in an inert solvent or in the absence of a solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; ethers, e.g. tetrahydrofuran; alcohols, e.g. methanol, ethanol; dimethylformamide, dimethylsulfoxide, hexamethyl phosphoric triamide. It is preferable to perform this reaction step at a temperature between about 50°C and 200°C , most preferably between about 100°C and 150°C , applying atmospheric pressure or pressure above atmospheric pressure.

It is evident that any haloalkyl or ROOC - substituent has to be formed subsequent to production of the formula XXVII-compound.

The step XVIII $\rightarrow$ XXVII is conveniently effected in an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; ethers, e.g. tetrahydrofuran, chlorinated hydrocarbons, e.g. methylene chloride, chlorobenzene. It is preferable to perform this reaction at a temperature between about -20°C and the boiling point of the reaction mixture, most preferably between about 0°C and 50°C .

It is evident that a hydroxyalkyl substituent has to be protected during this reaction step.

Step XXVII $\rightarrow$ XXVIII

Formula XXVIII compounds are formed by dehydration of formula XXVII compounds where R_{12} and R_{13} are hydrogen. Dehydration is accomplished by reactants such as phosphorus pentoxide, phosphorus oxy chloride in a compatible solvent. Suitable solvents are pyridine, hydrocarbons, e.g. hexane, toluene; chlorinated hydrocarbons, e.g. methylene chloride. Preferably this reaction is conducted at a temperature between room temperature and the boiling point of the reaction mixture, most preferably between about 50°C and 120°C .

Step XII or XVIII $\rightarrow$ XXIX

Formula XXIX compounds are formed by direct hydrazinolysis or conversion to acid chloride, e.g. by treatment with phosphorous pentachloride, and subsequent treatment by a hydrazine. The symbols R_{12} , R_{17} and R_{18} in formula XXIX have the same meaning as indicated in formula I. The same reaction conditions as indicated for the step XVIII $\rightarrow$ XXVII can also be used for the step XVIII $\rightarrow$ XXIX and the same restrictions as to substituents liable to being affected during the reaction should be observed. The reaction XII $\rightarrow$ XXIX is conveniently performed in an inert solvent or in the absence of a solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; ethers, e.g. tetrahydrofuran; alcohols, such as methanol, ethanol. Preferably this reaction is conducted at a temperature between about 50°C and 150°C , most preferably between about 80°C and 100°C . The same restrictions as to substituents liable to being affected during this reaction step should be observed as indicated for the reaction step XII $\rightarrow$ XXVII.

Step XVIII $\rightarrow$ XXX

Formula XXX compounds are formed by decarboxylation with or without catalyst and with or without solvent. This decarboxylation is conveniently effected by application of heat; e.g. at a temperature between about 100°C and 350°C , preferably about 150°C and 230°C . Solvents that can be used in this reaction step are hydrocarbons, e.g. mineral, oil; chlorinated hydrocarbons, ethers, alcohols, e.g. ethylene glycol, dimethylformamide, dimethylsulfoxide, hexamethyl phosphoric triamide. Useful catalysts are for instance metals such as copper powder or metal salts such as Cu^+ or Ag^+ salts.

Step XVIII→XXV

Formula XXV compounds are formed by modified Curtius reaction, i.e., by reaction of formula XVIII compounds with phosphoryl azides, e.g. $N_3PO(OC_6H_5)_2$, to form azides, i.e., formula XXIV compounds, and subsequent heating of these azides with an alcohol which takes part in reaction. The azide formation is conveniently performed in an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; ethers, e.g. tetrahydrofuran. This reaction step is preferably conducted at a temperature between about 0°C and 100°C, preferably at room temperature, if desired, utilizing pressure above atmospheric pressure.

It is obvious that any amino and substituted amino group present has to be protected during this reaction step. It is also advisable to use a compound of formula XVIII with protected hydroxyalkyl groups. Removal of the protecting group(s) can be effected after formation of compound of formula XXV.

The conversion of the azide of formula XXIV to the carbamic acid ester of formula XXV, wherein R_{10} is lower alkyl or aralkyl, is conveniently effected in the alcohol reactant serving as solvent. Additionally, inert solvents may be present such as hydrocarbons, e.g. hexane, toluene; chlorinated hydrocarbons, e.g. methylene chloride; ethers, e.g. tetrahydrofuran; pyridine, triethylamine. Preferably the reaction is conducted at a temperature between about 50°C and 200°C, most preferably between about 80°C and 160°C.

It is evident that a haloalkyl substituent present would be affected during this reaction step and thus has to be formed subsequent to the production of compound of formula XXV in known manner.

Step XXV→XXVI

Formula XXVI compounds are formed by reaction of formula XXV compounds where R_{10} is benzyl with palladium and hydrogen to yield a free amine which is acylated with an acid halide or acid anhydride. The formation of the free amine is conveniently effected in an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; ethers, e.g. tetrahydrofuran, alcohols, e.g. methanol, ethanol; organic acids, e.g. acetic acid, acid anhydrides, e.g. acetic anhydride, in which case the acylation occurs in situ. The preferred temperature range for this reaction step is between room temperature and about 100°C, if desired, using pressure above atmospheric pressure. For the acylation the same reaction conditions can be used as indicated for the step XIV→XIX.

It is evident that any haloalkyl, nitro and cyano substituents has to be formed subsequent to the production of the compound of formula XXVI in known manner. It is also evident that an amino group has to be protected, e.g. in form of the corresponding phthalyl derivative.

Step XII'→XXXIII

Formula XXXIII compounds are formed by alkylation of formula XII' compounds with alkyl halides in the presence of strong base, e.g., methyl iodide in the presence of potassium tertiary butoxide. This reaction step is conveniently effected in an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; ethers, e.g. tetrahydrofuran; dimethylformamide, dimethylsulfoxide. Preferably the reaction is conducted at a temperature between about -50°C and room temperature, most preferably between about -30°C and -10°C.

It is evident that any substituent present should not be a haloalkyl substituent or a substituent with active hydrogen in case alkylation of such latter substituent is undesirable.

Step XXII→XXXIV

Formula XXXIV (including XV) compounds are formed by oxidation of formula XXII compounds as carried out in step XIV→XV (R_{10} is hydrogen or lower alkyl).

Step XXXIV→XXXI

Formula XXXI compounds, wherein R_{10} is hydrogen or lower alkyl are formed by treatment of formula XXXIV (including XV) compounds with a hydrazine of formula NH_2R_{20} , wherein R_{20} is amino, mono- or dialkyl amino or arylamino. This reaction is conveniently effected in an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; chlorinated hydrocarbons, e.g. methylene chloride; ethers, e.g. tetrahydrofuran; alcohols, e.g. methanol, ethanol; organic acids, e.g. acetic acid; pyr-

idine. Preferably the reaction is conducted at a temperature between room temperature and the boiling point of the reaction mixture.

It is evident that any R_1 and/or R_4 acyl group has to be protected during this reaction step and that any haloalkyl group has to be formed subsequent to the production of the compound of formula XXXI.

Step XXXIV→XXV

Formula XXXV compounds wherein R_{21} is hydrogen, hydroxy, lower alkyl or lower alkoxy and R_{10} is hydrogen or lower alkyl are formed by reaction of formula XXXIV (including XV) compounds with ammonia hydroxyl amine, a lower alkylamine or a lower alkoxyamine. This reaction step is conveniently effected in an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; chlorinated hydrocarbons, e.g. methylene chloride; ethers, e.g. tetrahydrofuran; alcohols, e.g. methanol, ethanol; organic acids, e.g. acetic acid; pyridine. Preferably the reaction is conducted at a temperature between room temperature and about 150°C, if desired, at a pressure above atmospheric pressure.

It is evident that any R_1 and/or R_4 acyl group has to be protected during this reaction step and that any haloalkyl group has to be formed subsequent to the production of the compound of formula XXXV.

Step XXXI or XXV→XXXVI

Formula XXXVI compounds, wherein R_{10} is hydrogen or lower alkyl are obtained by reduction of formula XXXI or XXXV compounds e.g. utilizing Raney nickel and hydrogen. This reaction step is conveniently effected in an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; ethers, e.g. tetrahydrofuran; alcohols, e.g. methanol, ethanol; dimethylformamide; organic acids, e.g. acetic acid; organic acid anhydrides, e.g. acetic acid anhydride, in which case acylation at the amino group formed occurs in situ leading to an acylated compound of formula XXXVI. It is preferable to conduct this reaction step at a temperature between about 0°C and 100°C, most preferably at room temperature, if desired, applying pressure above atmospheric pressure.

It is evident that any haloalkyl, nitro and cyano group has to be formed subsequent to the production of the compound of formula XXXVI.

Step XXXVII→XL

Formula XL compounds wherein X is chloro, bromo or iodo are obtained by reacting formula XXXVII compounds wherein R_{22} is hydrogen with an appropriate halogenating agent such as bromine, N-bromosuccinimide, N-chlorosuccinimide, etc. This reaction step is conveniently effected in an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; chlorinated hydrocarbons, e.g. methylene chloride; organic acids, e.g. acetic acid; inorganic acids, e.g. sulfuric acid. Preferably the reaction is conducted at a temperature between about 0°C and the boiling point of the reaction mixture depending on the reagent used.

It is evident that any hydroxyalkyl and aminoalkyl substituent present must be protected during this reaction step. Furthermore the meaning of R_1 must be different from hydrogen. A compound of formula XL wherein R_1 is hydrogen can be produced from a corresponding compound wherein R_1 is $-\text{COOR}$ by means of saponification and subsequent decarboxylation.

Step XXXVII→XXXVIII→XLI

Formula XXXVIII compounds wherein R_{22} is hydrogen, lower alkyl, lower alkoxy alkyl or acyloxy lower alkyl are obtained by reacting corresponding formula XXXVII compounds with a peracid such as meta chloro perbenzoic acid or peracetic acid. In the instances where R_1 is lower alkyl and R_2 is hydrogen, a compound of the formula XLI is formed by subsequent reaction with an acid anhydride. The symbol A in formulae XXXVIII and XLI stand for the group $-\text{C}(R_6)=\text{N}-$ and $-\text{C}(R_6)=\text{N}(\rightarrow\text{O})-$. The reaction step XXXVII→XXXVIII is conveniently effected in an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; chlorinated hydrocarbons, e.g. methylene chloride; organic acids, e.g. acetic acid. Preferably the reaction is conducted at a temperature between about 0°C and 50°C.

It is evident that any acyl group and preferably also any hydroxyalkyl group present should be protected during this reaction step. Furthermore, the presence of tertiary amino groups, ROOC-groups as well as Z in the meaning of pyrazol and R_6 is the meaning of pyridyl is excluded for this reaction step. An acyloxy alkyl group present

may be transformed into a hydroxyalkyl, a haloalkyl, an aminoalkyl, a substituted aminoalkyl or a cyanoalkyl group subsequent to the formation of the compound of formula XXXVIII.

The treatment with an acid anhydride, e.g. acetic acid anhydride for the conversion XXXVIII→XLI is conveniently effected in an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; chlorinated hydrocarbons, e.g. methylene chloride; ethers, e.g. tetrahydrofuran; dimethylformamide; dimethylsulfoxide. Acid anhydrides taking part in the reaction can also be used as solvents. This reaction step is advantageously effected at a temperature between room temperature and about 150°C, preferably between about 80°C and 100°C.

It is evident that any amino group present will be acylated and any hydroxyalkyl group present will be esterified during this reaction step.

Step XLI→XLII

Formula XLII compounds wherein A is as in formula XXXVIII are obtained by reacting corresponding formula XLI compounds with an alkali metal alkoxide or hydroxide. This reaction step is conveniently effected in an inert solvent. Suitable solvents are hydrocarbons, e.g. hexane, toluene; chlorinated hydrocarbons, e.g. methylene chloride; ethers, e.g. tetrahydrofuran; alcohols, e.g. methanol, ethanol; dimethylformamide; dimethylsulfoxide; hexamethyl phosphoric triamide; pyridine, amines, e.g. triethylamine. This reaction is preferably conducted at a temperature between about 0°C and the boiling point of the reaction mixture depending on the reagent used.

Step XLII→XXXIX

Formula XXXIX compounds wherein A is as in formula XXXVIII are formed by oxidation as in step XIV→XV.

Step IX'→XLV

Compounds of the formula XLV are prepared by reacting a formula IX' compound with a nitron anion formed by the reaction of a formula XLVI compound wherein R₂ is phenyl, substituted phenyl or pyridyl and R₄ is lower alkoxy or di-lower alkyl amino with a strong base, such as, butyl lithium, potassium tertiary butoxide, etc. The reaction (IX'→XLV) is effected in situ without isolation of intermediate compounds such as XLIII and XLIV. Solvents suitable for this reaction include hydrocarbons such as hexane, toluene, etc., ethers, e.g. THF, DMF and DMSO. Reaction temperature should be in the range of -100°C to room temperature, preferably -80°C to 25°C e.g. about -70°C with subsequent warming to room temperature to effect in situ cyclization.

Homologs of compounds of formulae XVI, XVII, XIX, XX, XXI and XXIII and compounds of formula XXII where the functional group in the substituent R₂ is in another position than the α-position can be prepared by homologation and/or modification of appropriate compounds disclosed above. For instance compounds of formula XVII can be converted to the corresponding ester which in turn can be subjected to similar reactions as disclosed above for the conversion of compounds of formula XII.

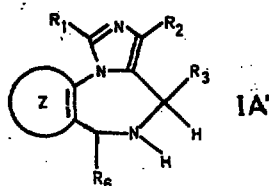
Compounds of the formula IA where A is $-\text{C}(\text{R}_6)=\text{N}(\rightarrow\text{O})-$ are formed by the conversion of corresponding formula I compounds into the N-oxides thereof. This conversion is affected by oxidizing a formula I compound with an organic peracid. A conventional organic peracid, such as peracetic acid, perpropionic acid, m-chloropero-benzoic acid, etc., can be utilized in carrying out this reaction. The oxidation can be effected at room temperature, or above or below room temperature.

Similar reactions as described above for the conversion of the R₂ substituent in formula I' can also be performed with respect to the R₁ substituent in formula I', for instance amination of a halo lower alkyl group, if desired, via the corresponding azido compound, or conversion of a halo lower alkyl group into the corresponding acyloxy lower alkyl group.

Compounds of the formula IA where A is $-\text{C}(\text{R}_6)=\text{N}(\rightarrow\text{O})-$ may be then utilized to produce compounds of formula I wherein R₃ is alkanoyloxy or hydroxy by methods known in the art, such as, for example, a Polonovski rearrangement utilizing an acid anhydride to form the alkanoyloxy radical which may be converted to the hydroxy by treatment with an alkali metal hydroxide such as sodium hydroxide. An example of such a Polonovski rearrangement is found in U.S. Patent No. 3,296,249.

Compounds of the formula IA where A is $-\text{CH}(\text{R}_6)\text{NH}-$ are formed by the reduction of corresponding formula I compounds to compounds of the formula

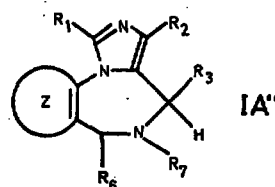
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wherein R_1 , R_2 , R_3 , R_6 and



are as in formula I, which may then be converted to other compounds of the formula



wherein R_1 , R_2 , R_3 and R_6 are as in formula IA' and R_7 is hydroxy, acyl or an aromatic or aliphatic sulfonyl group.

The reduction of formula I compounds to IA' compounds is accomplished by any suitable reducing agent but most preferably accomplished by hydrogen in the presence of a platinum oxide catalyst or zinc in the presence of acetic acid. In case R_4 is nitro or R_4 is nitro substituted it is recommended to use an alkali metal borohydride, e.g. sodium borohydride. These compounds (IA') may be converted to IA'' compounds having an R_7 -radical other than hydroxy by reaction with an alkyl or aryl sulfonyl halide, e.g. tosyl chloride, mesyl chloride or a lower alkanoyl group providing agent, e.g. acetyl chloride.

This process aspect is conveniently effected in the presence of an inert organic solvent such as an alkanol, e.g., ethanol or methanol, an ether such as diethyl ether and tetrahydrofuran, dimethylformamide and the like. Suitably, an acid acceptor is provided to the reaction zone to accept the hydrogen halide formed when utilizing a halide, e.g., an aryl sulfonyl (e.g., tosyl) halide or an alkyl sulfonyl (e.g., mesyl) halide, with a compound of the formula IA' above. Suitable acid acceptors are tertiary amines, e.g., triethylamine, pyridine and the like.

Temperature and pressure are not critical aspects of the first stage of the process involving the conversion of the compound of the formula I above to the corresponding compound of the formula IA. However, the reaction is most preferably effected at about room temperature and atmospheric pressure for the preparation of compounds IA' and room temperature and above for the conversion of compounds IA' to IA'' bearing an R_7 radical other than hydroxy.

Reduction of IA compounds wherein A is $-(R_6)=N(\rightarrow O)-$ with hydrogen in the presence of platinum catalyst and acetic acid leads to IA'' compounds wherein R_7 is hydroxy.

Compounds of formula IA'' wherein R_7 is hydroxy, may be converted to the corresponding formula I unsaturated imine by treatment of the IA'' compound with an acetic anhydride/pyridine mixture. No other solvent is necessary for this reaction and temperature is not critical although the reaction is best effected at room temperature.

Compounds of formula IA'' above wherein R_7 is acyl, e.g. acetyl, an aliphatic sulfonyl group, e.g. mesyl or an aromatic sulfonyl group, e.g. tosyl may be converted to the corresponding formula I unsaturated imine by treatment of the IA'' compound with a non-aqueous base, e.g., potassium tertiary butoxide, in the presence of an inert solvent e.g., THF, DMF, etc. Such a reaction and the conditions at which it is run are well known in the art, see, for example U.S. Patent No. 3,625,957.

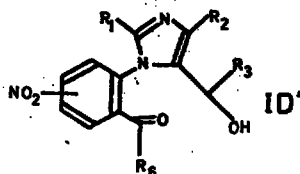
Compounds of formula IA' above may be converted to the analogous formula I unsaturated compounds by oxidation of the secondary amine at the 5-position. Such a selective oxidation may be accomplished by known oxidants and reaction schemes see, for example, U.S. Patent No. 3,322,753.

Conversion of compounds of formula I wherein R_4 is amino to compounds wherein

R_4 is nitro may be suitably affected by, for example, the Sandmeyer reaction wherein the amino group is replaced by a nitro group. The treatment of a formula I compound wherein



is aminophenyl with excess sodium nitrite in the presence of a copper sulfate/sodium sulfite mixture and utilizing as a solvent dilute sulfuric acid may result in an intermediate of the formula



wherein R_1 , R_2 , R_3 and R_6 are as in formula I which may then be converted to an analogous formula I compound. This process may be effected in a two-step sequence without isolation of the intermediate formed by treatment of the above formula ID' compound with phosphorus tribromide in an inert organic solvent e.g., dichloromethane at about -10° to 25°C (although temperature is not critical) and then subsequent treatment in situ with ammonia, preferably liquid ammonia which is allowed to warm to room temperature.

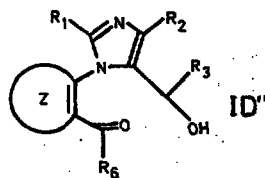
The Sandmeyer reaction has been found to also be applicable in producing compounds which contain a cyano, chloro or bromo group in place of a nitro group. Corresponding compounds of formula ID' can be converted to their ring closed analogs in the same manner as described above for the nitro compounds.

It is obvious to one skilled in the art that certain substituents may be attached during the above reactions, such as for example where R_1 or R_2 are a primary amine, alcohols, carboxylic acids or esters thereof, etc., but such vulnerable groups may be blocked by a suitable protecting group or modified before the above reaction sequence is carried out. Such methods of modifying or protecting groups subject to attack are well known in the art.

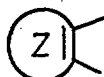
Compounds of the formula IA where A is



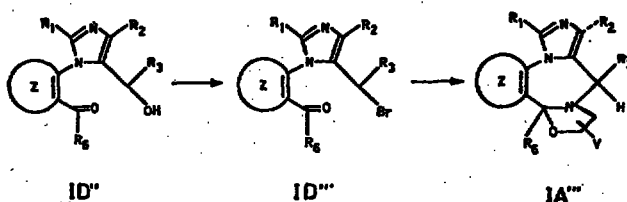
may be formed by the direct reaction of formula I compounds with ethylene oxide or propylene oxide in the presence of a Lewis acid catalyst (yielding a compound wherein V is hydrogen or methyl) or by the reaction of a compound of the formula



wherein R_1 , R_2 , R_3 ,



and R_6 are as in formula I, except that R_4 is not amino or substituted amino with phosphorus tribromide and subsequent treatment of the intermediate (ID''') with ethanolamine, a 1-alkyl substituted ethanolamine or a 2-alkyl substituted ethanolamine as shown in the following reaction scheme



The compounds of formula ID'' can be prepared by reacting a compound of formula ID or a corresponding thieno analog thereof with sodium nitrite in the presence of a compatible solvent such as water or dilute mineral acid. The temperature of the reaction may be -10°C to room temperature. The reaction of formula ID'' compounds with phosphorus tribromide is effected preferably in an inert organic solvent such as dichloromethane at about room temperature although such temperature is not critical.

The reaction of the compound of formula ID''' with ethanolamine or 1-alkyl or 2-alkyl substituted ethanolamine is effected in situ, i.e., with a suitable inert solvent such as dichloromethane, at a temperature range of -10°C to reflux, with about room temperature preferred.

The direct reaction of formula I compounds with ethylene oxide or propylene oxide is preferably catalyzed by a Lewis acid, e.g. titanium tetrachloride, boron trifluoride, etc.

In compounds of formula I and their analogs wherein a ketal group e.g. an ethylenedioxy group is present in an imidazobenzodiazepine, such ketal group may be converted to the corresponding ketone by subjecting the ketal group to a mild acid hydrolysis. The ketone can then be converted to a secondary or tertiary alcohol which is racemic in nature. The reaction conditions therefor, for the above two steps, are found in U.S. Patent No. 3,846,410.

As stated above compounds of formula I may be directly reacted with ethylene oxide or propylene oxide to produce formula IA''' compounds i.e., oxazolo type compounds. Reaction parameters and conditions to effect such a reaction are known in the art, see for example U.S. Patent No. 3,868,362.

Some functional groups in compounds of formula I and ID'' are liable to attack during formation of compounds of formula IA. They should be either suitably protected or introduced afterwards from other functional groups in similar manner as described herein.

Compounds of the formulae I, IA and ID and their pharmaceutically acceptable acid addition salts are useful as muscle relaxants, sedatives and Anticonvulsants and many are particularly useful when utilized in intravenous and intramuscular preparations because of the acid addition salts' solubility in aqueous solution.

The pharmacological activity of some representative compounds of the present invention was determined in standard screening tests. The compounds which were employed in these experiments were as follows:

- | | |
|--|---------------|
| 8-Chloro-6-(2-chlorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxamide | (Compound A); |
| 8-Chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid, 2,2-dimethylhydrazide | (Compound B); |
| 8-Chloro-N,N-diethyl-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxamide | (Compound C); |
| 8-Chloro-3-hydroxymethyl-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine | (Compound D); |
| and | |
| 8-Chloro-6-(2-fluorophenyl)-3-hydroxymethyl-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine | (Compound E). |

The results obtained in the inclined screen test, the foot shock test and the unanesthetized cat test using indicated compounds of the present invention are summarized in the following table.

33

Compound	Inclined Screen PD 50	Foot Shock 100% blocking dose	Unanesthetized Cat MED
A	3 mg/kg p.o.	0,5 mg/kg p.o.	
B	5 mg/kg p.o.	0,5 mg/kg p.o.	0,5 mg/kg p.o.
C	24,5 mg/kg p.o.	1 mg/kg p.o.	2,5 mg/kg p.o.
D	20 mg/kg p.o.	5 mg/kg p.o.	
E	150 mg/kg p.o.	1 mg/kg p.o.	0,25 mg/kg p.o.

As contemplated by this invention, the novel compounds of the formula I and their acid addition salts can be embodied in pharmaceutical dosage formulations containing from about 0.1 to about 40 mgs most preferably 1—40 mg with dosage adjusted to species and individual requirements. The novel compounds of formulae I, IA and ID and their pharmaceutically acceptable salts can be administered internally, for example, parenterally or enterally, in conventional pharmaceutical dosage forms. For example, they can be incorporated in conventional liquid or solid vehicles such as water, gelatin, starch, magnesium stearate, talc, vegetable oils and the like to provide tablets, elixirs, capsules, solutions, emulsions and the like according to acceptable pharmaceutical practices.

Certain intermediates are claimed *per se* in Specification No. 1,527,131 and applications Nos. 45342/78 (Serial No. 1 549 832), 45343/78 (Serial No. 1 549 833), 45344/78 (Serial No. 1 549 834) and 45345/78 (Serial No. 1 549 835), and a decarboxylation process is claimed in application No. 45346/78 (Serial No. 1 549 836).

The following examples illustrate the compounds according to the invention and their preparation.

Example 1.

A solution of 260 g (0.695 m) of 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one in 2 l of tetrahydrofuran and 250 ml of benzene was saturated with methylamine with cooling in an ice bath. A solution of 190 g (1 m) of titanium-tetrachloride in 250 ml of benzene was added through a dropping funnel within 15 minutes. After addition the mixture was stirred and refluxed for 3 hours. Water (600 ml) was added slowly to the cooled reaction mixture. The inorganic material was separated by filtration and was washed well with tetrahydrofuran. The water layer was separated and the organic phase was dried over sodiumsulfate and evaporated. The crystalline residue of 7-chloro-5-(2-fluorophenyl)-2-methylamino-3H-1,4-benzodiazepine was collected, m.p. 204—206°. The analytical sample was recrystallized from methylene chloride/ethanol, m.p. 204—206°.

A) Sodium nitrite, 8.63 g (0.125 m), was added in three portions over a 15 minute period to a solution of 30.15 g (0.1 m) of 7-chloro-5-(2-fluorophenyl)-2-methylamino-3H-1,4-benzodiazepine in 150 ml of glacial acetic acid. After stirring for 1 hour at room temperature the reaction mixture was diluted with water and extracted with methylene chloride. The extracts were washed with saturated sodium bicarbonate solution, were dried over sodium sulfate and evaporated, at the end azeotropically with toluene to yield 29 g of crude 7-chloro-5-(2-fluorophenyl)-2-(N-nitrosomethylamino)-3H-1,4-benzodiazepine as a yellow oil.

B) Sodium nitrite (27.6 g, 0.4 m) was added in portions over a period of 30 minutes to a solution of 90.45 g (0.3 m) of 7-chloro-5-(2-fluorophenyl)-2-methylamino-3H-1,4-benzodiazepine in 400 ml of glacial acetic acid. Following completed addition, the mixture was stirred at room temperature for 1 hour and was diluted with 1 l of water and extracted with methylene chloride. The extracts were washed twice with water and then with 10% aqueous sodium carbonate solution. The solution was dried and evaporated to yield crude 7-chloro-5-(2-fluorophenyl)-2-(N-nitrosomethylamino)-3H-1,4-benzodiazepine as a yellow oil.

This material was dissolved in 300 ml of dimethylformamide and was added to a mixture of 150 ml of dimethyl malonate, 40.4 g of potassium t-butoxide and 500 ml of dimethylformamide which had been stirred at room temperature for 10 minutes. The reaction mixture was stirred under nitrogen overnight at room temperature, was acidified by addition of 50 ml of glacial acetic acid, diluted with water and aqueous sodium carbonate solution, were dried over sodium sulfate and evaporated. Crystallization of the residue from ethanol yielded 7-chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine as colorless crystals, m.p. 170—172°. For analysis the product was recrystallized from methylene chloride/ethanol, melting point unchanged.

A mixture of 20 g (0.05 m) of 7-chloro-1,3-dihydro-2-(dimethoxymalonylidene)-

5-(2-fluorophenyl)-2H-1,4-benzodiazepine, 400 ml of methanol and 3.3 g (0.059 m) of potassium hydroxide was heated to reflux under nitrogen for 5 hours. After evaporation of the bulk of the solvent, the residue was gradually diluted with water and the precipitated crystals were collected, washed with water and dried to leave 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2-(dimethoxycarbonylmethylene)-2H-1,4-benzodiazepine, m.p. 158—160°.

For analysis it was recrystallized from methylene chloride/hexane, m.p. 161—162°.

Sodium nitrite (8.8 g, 0.125 m), was added to a solution of 28 g (0.08 m) of 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2-(methoxycarbonylmethylene)-2H-1,4-benzodiazepine in 250 ml glacial acetic acid. The mixture was stirred at room temperature for 10 minutes and then diluted with 250 ml of water. The crystalline product was filtered off, washed with water, methanol and ether and dried to leave 7-chloro-5-(2-fluorophenyl)- α -hydroxyimino-3H-1,4-benzodiazepine-2-acetic acid methyl ester as yellow crystals, m.p. 238—241° (dec.).

7-Chloro-5-(2-fluorophenyl)- α -hydroxyimino-3H-1,4-benzodiazepine-2-acetic acid methyl ester (11.25 g, 0.03 m) was hydrogenated at atmospheric pressure with Raney nickel in a mixture of 750 ml of tetrahydrofuran and 500 ml of methanol. The nickel was filtered off and the filtrate was evaporated. The residue was dissolved in 100 ml of methanol and 11 ml of triethyl orthoacetate and 5 ml of ethanolic hydrogen chloride (5%) was added. The mixture was heated to reflux for 10 minutes, was evaporated and the residue was partitioned between methylene chloride and aqueous sodium bicarbonate solution. The methylene chloride solution was dried and evaporated and the residue was chromatographed over 300 g of silica gel using methylene chloride/ethyl acetate 1:3 (v/v). The clean fractions were combined and evaporated and crystallized from ether to yield methyl-8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate, m.p. 162—164°. The analytical sample was recrystallized from ethyl acetate/hexane.

Example 2.

7-Chloro-5-(2-fluorophenyl)- α -hydroxyimino-3H-1,4-benzodiazepine-2-acetic acid methyl ester (11.25 g, 0.03 m) was dissolved in a mixture of 750 ml of tetrahydrofuran and 500 ml of methanol by warming. Raney nickel (20 g) was added and the mixture was hydrogenated at atmospheric pressure for 4 hours. The catalyst was removed by filtration and the filtrate was evaporated at the end azeotropically with toluene. The residue was dissolved in 100 ml of methanol. After addition of 10 ml of triethyl orthoformate and 5 ml of ethanolic hydrogen chloride (5%), the mixture was heated to reflux for 10 minutes. It was then evaporated and the residue was partitioned between methylene chloride and saturated aqueous sodium bicarbonate solution. The methylene chloride layer was separated, dried and evaporated and the residue was crystallized from ether to yield methyl-8-chloro-6-(2-fluorophenyl)-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate which was recrystallized from methylene chloride/ether/hexane, m.p. 179—181°.

Example 3.

A mixture of 7.7 g (0.02 m) of methyl-8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate, 2.24 g (0.04 m) of potassium hydroxide, 200 ml of methanol and 6 ml of water was heated to reflux for 3 1/2 hours. The solvent was partially evaporated and the residue was acidified with glacial acetic acid and diluted with water while hot. The precipitated crystals were collected after cooling in ice/water and were dried to yield 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid. For analysis it was recrystallized from methylene chloride/methanol/ethyl acetate, m.p. 271—274° (dec.).

Example 4.

A suspension of 1.85 g (5 mmol) of 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid in 25 ml of 2-propanol was heated on the steam bath and treated with 2.2 ml, 5N potassium hydroxide solution. After complete solution, the potassium salt was crystallized by cooling in ice/water. It was collected, washed with 2-propanol and ether and dried in high vacuum at 90° to yield potassium 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate hydrate as colorless crystals, m.p. 245—255°.

(2)

Example 5.

A mixture of 1.48 g (0.004 m) of methyl 8-chloro-6-(2-fluorophenyl)-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylate, 0.5 g (0.009 m) of potassium hydroxide, 50 ml of methanol and 2 ml of water was heated to reflux for 3 hours under an atmosphere of nitrogen. The methanol was partially evaporated and the residue was acidified with glacial acetic acid and diluted with water while the solution was still hot. The crystals were collected after cooling in ice/water and were dried in vacuum to yield 8-chloro-6-(2-fluorophenyl)-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylic acid, m.p. 245—247° (dec.).

Example 6.

A solution of 7.7 g (0.02 m) of methyl 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylate in 100 ml of tetrahydrofuran was added at 0—5° to a suspension of 2 g (0.05 m) of lithium aluminium hydride in 100 ml of ether. After addition the mixture was stirred for 15 minutes without cooling and then hydrolyzed by addition of 15 ml of water. The inorganic material was separated by filtration and washed with methylene chloride. The filtrate was dried and evaporated. Crystallization of the residue from methylene chloride/ether/hexane yielded 8-chloro-6-(2-fluorophenyl)-3-hydroxymethyl-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine which was recrystallized from ethyl acetate/methanol for analysis, m.p. 233—235°.

Example 7.

A mixture of 4 g of 8-chloro-6-(2-fluorophenyl)-3-hydroxymethyl-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine, 200 ml of methylene chloride and 20 g of activated manganese dioxide was stirred at room temperature for 1 hour. The manganese dioxide was removed by filtration and washed well with methylene chloride. The filtrate was evaporated and the residue was crystallized from methylene chloride/ether/hexane to yield 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxaldehyde with m.p. 190—192° after recrystallization from methylene chloride/ethyl acetate/hexane.

Example 8.

A solution of 0.71 g (2 mmol) of 8-chloro-6-(2-fluorophenyl)-3-hydroxymethyl-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine in 20 ml of pyridine was treated with 2 ml of acetic anhydride. After standing at room temperature overnight, the solvent was evaporated under reduced pressure and the residue was partitioned between methylene chloride and sodium bicarbonate solution. The organic phase was dried and evaporated. The residue did not crystallize and was purified by chromatography over 30 g of silica gel using methylene chloride/ethyl acetate 1:3. The homogeneous fractions were combined and evaporated, yielding 3-acetoxymethyl-8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine which did not crystallize and was characterized spectroscopically.

Example 9.

Potassium t-butoxide (26 g, 0.232 m) was added to a mixture of 300 ml of dimethylformamide and 50 ml (0.44 m) of dimethyl malonate. After stirring under nitrogen for 10 minutes a solution of 66 g (0.209 m) of 7-chloro-2-(N-nitrosomethylamino)-5-phenyl-3H-1,4-benzodiazepine 4-oxide in 100 ml of dimethyl formamide was added over a 10 minute period. The mixture was then slowly heated on the steam bath and kept for 10 minutes at 65°. After cooling to room temperature 40 ml of glacial acetic acid was added followed by 1 l of water over a period of 30 minutes with occasional scratching. The precipitated crystals were collected, washed with water and dissolved in methylene chloride. The solution was dried over sodium sulfate and concentrated to a small volume. The product was crystallized by addition of hexane to yield 7-chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2H-1,4-benzodiazepine 4-oxide, m.p. 188—190°. The analytical sample was recrystallized from methylene chloride/hexane, m.p. 194—195°.

A mixture of 40.8 g (0.1 m) of 7-chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2H-1,4-benzodiazepine 4-oxide, 250 ml of methanol, 250 ml of tetrahydrofuran and 1 tablespoonful of Raney nickel was hydrogenated at atmospheric pressure for 5 hours. The catalyst was removed by filtration and the filtrate was evaporated. Crystallization of the residue from methylene chloride/2-propanol yielded 7-chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2H-1,4-benzo-

diazepine as colorless crystals, m.p. 160—163°. For analysis it was recrystallized from 2-propanol, m.p. 165—166°.

A second modification of crystals with m.p. 138—140° was obtained in some instances.

5 B) Phosphorus trichloride (4 ml) was added to a solution of 4 g (0.01 m) of 7-chloro-1,3-dihydro-2-(2-dimethoxymalonylidene)-5-phenyl-2H-1,4-benzodiazepine 4-oxide in 100 ml of methylene chloride. After sitting at room temperature overnight, the solution was washed with 10% aqueous sodium carbonate solution. The methylene chloride layer was dried and evaporated. Crystallization of the residue from 2-propanol and recrystallization from methylene chloride/2-propanol yielded 7-chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2H-1,4-benzodiazepine m.p. 165—166°.

10 A mixture of 115 g (0.3 m) of 7-chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2H-1,4-benzodiazepine, 1.5 l of methanol and 14.4 g (0.36 m) of sodium hydroxide was heated to reflux for 5 hours under an atmosphere of nitrogen. The cool reaction mixture was gradually diluted with 2.5 l of water with ice cooling. The precipitated crystals were collected, washed with water and dried in vacuum at 60° to yield 7-chloro-1,3-dihydro-2-(methoxycarbonylmethylene)-5-phenyl-2H-1,4-benzodiazepine as an off-white product, m.p. 167—170°. The analytical sample was recrystallized from ether, m.p. 171—173°.

15 Sodium nitrite (2.8 g, 0.04 m) was added to a solution of 8 g (0.025 m) of 7-chloro-1,3-dihydro-2-(methoxycarbonylmethylene)-5-phenyl-2H-1,4-benzodiazepine in 100 ml of glacial acetic acid. The mixture was stirred under nitrogen for 10 minutes. The product started to crystallize out after a few minutes. After dilution with 100 ml of water, the precipitated product was collected, washed with water, dried and recrystallized from tetrahydrofuran/methanol to yield 7-chloro- α -hydroxyimino-5-phenyl-3H-1,4-benzodiazepine-2-acetic acid methyl ester as yellow crystals, m.p. 235—237° (dec.).

20 7-Chloro- α -hydroxyimino-5-phenyl-3H-1,4-benzodiazepine-2-acetic acid methyl ester (3.6 g, 0.01 m) was dissolved in a mixture of 200 ml of tetrahydrofuran and 100 ml of methanol by warming. Raney nickel (1 teaspoonful) was added and the mixture was hydrogenated at atmospheric pressure until hydrogen uptake flattened (1 hour and 10 minutes). The catalyst was removed by filtration and the filtrate was evaporated at the end azeotropically with toluene. The residue was dissolved in 20 ml of methanol. Following the addition of 3 ml of triethyl ortho-acetate and 0.3 ml ethanolic hydrogen chloride (5%), the solution was heated to reflux for 5 minutes. The residue left after evaporation was partitioned between methylene chloride and saturated aqueous sodium bicarbonate solution. The organic phase was separated, dried and evaporated. Crystallization of the residue from ether yielded methyl-8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylate, which after recrystallization from methylene chloride/ether/hexane has a melting point of 254—256°.

Example 10.

45 A mixture of 7.3 g (0.02 m) of methyl 8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylate, 2.24 g (0.04 m) of potassium hydroxide, 200 ml of methanol and 6 ml of water was heated to reflux for 4 hours. The methanol was partially removed under reduced pressure and the residue was acidified with glacial acetic acid and crystallized by addition of water. The crystals were collected, washed with water and dried to yield 8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylic acid as an off-white product. For analysis it was recrystallized from ethyl acetate, m.p. 270—273° (dec.).

Example 11.

55 A solution of 0.73 g (2 mmol) of methyl 8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylate in 50 ml of tetrahydrofuran was added to a suspension of 0.3 g (7.5 mmol) of lithium aluminum hydride in 20 ml of tetrahydrofuran cooled to -10°.

60 Following addition the mixture was stirred for 30 minutes without cooling and was hydrolyzed by addition of 2 ml of water. The inorganic material was filtered off and the filtrate was dried and evaporated. Crystallization of the residue from methylene chloride/ether/hexane yielded 8-chloro-3-hydroxymethyl-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine as colorless crystals, m.p. 252—255°.

Example 12.

A mixture of 3 g of 8-chloro-3-hydroxymethyl-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine, 300 ml of methylenechloride and 15 g of activated manganese dioxide was stirred at room temperature for 1 hour. The manganese dioxide was filtered off and washed with methylene chloride. The filtrate was evaporated and the residue was crystallized from methylene chloride/ether/hexane to yield 8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxaldehyde, m.p. 218—220°.

Example 13.

Methyl 8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylate (0.74 g, 2 mmol) was heated in 30 ml methanolic ammonia at 120° for 18 hours in a sealed vessel. The solvent was evaporated and the residue was recrystallized from methylene chloride/ethanol to yield 8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxamide as colorless crystals, m.p. 335—340°.

Example 14.

A mixture of 0.74 g (2 mmol) of methyl 8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylate and 20 ml of ethanol containing 25% of methylamine was heated at 120° for 18 hours in a sealed vessel. The solvent was evaporated and the residue was crystallized from methylene chloride/ethanol to yield 8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-N-methyl-carboxamide m.p. 260—263°. The analytical sample was recrystallized from tetrahydrofuran/ethanol.

Example 15.

Zinc dust (2 g) was added to a solution of 1.83 g (5 mmol) of methyl 8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylate in 50 ml of methylene chloride and 10 ml of glacial acetic acid. The mixture was stirred for 2 hours at room temperature. The inorganic material was filtered off and the filtrate was washed with dilute aqueous ammonia. The methylene chloride solution was dried and evaporated. Crystallization of the residue from methylene chloride/ethyl acetate/ether yielded methyl 8-chloro-5,6-dihydro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylate as colorless crystals, m.p. 233—235°. The analytical sample was recrystallized from ethyl acetate/methylene chloride/methanol, m.p. 234—236°.

Example 16.

A mixture of 7.7 g of methyl 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylate, 100 ml of isobutanol and 20 ml of hydrazine was heated to reflux for 1 hour. The crude product obtained after evaporation was chromatographed over 250 g of silica gel using 5% ethanol in methylene chloride. The clean fractions were combined and evaporated. Crystallization of the residue from methylene chloride/ether yielded 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylic acid hydrazide as colorless crystals, m.p. 235—237°.

Example 17.

A mixture of 7.4 g of methyl 8-chloro-5,6-dihydro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylate, 20 ml of hydrazine and 200 ml of isobutanol was heated to reflux for 3 hours. After evaporation under reduced pressure, the residue was crystallized from ethanol/ether to yield 8-chloro-5,6-dihydro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylic acid hydrazide, m.p. 225—230°. The analytical sample was recrystallized from ethyl acetate/methanol, m.p. 228—230°.

Example 18.

A solution of 0.73 g (2 mmol) of methyl 8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylate in 20 ml of dry dimethylformamide was cooled to -30° with stirring under nitrogen. Potassium t-butoxide (0.25 g, 2.2 mmol) was added and after stirring for 5 minutes 0.3 g (2.1 mmol) of methyl iodide was added. The mixture was allowed to reach room temperature within 1 hour and was then partitioned between saturated aqueous bicarbonate and methylene chloride. The methylene chloride layer was washed with water, dried and evaporated. Crystallization of the residue from ether yielded methyl 8-chloro-1,4-dimethyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylate as colorless crystals, m.p. 217—221°. The analytical sample was recrystallized from ethyl acetate/hexane, m.p. 220—222°.

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Example 19.

Potassium t-butoxide (0.25 g, 2.2 mmol) was added to a solution of 0.74 g (2 mmol) of methyl 8-chloro-6-(2-fluorophenyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate in 20 ml of dimethylformamide cooled to -30°. After stirring for 5 minutes under nitrogen 0.32 g (2.26 mmol) of methyl iodide was added and the reaction mixture was allowed to warm to room temperature within 30 minutes. It was then partitioned between aqueous bicarbonate and methylene chloride. The organic layer was washed with water, dried and evaporated. The residue was crystallized from ether to yield methyl 8-chloro-6-(2-fluorophenyl)-4-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate, which after recrystallization from ethyl acetate/hexane, had a melting point of 190—191°.

Example 20.

8 - Chloro - 1 - methyl - 6 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine-3 - carboxaldehyde (3.4 g, 0.01 m) was partially dissolved by heating in 200 ml of ethanol. Hydroxyamine hydrochloride (1.05 g, 0.015 m) and 4 ml of triethylamine was added and the mixture was heated on the steambath until solution was complete. The solvent was partially evaporated and the product was crystallized by dilution with water. The crystals were collected, washed with ethanol and ether and dried to yield 8 - chloro - 1 - methyl - 6 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxaldoxime, m.p. 280—282°C (dec.). The analytical sample was recrystallized from ethanol/tetrahydrofuran.

Example 21.

8 - Chloro - 1 - methyl - 6 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine-3 - carboxaldoxime (2.1 g) was dissolved by warming in 100 ml of ethanol and 100 ml of tetrahydrofuran. The solution was hydrogenated at atmospheric pressure in presence of Raney nickel (1 teaspoonful) for 3 hours. The catalyst was filtered off and the filtrate was evaporated. Crystallization of the residue from 2-propanol/ether yielded 3 - aminomethyl - 8 - chloro - 1 - methyl - 6 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine. For analysis it was recrystallized from ethanol/ether, m.p. 217—219°.

Example 22.

A solution of 1.7 g (0.005 m) of 8-chloro-3-hydroxymethyl-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine in 5 ml of thionyl chloride was stirred at room temperature for 30 minutes. The hydrochloride of 8-chloro-3-chloromethyl-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine was crystallized by addition of ethyl acetate and ether. The collected crystals were partitioned between methylene chloride and saturated aqueous sodium bicarbonate solution. The organic phase was dried and evaporated. Crystallization of the residue from methylene chloride/ether yielded 8-chloro - 3 - chloromethyl - 1 - methyl - 6 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine which was heated to reflux for 10 minutes in 50 ml of methanol containing 0.5 g of sodium methoxide. The methanol was evaporated and the residue was partitioned between methylene chloride and saturated sodium bicarbonate solution. The organic phase was dried and evaporated.

Chromatography of this crude material over 30 g of silica gel using methylene chloride/ethyl acetate 1:3 (v/v) yielded 8-chloro-3-methoxymethyl-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine as colorless crystals, m.p. 163—165°C., crystallized from ethylacetate/hexane.

Example 23.

Triethylamine (2 ml) and 0.5 g of methoxyamine hydrochloride was added to a warm solution of 0.67 g (0.002 m) of 8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxaldehyde in 40 ml of ethanol. The mixture was allowed to sit for 30 minutes. The solvent was partially evaporated and the product was crystallized by diluting with water. The crystals were collected and dried to leave 8 - chloro - 3 - (N - methoxyiminomethyl) - 1 - methyl - 6 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine. The analytical sample was recrystallized from ether, m.p. 193—195°C.

Example 24.

Pyrrolidine (4 ml) was added to a solution of acid chloride prepared from 1.85 g of 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylic acid and 1.25 g of phosphorus pentachloride in 250 ml of methylene chloride. Subsequently 100 ml of 10% aqueous sodium carbonate solution was added and the two phase mixture was stirred at room temperature for 1 hour. The organic phase was separated, dried and evaporated. Crystallization of the residue from 2 - propanol/ether gave 1 - [8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H-

imidazo[1,5-a][1,4]benzodiazepin - 3 - oyl]pyrrolidine as a colorless product, m.p. 220—221° after recrystallization from ethyl acetate/hexane.

Example 25.

2,2-Dimethylhydrazine (10 ml) was added to a solution of acid chloride prepared as described in Example 56 from 1.85 g of 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid and 1.25 g of phosphorus pentachloride in 250 ml of methylene chloride. After addition of 100 ml of 10% aqueous sodium carbonate solution the mixture was stirred for 30 minutes at room temperature. The organic layer was separated, dried and evaporated. Crystallization of the residue from ether/ethanol yielded 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid, 2,2-dimethylhydrazide as a colorless product. The analytical sample was purified by chromatography over 30 fold amount of silica gel, using 10% (v/v) of ethanol in methylene chloride. It was crystallized from methylene chloride/ethyl acetate/hexane, m.p. 238—240°.

Example 26.

A mixture of 1.85 g (5 mmol) of 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid, 1.5 g of diphenylphosphoric azide, 30 ml of dimethylformamide and 2 ml of triethylamine was stirred at room temperature for 15 minutes. The solvent was removed under reduced pressure, at the end azeotropically with xylene. Crystallization of the residue from ethyl acetate yielded 8-chloro-6-(2-fluorophenyl)-3-(methoxycarbonylamino)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine which was recrystallized from methylene chloride/methanol/ethyl acetate, m.p. 270—275°. The analytical sample was recrystallized from tetrahydrofuran/ethanol, m.p. 272—275° (dec.).

Example 27.

A mixture of 1.85 g (5 mmol) of 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid, 1.5 g of diphenylphosphoric azide, 10 ml of dimethylformamide, 25 ml of toluene and 2 ml of triethylamine was stirred at room temperature for 10 minutes. Benzyl alcohol (10 ml) was added and the mixture was heated to reflux for 30 minutes. After evaporation of the solvents under reduced pressure, the residue was crystallized from ether to yield 3-(benzyloxycarbonylamino)-8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine, m.p. 250—253°. The analytical sample was recrystallized from methylene chloride/methanol/ethyl acetate, m.p. 253—255°.

Example 28.

Sodium nitrite (1.8 g, 2.5 mmol) was added in portions over a 5 minute period to a solution of 3.7 g (10 mmol) of 8-chloro-5,6-dihydro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid hydrazide in 35 ml of glacial acetic acid. After stirring for 30 minutes at room temperature, the azide was precipitated by addition of ice and water. The solids were collected and dissolved in methylene chloride. The solution was washed with water, sodium bicarbonate solution and ice, dried and evaporated. The residue was dissolved in a mixture of 100 ml of dimethylformamide and 25 ml of methanol and heated to reflux for 20 minutes (temperature ca. 103°). The solvents were removed under reduced pressure and the residue was crystallized from methanol/ethyl acetate to yield 8-chloro-3-methoxycarbonylamino-1-methyl-5-nitroso-6-phenyl-5,6-dihydro-4H-imidazo[1,5-a][1,4]benzodiazepine as colorless crystals, m.p. 255—258° (dec). The analytical sample was recrystallized from tetrahydrofuran/ethanol and had the same melting point.

Example 29.

8-Chloro-3-methoxycarbonylamino-1-methyl-5-nitroso-6-phenyl-5,6-dihydro-4H-imidazo[1,5-a][1,4]benzodiazepine (2.06 g, 5 mmol) was dissolved by warming in a mixture of 200 ml of tetrahydrofuran and 100 ml of methanol. After addition of Raney nickel (2 teaspoonsful) the mixture was hydrogenated at atmospheric pressure for 1 hour. The catalyst was separated by filtration and the filtrate was evaporated. Crystallization of the residue from methanol yielded 8-chloro-5,6-dihydro-3-(methoxycarbonylamino)-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine as colorless crystals, m.p. 280—290° (dec). The analytical sample was recrystallized from ethyl acetate/methanol.

Example 30.

Sodium methoxide (0.3 g) was added to a solution of 1 g of 1 - acetoxymethyl-8 - chloro - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine in 20 ml of methanol. After standing for 10 minutes at room temperature, the separated crystals were collected, washed with aqueous methanol, methanol and ether to yield colorless 8 - chloro - 6 - (2 - fluorophenyl) - 1 - hydroxymethyl - 4H - imidazo[1,5-a][1,4]benzodiazepine. The analytical sample was recrystallized from methylene chloride/ethanol, m.p. 258—260°.

Example 31.

A mixture of 0.2 g of 8-chloro-6-(2-fluorophenyl)-1-hydroxymethyl-4H-imidazo[1,5-a][1,4]benzodiazepine, 20 ml of methylene chloride and 1 g of activated manganese dioxide was stirred at room temperature for 2 hours. The manganese dioxide was removed by filtration over Celite (trade mark) and the filtrate was evaporated. Crystallization of the residue from methylene chloride/ethyl acetate/hexane gave 8 - chloro - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 1 - carboxaldehyde as colorless crystals, m.p. 182—183°.

Example 32.

N-bromosuccinimide (13.7 g, 0.077 m) was added to a stirred solution of 8-chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine (10 g, 0.030 m) in 450 ml of chloroform and 30 ml of glacial acetic acid. The mixture was stirred under reflux for 1.5 hours and then cooled. The mixture was then washed with saturated sodium bicarbonate solution and the chloroform layer dried and evaporated. The oily residue was chromatographed using 150 g of Woelm neutral aluminum oxide. Impurities were removed first with methylene chloride, followed by ethyl acetate to remove the product. The fractions containing product were combined and evaporated. Crystallization of the residue with ether yielded 3 - bromo - 8-chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine, m.p. 201—205°. The analytical sample was recrystallized from ether/hexane, m.p. 203—205°.

Example 33.

Phosphorus pentachloride (1.25 g, 0.006 m) was added to a suspension of 1.85 g (0.005 m) of 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylic acid in 250 ml of methylene chloride. After stirring for 30 minutes in an ice bath, 15 ml of diethylamine was added followed by 100 ml of 10% aqueous sodium carbonate solution. The two phase system was stirred for 30 minutes at room temperature. The organic layer was separated, dried over sodium sulfate and evaporated. Crystallization of the residue from methylene chloride/ether yielded 8 - chloro - N,N - diethyl - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide, m.p. 182—188°. The analytical sample was recrystallized from ethyl acetate/hexane, m.p. 183—185°.

Example 34.

2-(Dimethylamino)ethylamine (5 ml) was added to a solution of acid chloride prepared as described in Example 71 from 1.85 g (5 mmol) of 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid and 1.25 g of phosphorus pentachloride in 250 ml of methylene chloride. Following the addition of 100 ml of 10% aqueous sodium carbonate solution, the mixture was stirred for 30 minutes at room temperature. The methylene chloride layer was separated, dried and evaporated. Crystallization of the residue from 2-propanol/ether yielded 8 - chloro - N - (2 - dimethylaminoethyl) - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide, m.p. 209—211°. The analytical sample was recrystallized from ethyl acetate/hexane, m.p. 210—213°.

Example 35.

Methanolic ammonia (20 ml, 25%) was added to a solution of acid chloride prepared as described in Example 71 from 1.85 g of 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid and 1.25 g of phosphorus pentachloride in 250 ml of methylene chloride. After stirring for 10 minutes, 50 ml of 10% aqueous sodium carbonate solution was added and stirring was continued for 1 hour at room temperature. The methylene chloride layer was separated, dried and evaporated. The residue was dissolved in a mixture of methylene chloride and ethanol. The solution was filtered over a bed of silica gel and the filtrate was evaporated. Crystallization of the residue from ethanol gave 8-chloro-6-(2-fluorophenyl)-1-methyl-

4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxamide as colorless crystals. The analytical sample was recrystallized from ethanol/tetrahydrofuran, m.p. 300—305°.

Example 36.

Dimethylamine (4 ml) was added to a solution of the acid chloride prepared as in Example 71 from 1.85 g (0.005 m) of 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid, and 1.25 g (0.006 m) of phosphorus pentachloride in 250 ml of methylene chloride. After stirring at room temperature for 1 hour, the reaction mixture was washed with 10% aqueous sodium carbonate solution, was dried and evaporated. The residue was purified by chromatography over 40 g of silica gel using 5% (v/v) of ethanol in methylene chloride. Crystallization of the combined clean fractions from ether/hexane yielded 8-chloro-6-(2-fluorophenyl)-1-N,N-trimethyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxamide as colorless crystals, m.p. 177—179°. A lower melting modification with m.p. 158—160° was also observed.

Example 37.

A solution of 10 g (0.0358 m) of 7-cyano-2,3-dihydro-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one in 150 ml of dry tetrahydrofuran under argon was treated with 2.4 g (0.0537 m) of 54% sodium hydride and the reaction was stirred and refluxed for 1 hour. This was cooled to 0° and 13.7 g (0.0537 m) of phosphorodimorpholidic chloride was added. After 18 hours the reaction mixture was filtered, concentrated to a small volume and ether was added. The precipitate was filtered and recrystallized from a mixture of dichloromethane and ether to give 7-cyano-5-(2-fluorophenyl)-2-bis-(morpholino)phosphinyloxy-3H-1,4-benzodiazepine as white rods, m.p. 194—197°.

Example 38.

To 100 ml of dry N,N-dimethylformamide under nitrogen was added 1.6 g (0.036 m) of 54% sodium hydride, and 8.3 g (0.038 m) of acetamidodiethyl malonate was added with stirring. After 30 minutes 10 g (0.02 m) of 7-cyano-5-(2-fluorophenyl)-2-bis-(morpholino)phosphinyloxy-3H-1,4-benzodiazepine was added and after 64 hours the reaction was poured into ice water containing 4 ml of acetic acid. This was filtered and the solid was dissolved in 100 ml of dichloromethane, which was washed with 50 ml of water, dried over anhydrous sodium sulfate and concentrated to a small volume. This solution was chromatographed over a column of Florisil (trade mark) and eluted with 2 l of dichloromethane which was discarded. It was then eluted with 1 l of a mixture of dichloromethane and ether (10/1) and then with 2 l of ether. The ether fraction was recrystallized twice from a mixture of dichloromethane and ether to give (acetyl amino) [7-cyano-5-(2-fluorophenyl)-3H-1,4-benzodiazepine-2-yl]malonic acid diethyl ester as white prisms, m.p. 138—140°.

The column was eluted with 1.5 l of a mixture of ethyl acetate and methanol (10/1). The eluent was concentrated and the residue was crystallized from ether. Recrystallization from a mixture of dichloromethane and ether gave ethyl 8-cyano-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate as off white prisms, m.p. 272—274°.

Example 39.

A solution of 0.5 g (0.00129 m) of ethyl 8-cyano-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate in 100 ml of ethanol and 10 ml of water was treated with 0.14 g (0.0026 m) of potassium hydroxide. After refluxing for 30 minutes the reaction was evaporated and 10 ml of water was added. This was acidified with acetic acid, filtered and extracted with 20 ml of dichloromethane, which was separated, dried and evaporated. About 0.2 g of the hydrolyzed product was obtained from the filtration, and the same amount was obtained from the extraction.

Example 40.

A solution of 3.75 g (0.01 m) of 7-chloro-5-(2-fluorophenyl)-alpha-hydroxyimino-3H-1,4-benzodiazepine-2-acetic acid methyl ester in 300 ml of tetrahydrofuran and 200 ml of methanol was hydrogenated at atmospheric pressure for 1 1/2 hour in presence of one teaspoonful of Raney nickel. The catalyst was separated by filtration over Celite and the filtrate was evaporated under reduced pressure, at the end azotropically with toluene. The residue was dissolved in 20 ml of pyridine and treated with 4 ml of benzoylchloride. After sitting at room temperature for 15 minutes, the reaction mixture was partitioned between methylene chloride and 1N sodium hydroxide solution. The organic layer was dried and evaporated, at the end azeotropic-

ally with toluene. Crystallization of the residue from ether yielded 2 - [benzoylamino]-methoxycarbonylmethylene] - 7 - chloro - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepine, m.p. 210—213°. The analytical sample was recrystallized from ethyl acetate/hexane, m.p. 217—219° with softening at 150—160°.

A solution of 1.15 g (2.5 mmol) of 2 - [(benzoylamino) - methoxycarbonylmethylene] - 7 - chloro - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepine in 10 ml of hexamethyl phosphoric triamide was heated to reflux for 10 minutes. The dark mixture was partitioned between water and ether/methylene chloride. The organic layer was washed with water, dried and evaporated. The residue was dissolved in methylene chloride and filtered over activated aluminum oxide with ethyl acetate. The filtrate was evaporated and chromatographed over 20 g of silica gel using 10% (v/v) ethyl acetate in methylene chloride. Crystallization of the combined clean fractions from ether/hexane gave methyl 8 - chloro - 6 - (2 - fluorophenyl) - 1 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate, mp. 208—209°.

Example 41.

To a solution of 2.66 g (5.77 mmol) of methyl 8 - chloro - 6 - (2 - fluorophenyl) - 1 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate in 50 ml of refluxing methanol was added a solution of 755 mg (11.5 mmol) of potassium hydroxide in 10 ml of water and the resulting mixture was heated for 2.5 hr. The solvent was removed in vacuo, the residue was dissolved in 50 ml of hot acetic acid and the solution was then poured into 100 ml of cold water. The product was collected, washed with water and air dried to give 8 - chloro - 6 - (2 - fluorophenyl) - 1 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylic acid as an off-white solid. An analytical sample was recrystallized from benzene, mp. 267—269°.

Example 42.

A solution of 1.0 g (2.31 mmol) of 8 - chloro - 6 - (2 - fluorophenyl) - 1 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylic acid in 5 ml of thionyl chloride was refluxed for 1/2 hr., then cautiously added dropwise to 70 ml of cold 40% aqueous dimethylamine. The brown solid was collected, washed with water, dried and chromatographed on silica gel using ethyl acetate as the eluent to give N,N - dimethyl - [8 - chloro - 6 - (2 - fluorophenyl) - 1 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine] - 3 - carboxamide as a brown foam. Recrystallization three times from acetone/water gave the analytical sample, mp. 221—223°.

Example 43.

A solution of 1.0 g (2.31 mmol) of 8 - chloro - 6 - (2 - fluorophenyl) - 1 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylic acid in 5 ml of thionyl chloride was refluxed for 1/2 hr., then cautiously added dropwise to 70 ml of cold ammonium hydroxide. The pink solid was collected, washed with water, air dried and chromatographed on silica gel using ethyl acetate as the eluent to give 8 - chloro - 6 - (2 - fluorophenyl) - 1 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide as a brown foam. Trituration with acetone gave the analytical sample as a white powder, mp. 260—262°.

Example 44.

7 - Chloro - 5 - (2 - fluorophenyl) - 2 - [bis(morpholino)phosphinyloxy] - 3H - 1,4 - benzodiazepine (5.3 g, 0.01 m) was added to a mixture of 10 ml of dimethyl malonate, 20 ml of dimethylformamide and 2.2 g (0.02 m) of potassium t-butoxide which had been stirred at room temperature for 5 minutes under nitrogen. The reaction mixture was then stirred and heated on the steam bath for 15 minutes. After addition of 1.5 ml of glacial acetic acid the product was crystallized by gradually diluting with water. The precipitated crystals were collected, washed with water and dried in vacuo to yield 7 - chloro - 5 - (2 - chlorophenyl) - 2 - dimethoxymalonylidene - 1,3 - dihydro - 2H - 1,4 - benzodiazepine which was recrystallized for analysis from ethyl acetate, mp. 205—207°.

A mixture of 12.6 g (0.03 m) of 7 - chloro - 5 - (2 - chlorophenyl) - 2 - dimethoxymalonylidene - 1,3 - dihydro - 2H - 1,4 - benzodiazepine, 300 ml of methanol and 2.1 g (0.0375 m) of potassium hydroxide was heated to reflux under nitrogen for 4 1/2 hours, 200 ml of methanol were distilled off and the residue was diluted with water. The separated crystals were collected, washed with water and dried to yield 7 - chloro - 5 - (2 - chlorophenyl) - 2,3 - dihydro - 2 - [(methoxycarbonyl)methylene] - 1H - 1,4 - benzodiazepine, m.p. 154—158°. For analysis it was recrystallized from methylene chloride/methanol, m.p. 158—159°.

Sodium nitrite (2.2 g, 0.031 m) was added in portions over 5 minutes to a stirred solution of 7.2 g (0.02 m) of 7 - chloro - 5 - (2 - chlorophenyl) - 2,3 - dihydro - 2 - [(methoxycarbonyl) - methylene] - 1H - 1,4 - benzodiazepine in 75 ml of glacial acetic acid. After stirring for additional 15 minutes, the mixture was diluted with 100 ml of water and the precipitated crystals were collected, washed with water, methanol and ether to leave crude 7 - chloro - 5 - (2 - chlorophenyl) - alpha - hydroxyimino - 3H - 1,4 - benzodiazepine - 2 - acetic acid methyl ester which was recrystallized from tetrahydrofuran/methanol to yield light yellow crystals, m.p. 223—225° (dec.).

A solution of 3.9 g (0.01 m) of 7 - chloro - 5 - (2 - chlorophenyl) - alpha - hydroxyimino - 3H - 1,4 - benzodiazepine - 2 - acetic acid methyl ester in 100 ml of tetrahydrofuran and 50 ml of methanol was hydrogenated in the presence of 2 teaspoonsful of Raney nickel for 1 1/2 hours at atmospheric pressure. The catalyst was removed by filtration and the filtrate was evaporated, at the end azeotropically with toluene. The residue was dissolved in 20 ml of ethanol. Triethylorthoacetate (3 ml) and 0.2 ml of ethanolic hydrogen chloride (10%) was added and the mixture was heated to reflux for 15 minutes, and then evaporated to dryness. The residue was partitioned between methylene chloride and saturated aqueous bicarbonate solution. The organic layer was separated, dried over sodium sulfate and evaporated. Crystallization of the residue from methylene chloride/ether yielded methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate, m.p. 225—227°. The analytical sample was recrystallized from 2-propanol and ethyl acetate, m.p. 228—230°.

Example 45.

A solution of 1.2 g (3 mmol) of methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate in 10 ml of tetrahydrofuran was added to a suspension of 0.4 g (10 mmol) of lithium aluminum hydride in 30 ml of ether cooled to 10°. Following the addition, the mixture was stirred at room temperature for 10 minutes and hydrolyzed by addition of 2 ml of water. The inorganic material was filtered off and the filtrate was evaporated. Crystallization of the residue from methylene chloride/ether yielded 8 - chloro - 6 - (2 - chlorophenyl) - 3 - hydroxymethyl - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine, m.p. 215—217°. The analytical sample was recrystallized from tetrahydrofuran/hexane, m.p. 217—218°.

Example 46.

7 - Chloro - 5 - (2 - chlorophenyl) - alpha - hydroxyimino - 3H - 1,4 - benzodiazepine - 2 - acetic acid methyl ester (7.8 g, 0.02 m) was dissolved in a mixture of 200 ml of tetrahydrofuran and 100 ml of ethanol by warming. The solution was hydrogenated in the presence of Raney nickel (2 teaspoonsful) at atmospheric pressure for 2 hours. The catalyst was separated by filtration over Celite and the filtrate was evaporated under reduced pressure. Crystallization of the residue from ethanol gave 2 - [(amino) - methoxycarbonylmethylene] - 7 - chloro - 5 - (2 - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepine as orange crystals with m.p. 115—117° (dec.). Recrystallization of this solvated product from ether/hexane gave yellow needles with m.p. 145—150° (dec.).

Acetaldehyde (0.25 ml) was added to a solution of 0.5 g of 2 - [(amino)methoxycarbonylmethylene] - 7 - chloro - 5 - (2 - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepine in 25 ml of methylene chloride. Following the addition of molecular sieves 5A, the mixture was stirred at room temperature for 15 minutes. Activated manganese dioxide (1 g) was then added and stirring was continued for 30 minutes. The solid material was separated by filtration over Celite and the filtrate was evaporated. Crystallization of the residue from ethyl acetate/hexane gave methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate, m.p. 228—230°.

Example 47.

A stirred suspension of 4 g (0.09 m) of a 54% mineral oil dispersion of sodium hydride in 315 ml of dimethylformamide under argon was treated with 21 g (0.096 m) of diethyl acetamidomalonate in several portions. Stirring at room temperature was continued for 30 minutes and then 31.4 g (0.06 m) of 7 - chloro - 5 - (2 - chlorophenyl) - 2 - [bis(morpholino)phosphinyloxy] - 3H - 1,4 - benzodiazepine was added in one portion. After stirring an additional 7 hours at room temperature the dark mixture was poured over ice and acetic acid with stirring and diluted with water (ca. 2 l) to give a cream colored solid. The solid was filtered, washed with water and air dried on the funnel to give acetyl amino[7 - chloro - 5 - (2 - chlorophenyl) - 3H - 1,4 -

benzodiazepin - 2 - yl]malonic acid diethyl ester. The dried product was stirred with a small amount of 2-propanol while warming on a steam bath until solution occurred. Cooling to room temperature gave an off-white solid. Recrystallization of a sample from 8-fold amount of ethanol gave off-white micro-needles, m.p. 153—155°.

- 5 A solution of sodium ethylate was prepared by dissolving 0.8 g (0.04 g atm) of sodium metal in 50 ml of absolute ethanol and protected by a drying tube. Acetyl- amino[7 - chloro - 5 - (2 - chlorophenyl) - 3H - 1,4 - benzodiazepin - 2 - yl]malonic acid diethyl ester (10.1 g, 0.02 m) was added in one portion to the stirred solution and stirring in a dry atmosphere was continued at room temperature for 5 hours. The resulting mixture was acidified with acetic acid and concentrated in vacuo. The residue was partitioned between dilute ammonium hydroxide and methylene chloride. After separating the layers, the organic layer was dried over sodium sulfate and evaporated at reduced pressure to give a tan, amorphous solid. The solid was dissolved in 75 ml of anhydrous ether and added to a warm solution of 4 g of maleic acid in 200 ml of ether. After decanting from a small amount of brown gum, the solution was concentrated on a steam bath to about 100 ml. Cooling at room temperature with occasional scratching gave crystallization after about 30 minutes. When crystallization was complete, the orange crystals were filtered, washed with ether and air dried on the funnel to give 2 - [(acetylamino)ethoxycarbonylmethylene] - 7 - chloro - 5 - (2 - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepine maleate. Recrystallization of a small sample from ethyl acetate (5 ml/g) gave yellow microneedles, m.p. 139—142° (dec.).

- 10 20 A solution of 3.2 g (0.0073 m) of 2 - [(acetylamino)ethoxycarbonylmethylene] - of hexamethylphosphoramide was stirred under nitrogen and heated at 200—210° for 7 - chloro - 5 - (2 - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepine in 15 ml of hexamethylphosphoramide was stirred under nitrogen and heated at 200—210° for 10 minutes. After cooling to room temperature the solution was poured into ice water and diluted with more water until precipitation was complete. The tan solid was filtered, washed with water and air dried on the funnel. When stirred with ethyl acetate (2 ml/g) the solid dissolved and immediately recrystallized. The tan solid was filtered, washed with 1:1 ethyl acetate/petroleum ether and air dried to give ethyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate. Recrystallization of a sample from methylene chloride/ethyl acetate solution by removal of the methylene chloride by boiling gave off-white needles, m.p. 214—215°.

Example 48.

- 35 40 A stirred solution of 4.1 g (0.01 m) of ethyl 3 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate in 100 ml of methanol containing 3 ml of water and 1.2 g (0.02 m) of potassium hydroxide was heated at reflux under nitrogen for 4.5 hours and concentrated at reduced pressure to remove the methanol. The residue was dissolved in cold water and acidified with acetic acid to give an off-white solid. After air drying on the funnel overnight, 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylic acid was obtained. Recrystallization of a sample from 1:1 methylene chloride/ethanol gave white platelets, m.p. 265—267° (dec.).

Example 49.

- 45 50 55 A stirred suspension of 1.2 g (0.0031 m) of ethyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate in 25 ml of methylene chloride was cooled in an ice bath and treated with 0.7 g (0.004 m) of phosphorus pentachloride in portions. The mixture was protected by a drying tube and stirring in the cold was continued 30 minutes longer during which time most of the solid dissolved. With continued cooling and stirring, the mixture was treated with gaseous ammonia for 5 minutes and stirred an additional 30 minutes in the cold. The mixture was evaporated in vacuo to give a light solid which was stirred with dilute aqueous ammonia and filtered through a coarse sintered glass funnel. After washing with water the solid was air dried on the funnel to give 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide. Recrystallization of a sample from 2:1 methylene chloride/ethanol solution gave white plates, m.p. 318—320° (dec.).

Example 50.

- 60 8 - Chloro - 6 - (2 - chlorophenyl) - 3 - hydroxymethyl - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine (3.7 g, 0.01 m) was added with stirring to 20 ml of thionylchloride. After stirring for 30 minutes at room temperature, the hydrochloride

of the product was crystallized by dilution with 30 ml of ethyl acetate and 100 ml of ether. The crystals were collected, washed with ether and partitioned between methylene chloride and saturated aqueous sodium bicarbonate solution. The methylene chloride layer was dried and evaporated and the residue was crystallized from ether to yield 8 - chloro - 3 - chloromethyl - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine as colorless crystals which did not melt on slow heating but on immersion of the capillary at 200—210°. The analytical sample was recrystallized from ethyl acetate/hexane.

Example 51.

A mixture of 2 g of 8 - chloro - 3 - chloromethyl - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine, 10 ml of dimethylamine and 10 ml of tetrahydrofuran was heated in a sealed tube at 100° for 2 hours. The solvents were evaporated and the residue was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The organic phase was dried and evaporated and the residue was crystallized from ether to give 8 - chloro - 6 - (2 - chlorophenyl) - 3 - dimethylaminomethyl - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine, m.p. 136—138°.

This material was dissolved in 10 ml of ethanol and treated with two equivalents of ethanolic hydrogen chloride. Crystallization by dilution with ether yielded 8 - chloro - 6 - (2 - chlorophenyl) - 3 - dimethylaminomethyl - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine dihydrochloride — ethanol as colorless crystals which were recrystallized from ethanol/ether for analysis, m.p. 275—277°.

Example 52.

A mixture of 1 g of 8 - chloro - 3 - chloromethyl - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine, 250 mg of potassium cyanide and 20 ml of dimethylformamide was heated on the steambath with stirring for 3 hours. After dilution with water, the mixture was extracted with methylene chloride. The extracts were washed with water, dried and evaporated. Chromatography of the residue on 30 g of silica gel using methylene chloride/ethyl acetate 1:2 and crystallization of the clean fractions from ether yielded 8 - chloro - 6 - (2 - chlorophenyl) - 3 - cyanomethyl - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine, m.p. 212—214°. The analytical sample was recrystallized from ethyl acetate/hexane, m.p. 215—217°.

Example 53.

A stirred solution of 29.9 g (0.1 m) of 1,3 - dihydro - 5 - (2 - fluorophenyl) - 7 - nitro - 2H - 1,4 - benzodiazepine - 2 - one in 500 ml of dry tetrahydrofuran was treated under argon portionwise with 5.5 g (0.125 m) of a 54% mineral oil dispersion of sodium hydride and stirring was continued for 1 hour longer. Dimorpholinophosphine chloride (38 g, 0.15 m) was added to the dark solution in one portion and stirring under argon was continued for 8 hours. The resultant dark mixture was filtered over filter aid and concentrated in vacuo at 50° to give a dark gum. When the dark gum was stirred at room temperature in 75 ml of ethyl acetate, crystallization occurred to give a paste. After cooling in an ice bath for 30 minutes the mixture was filtered and the light tan solid was washed 3 times with 35 ml portions of 2:1 ether/ethyl acetate and finally with ether. Air drying on the funnel yielded nearly pure 5 - (2 - fluorophenyl) - 2 - [bis(morpholino)phosphinyloxy] - 7 - nitro - 3H - 1,4 - benzodiazepine. Recrystallization from 15 fold amount of ethyl acetate gave off-white needles, m.p. 169—172°.

A stirred suspension of 0.85 g (0.018 m) of a 54% mineral oil dispersion of sodium hydride in 55 ml of dry dimethylformamide was treated with 3.5 g (0.016 m) of diethyl acetamidomalonate in several portions under argon. After stirring for 30 minutes, 5.2 g (0.01 m) of 5 - (2 - fluorophenyl) - 2 - [bis(morpholino)phosphinyloxy] - 7 - nitro - 3H - 1,4 - benzodiazepine was added in one portion and stirring under argon was continued for 7 hours longer. The dark mixture was poured into a stirred mixture of ice and acetic acid and diluted with water to give a brownish yellow solid. The solid was washed with water and air dried on the funnel to give a residue. Tlc (ethyl acetate) showed 3 yellow spots with Rf 0.8, 0.5 and 0.25. Chromatography over silica gel using ethyl acetate as eluent gave ethyl 6 - (2 - fluorophenyl) - 1 - methyl - 8 - nitro - 4H - imidazo[1,5-a][1,4]benzodiazepine 3 - carboxylate with Rf of 0.25 as a brownish yellow solid. Recrystallization of the sample from ethyl acetate (5 ml/g) by dissolving in hot ethyl acetate and cooling in an ice bath gave yellow prisms, m.p. 231—233°.

Example 54.

Fifty-four percent sodium hydride in mineral oil dispersion (11 g, 0.25 m) was added in portions to a stirred solution of 63.2 g (0.2 m) of 7 - bromo - 1,3 - dihydro-5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one in 1 l of tetrahydrofuran under argon. After refluxing on a steam bath for 1 hour, the solution was cooled to room temperature and treated with 76.2 g (0.3 m) of dimorpholinophosphinic chloride portionwise. Stirring at room temperature was continued for 5 hours. The dark mixture was filtered through Celite. Concentration of the filtrate in vacuo and boiling the dark residue with ether gave tan crystals of 7 - bromo - 2 - [bis(morpholino)phosphinyloxy] - 5 - (2 - pyridyl) - 3H - 1,4 - benzodiazepine. A sample was recrystallized by dissolving it in 2 ml of methylene chloride, filtering, diluting with 10 ml of ethyl acetate and cooling in an ice bath to give light tan plates, m.p. 180—182° (dec.).

Diethyl acetamidomalonate (43 g, 0.2 m) was added to a suspension of 10 g (0.2 m) of a dispersion (50%) of sodium hydride in mineral oil in 500 ml of dry dimethylformamide. This mixture was stirred under argon for 1 hour at room temperature and for 20 minutes with heating on the steam bath. 7 - Bromo - 2 - [bis(morpholino)phosphinyloxy] - 5 - (2 - pyridyl) - 3H - 1,4 - benzodiazepine (53.4 g, 0.1 m) was then added to the reaction mixture brought back to room temperature. After stirring for 1 hour at room temperature, it was again heated on the steam bath for 2 hours. The cooled solution was partitioned between water and methylene chloride/ether. The organic phase was separated, washed with water, dried and evaporated. The residue was crystallized with seeding from ethyl acetate/ether to give ethyl - 8 - bromo - 1 - methyl - 6 - (2 - pyridyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine 3 - carboxylate as off-white crystals, m.p. 240—243°. Seeds were obtained by chromatographic purification over 30 fold amount of silica gel using 5% (v/v) methanol in ethyl acetate. The analytical sample was recrystallized from ethyl acetate, m.p. 243—244°.

Example 55.

A mixture of 2.15 g (5 mmol) of ethyl 8 - bromo - 1 - methyl - 6 - (2 - pyridyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate, 50 ml of methanol, 0.84 g (15 mmol) of potassium hydroxide and 2.5 ml of water was heated to reflux for 5 hours. The bulk of the methanol was evaporated and the residue was partitioned between water and ether. The aqueous phase was acidified with acetic acid and extracted with methylene chloride. The extracts were dried and evaporated. Crystallization of the residue from methylene chloride/ethyl acetate gave 8 - bromo - 1 - methyl - 6 - (2 - pyridyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylic acid as colorless crystals which were recrystallized from methanol for analysis, m.p. 245—250° (dec.) with previous sintering.

Example 56.

A stirred suspension of 7.8 g (0.174 m) of a 54% mineral oil dispersion of sodium hydride in 480 ml of dimethylformamide was treated portionwise under argon with 39 g (0.18 m) of diethyl acetamidomalonate. When the reaction had abated (ca. 30 minutes), 48 g (0.096 m) of 7 - chloro - 5 - (2 - fluorophenyl) - 2 - [bis(morpholino)phosphinyloxy] - 3H - 1,4 - benzodiazepine was added in one portion. Stirring was continued at room temperature for 5 hours under argon. The dark mixture was poured, with stirring, into a mixture of ice and glacial acetic acid to give a light tan solid which was filtered, washed with water and partially air dried on the funnel. The damp solid was dissolved in methylene chloride. After separating the water layer the solution was dried over sodium sulfate, filtered and evaporated under reduced pressure to give a tan foam. The foam was dissolved in isopropanol (4 ml/g) with stirring and kept at room temperature for 1 hour with occasional scratching to give off-white crystals. An equal volume of petroleum ether (30—60°) was added and the mixture was kept at room temperature an additional 30 minutes before filtration. Washing with petroleum ether and air drying on the funnel yielded acetylamino[7 - chloro - 5 - (2 - fluorophenyl) - 3H - 1,4 - benzodiazepine - 2 - yl]malonic acid diethyl ester, m.p. 150—180°. Recrystallization of a sample from ethanol (10 ml/g) raised the melting point to 185—195° with previous softening.

A stirred solution of sodium ethoxide (prepared from 0.2 g, 0.01 g atom, of sodium metal in 25 ml of absolute ethanol) was treated with 2.4 g (0.005 m) of acetylamino[7 - chloro - 5 - (2 - fluorophenyl) - 3H - 1,4 - benzodiazepine - 2 - yl] - malonic acid diethyl ester, protected by a drying tube and stirred 5 hours longer at room temperature. The precipitated yellow solid was collected by filtration, washed successively with ethanol and ether and air dried to give product. The solid was partitioned between water and methylene chloride, acidified with acetic acid and extracted again with

methylene chloride. After washing with dilute ammonium hydroxide solution the methylene chloride extract was dried over sodium sulfate and evaporated in vacuo to give a tan foam. A solution of 1 g (0.0024 m) of the base in 25 ml of ether was mixed with a solution of 0.56 g (0.0048 m) of maleic acid in 25 ml of ether and kept at room temperature. Orange crystals were obtained after several minutes with occasional scratching. The crystals were collected by filtration, washed with ether and air dried to yield 2 - [(acetylamino)ethoxycarbonylmethylene] - 7 - chloro - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepine maleate, m.p. ca. 150°. Recrystallization from 30 ml of ethyl acetate after concentrating to 1/2 volume and seeding gave orange prisms, m.p. 149—151°.

Crude 2 - [(acetylamino)ethoxycarbonylmethylene] - 7 - chloro - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepine (6.3 g, 0.015 m) which was prepared from the maleate by basifying with ammonia, extracting with methylene chloride and evaporating in vacuo, was dissolved in 35 ml of hexamethylphosphoramide (HMPA) and heated, with stirring at 200—210° for 5 minutes. The dark solution was cooled and poured into ice water to give a tan solid. The solid was filtered, washed with water and partially air dried on the funnel. The damp solid was dissolved in methylene chloride, dried over sodium sulfate and evaporated at reduced pressure to give ethyl 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate as tan foam. Recrystallization of 1 g of the foam from 5 ml of ethyl acetate and 5 ml of petroleum ether (30—60°) gave the product as light tan prisms, which melted at 176—179°, slowly resolidified and melted again at 195—198°.

Example 57.

Diethyl acetamidomalonate (43 g, 0.2 m) was added to a suspension of 10 g (0.2 m) of sodium hydride (50% in mineral oil) in 500 ml of dry dimethylformamide. The mixture was heated to 50° for 30 minutes under argon. After addition of 53 g (0.1 m) of 5 - (2 - chlorophenyl) - 2 - [bis(morpholino) - phosphinyloxy] - 7 - nitro - 3H - 1,4 - benzodiazepine, the reaction mixture was heated on the steam bath for 1 hour. The cooled brown mixture was partitioned between water and methylene chloride/ether. The organic phase was washed with water, dried and evaporated. The residue was chromatographed over 1 kg of silica gel using ethyl acetate. The clean fractions were combined and evaporated. Crystallization of the residue from methylene chloride/ether yielded ethyl 6 - (2 - chlorophenyl) - 1 - methyl - 8 - nitro - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate as light yellow crystals, m.p. 233—234°. The analytical sample was recrystallized from ethyl acetate, m.p. 234—235°.

Example 58.

A mixture of 4.25 g (0.01 m) of ethyl 6 - (2 - chlorophenyl) - 1 - methyl - 8 - nitro - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate, 100 ml of methanol, 1.12 g (0.02 m) of potassium hydroxide and 4 ml of water was heated to reflux under nitrogen for 3 hours. The bulk of the methanol was evaporated and the residue was partitioned between water and ether. The aqueous phase was washed with ether, acidified with acetic acid and extracted with methylene chloride. The extracts were dried and evaporated. Crystallization of the residue from methylene chloride/ethyl acetate yielded 6 - (2 - chlorophenyl) - 1 - methyl - 8 - nitro - 4H - imidazo[1,5-a][1,4]benzodiazepine 3-carboxylic acid, m.p. 272—274° (dec.). The analytical sample was recrystallized from methanol/ethyl acetate, m.p. 274—276° (dec.).

Example 59.

6 g (0.125 m) of sodium hydride dispersion (50% in mineral oil), was added to a solution of 28.1 g (0.1 m) of 1,3 - dihydro - 7 - nitro - 5 - phenyl - 2H - 1,4 - benzodiazepine - 2 - one in 300 ml of dry tetrahydrofuran. After stirring for 1 hour at room temperature 30.2 g (0.12 m) of dimorpholinophosphinic chloride was added and stirring was continued for 4 hours. The product was crystallized by addition of water and ether. The precipitate was collected and dissolved in methylene chloride. The solution was dried and evaporated and the residue was crystallized from ethyl acetate to yield crude 7 - nitro - 2 - [bis(morpholino)phosphinyloxy] - 5 - phenyl - 3H - 1,4 - benzodiazepine, m.p. 208—209°.

Part of this material was added to a mixture of 8.6 g (0.04 m) of diethyl acetaminomalonate, 2 g (0.04 m) of sodium hydride suspension (50% in mineral oil) and 75 ml of dimethylformamide which had been heated at 40° for 30 minutes. After addition the reaction mixture was heated for 30 minutes on the steam bath and was then partitioned between water and ether. The organic phase was washed with water, dried and evaporated. The residue was chromatographed over 250 g of silica gel using ethyl

acetate. The combined clean fractions were evaporated and the residue was crystallized from methylene chloride/ether to yield ethyl 1 - methyl - 8 - nitro - 6 - phenyl - 4H-imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate as off-white crystals with m.p. 240—241°. The analytical sample was recrystallized from ethyl acetate.

Example 60.

A mixture of 1.95 g (5 mmol) of ethyl 1 - methyl - 8 - nitro - 6 - phenyl - 4H-imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate, 50 ml of methanol, 0.56 g (0.01 m) of potassium hydroxide and 2 ml of water was heated to reflux under nitrogen for 3 hours. After partial evaporation of the solvent the residue was acidified with 2 ml of glacial acetic acid and was partitioned between methylene chloride containing 10% (v/v) of ethanol and water. The organic phase was dried and evaporated. Crystallization of the residue from ethyl acetate/methanol yielded 1 - methyl - 8 - nitro - 6 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylic acid as straw colored crystals which were recrystallized from the same solvents for analysis, m.p. 240—243° (dec.).

Example 61.

A mixture of 2.45 g (0.07 m) of 8 - chloro - 1 - methyl - 6 - phenyl - 4H-imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide, 50 ml of pyridine and 7 g of phosphorus pentoxide was heated to reflux for 15 minutes. The pyridine was evaporated under reduced pressure and the residue was partitioned between ice, 10% sodium carbonate solution and methylene chloride. The organic layer was separated, dried and evaporated. The residue was chromatographed over 50 g of silica gel using ethyl acetate/methylene chloride 1:1. Crystallization from ethyl acetate/hexane yielded 8-chloro - 3 - cyano - 1 - methyl - 6 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine, m.p. 228—229°.

Example 62.

Activated manganese dioxide (5 g) was added to a solution of 1 g of 8 - chloro - 6 - (2 - chlorophenyl) - 3 - hydroxymethyl - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine in 50 ml of methylene chloride. The mixture was stirred at room temperature for 2 hours. The manganese dioxide was filtered off and the filtrate was evaporated. Crystallization of the residue from ethanol gave 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxaldehyde as colorless crystals, m.p. 237—239°. The analytical sample was recrystallized from tetrahydrofuran/ethanol.

Example 63.

A mixture of 1.4 g (4 mmol) of 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxaldehyde, 2 ml of triethylamine, 30 ml of ethanol and 0.56 g (8 mmol) of hydroxylamine hydrochloride was allowed to stand at room temperature for 1 1/2 hours. After dilution with water the precipitated crystals were collected and dried to yield 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxaldoxime, m.p. 269—271°. The analytical sample was recrystallized from tetrahydrofuran/ethanol, m.p. 272—275°.

Example 64.

A solution of 0.2 g of 3 - (benzyloxycarbonylamino) - 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine in 10 ml of glacial acetic acid and 2 ml of acetic anhydride was hydrogenated over palladium on charcoal (10%) for 1 hour at atmospheric pressure. The catalyst was filtered off and the filtrate was evaporated, at the end azeotropically with xylene. The residue was chromatographed over 6 g of silica gel using 10% ethanol in methylene chloride. Crystallization of the combined pure fractions from ethyl acetate/ether gave 3 - acetamino - 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine as colorless crystals, m.p. 175—178°.

Example 65.

Hydroxylamine hydrochloride (0.14 g, 2 mmol) was added to a suspension of 0.37 g (1 mmol) of 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxaldehyde in 10 ml of ethanol and 0.5 ml of triethylamine. The mixture was heated on the steambath until solution was complete and the solution was allowed to stand for 2 hours. The separated crystals were collected, washed with water, ethanol and ether to yield 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxaldoxime. The analytical sample was recrystallized from tetrahydrofuran/ethanol, m.p. 290—292° (dec.).

Example 66.

A solution of methyl magnesium iodide in ether (5 ml, ca. 1-molar) was added to a solution of 0.37 g (1 mmol) of 8-chloro-6-(2-chlorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxaldehyde in 10 ml of tetrahydrofuran. After stirring for 15 minutes at room temperature the mixture was decomposed with water. The inorganic material was filtered off and washed with methylene chloride. The filtrate was dried and evaporated. Crystallization of the residue from ether and recrystallization from ethyl acetate/hexane gave 8-chloro-6-(2-chlorophenyl)-3-(1-hydroxyethyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine as colorless crystals, m.p. 197—199°.

Example 67.

A solution of 0.1 g of 8-chloro-6-(2-chlorophenyl)-3-(1-hydroxyethyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine in 20 ml of methylene chloride was stirred at room temperature for 3 hours in the presence of 0.5 g of activated manganese dioxide. The manganese dioxide was filtered off and the filtrate was evaporated. The crystalline residue was recrystallized from ethyl acetate/hexane to yield 3-acetyl-8-chloro-6-(2-chlorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine as colorless crystals, m.p. 234—236°.

Example 68.

A stirred solution of 12.4 g (0.03 m) of ethyl 8-chloro-6-(2-chlorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate in 200 ml of methylene chloride was treated with 12 g (0.07 m) of m-chloroperoxybenzoic acid in portions at room temperature. Stirring was continued for 2.5 hours. The solution was washed with 1N sodium hydroxide solution and the turbid methylene chloride layer was separated, diluted with methanol and dried over sodium sulfate. Filtration and evaporation at reduced pressure gave a gum which gave ethyl 8-chloro-6-(2-chlorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate-4-oxide as off-white crystals when triturated with ether. An analytical sample was obtained after two recrystallizations from 1:1 ethanol/methylene chloride solution, m.p. 247—249°.

Example 69.

Phenylacetaldehyde (2.4 g, 0.02 m) was added to a solution of 3.8 g (0.01 m) of 2-[(amino)methoxycarbonylmethylene]-7-chloro-5-(2-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine in methylene chloride. Following the addition of 10 g of molecular sieves 5A the mixture was stirred at room temperature for 15 min and treated with 10 g of activated manganese dioxide for additional 15 min at room temperature. The inorganic material was separated by filtration over Celite. The filtrate was evaporated and the residue was crystallized from ether/hexane to yield methyl 1-benzyl-8-chloro-6-(2-chlorophenyl)-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate as colorless crystals with mp. 155—158°. The analytical sample was recrystallized from ethyl acetate/hexane, mp. 160—162°.

Example 70.

A mixture of 2 g (4.2 mmol) of methyl-1-benzyl-8-chloro-6-(2-chlorophenyl)-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate, 1 g of potassium hydroxide, 50 ml of methanol and 5 ml of water was heated to reflux for 4 hrs. under an atmosphere of nitrogen. The solvent was evaporated, the residue was dissolved in water and the solution was acidified with acetic acid. The precipitated crystals were collected, washed with water and dissolved in methylene chloride. The solution was dried and evaporated. Crystallization from methylene chloride/ethyl acetate yielded 1-benzyl-8-chloro-6-(2-chlorophenyl)-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid, mp. 305—310° (dec.).

Example 71.

The material of Example 128 was suspended in 30 ml of methylene chloride. Phosphorus pentachloride (0.8 g) was added and the mixture was stirred over ice/water for 30 min. Ammonia gas was then introduced until the reaction mixture was alkaline. After stirring for 15 min at room temperature, aqueous ammonia was added and the two phase system was stirred for another 15 min. The methylene chloride phase was separated, dried and evaporated. The crystalline residue was recrystallized from ethyl acetate/methanol to yield 1-benzyl-8-chloro-6-(2-chlorophenyl)-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxamide as colorless product, mp. 282—284°.

The analytical sample was chromatographed over silica gel (40 fold amount) using methylene chloride/ethyl acetate 1:1 (v/v) for elution, mp. 286—288°.

Example 72.

5 A mixture of 370 mg (1 mmol) of 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxaldehyde, 10 ml of ethanol and 0.5 ml of 1,1-dimethylhydrazine was heated to reflux for 15 minutes. The solvent was evaporated and the residue was crystallized from ethanol/water to yield light 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxaldehyde dimethylhydrazone ethanol (2/1) yellow crystals. The analytical sample was recrystallized from ethanol, mp. 238—242°. The crystals contained according to nmr-spectrum and analysis 0.5 equivalent of ethanol.

Example 73.

15 Phosphorus pentachloride (1.1 g, 5.2 mmol), was added to a suspension of 1.6 g (4 mmol) of 6 - (2 - chlorophenyl) - 1 - methyl - 8 - nitro - 4H - imidazo[1,5-a][1,4]benzodiazepine 3-carboxylic acid in 100 ml of methylene chloride cooled in ice-water. After stirring for 30 minutes in ice-water, a stream of ammonia was introduced until the mixture was alkaline and stirring was continued for one hour at room temperature. Water was added and the organic layer was separated, dried and evaporated. Crystallization of the residue from methanol/ethyl acetate yielded 6 - (2 - chlorophenyl) - 1 - methyl - 8 - nitro - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carb-oxamide as yellowish crystals, mp. 300°. The analytical sample was recrystallized from the same solvents.

Example 74.

25 A mixture of 10 g (0.036 m) of 1,3 - dihydro - 5 - phenyl - 2H - thieno - [3,2-e]-[1,4]diazepine - 2 - one in 50 ml of benzene and 300 ml of tetrahydrofuran was stirred on an ice bath and saturated with methylamine gas. To this mixture was added dropwise a solution of titanium tetrachloride (9.48 g, 0.05 m) in 50 ml of benzene. After the addition was complete, the mixture was stirred on the ice bath for 15 minutes. The ice bath was then replaced with a heating mantel and the mixture refluxed for 1/2 hour. The mixture was cooled and 100 g of ice carefully added. The mixture was filtered and the residue washed with tetrahydrofuran. The filtrates were combined, dried and evaporated. The product was crystallized from methylene chloride to yield 2 - methyl-amino - 5 - phenyl - 3H - thieno - [3,2-e] [1,4]diazepine, m.p. 223—227°. From the concentrated mother liquors was obtained additional product, m.p. 222—225°. The analytical sample was recrystallized from methylene chloride, m.p. 222—229°.

35 Nitrosyl chloride was introduced into a solution of 7.8 g (0.03 m) of 2 - methyl-amino - 5 - phenyl - 3H - thieno[3,2-e][1,4]diazepine in 100 ml of methylene chloride and 40 ml of pyridine cooled in ice water. The reaction was monitored by thin layer chromatography and when the starting material had disappeared the nitrosyl chloride addition was terminated and the reaction mixture was partitioned between methylene chloride and water. The methylene chloride solution was dried and evaporated. Crystallization of the residue from methylene chloride/hexane yielded 2 - (N - nitroso-methylamino) - 5 - phenyl - 3H - thieno[3,2-e][1,4]diazepine as yellow crystals, m.p. 156—159°. The analytical sample was recrystallized from ether/hexane, m.p. 158—160°.

Example 75.

50 A mixture of 7.7 g (0.0278 m) of 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H-thieno[2,3-e][1,4]diazepin - 2 - one, 50 ml of benzene and 250 ml of tetrahydrofuran was stirred on an ice bath and saturated with methylamine gas. To this mixture was added a solution of titanium tetrachloride (7.38 g, 0.0389 m) in 50 ml of benzene from a dropping funnel. After the addition was complete, the mixture was stirred on the ice bath for 15 minutes. The ice bath was then replaced by a heating mantel and the reaction mixture was refluxed for 20 minutes. The mixture was cooled and 100 g of ice were carefully added. The mixture was then filtered, and the residue washed with tetrahydrofuran. The filtrate were combined, dried and evaporated. The residue was crystallized from methylene chloride/ether yielding 7 - chloro - 5 - phenyl - 2 - methylamino-3H - thieno - [2,3-e][1,4]diazepine, m.p. 246—249°. The analytical sample was recrystallized from methylene chloride, m.p. 247—250°.

60 Nitrosyl chloride was introduced into a solution of 5.8 g (0.02 m) of 7 - chloro-5 - phenyl - 2 - methylamino - 3H - thieno[2,3-e][1,4]diazepine in 100 ml of methylene chloride and 50 ml of pyridine until the reaction was complete according to thin layer chromatogram. The mixture was partitioned between water and toluene. The

organic phase was dried and evaporated. Crystallization of the residue from ether/hexane yielded 7 - chloro - 2 - (N - nitrosomethylamino) - 5 - phenyl - 3H - thieno[2,3-e][1,4]diazepine as yellow crystals, m.p. 108—110°. For analysis it was recrystallized from ether/hexane, m.p. 111—113°.

Example 76.

A solution of 50 g (0.161 m) of 7 - chloro - 5 - (2 - chlorophenyl) - 1,3-dihydro - 2H - thieno[2,3-e][1,4]diazepine - 2 - one in 900 ml of dry tetrahydrofuran and 300 ml of dry benzene was cooled in an ice bath, methylamine was bubbled in until the solution was saturated and a solution of 40 g (0.209 m) of titanium tetrachloride in 100 ml of benzene was added dropwise with stirring. After 4 hours at room temperature a few grams of ice were added and the reaction was filtered. The precipitate was washed several times with hot tetrahydrofuran, and the combined filtrates were evaporated. The residue was partitioned between 250 ml of dichloromethane and 200 ml of water and filtered. The dichloromethane solution was separated, dried and evaporated. This residue and the precipitate were recrystallized from a mixture of tetrahydrofuran and ethanol to give 7 - chloro - 5 - (2 - chlorophenyl) - 2 - methylamino - 3H - thieno[2,3-e][1,4]diazepine. A sample was recrystallized for analysis from a mixture of tetrahydrofuran and hexane to give pale yellow prisms, m.p. 259—262°.

A mixture of 40 g (0.123 m) of 7 - chloro - 5 - (2 - chlorophenyl) - 2 - methylamino - 3H - thieno[2,3-e][1,4]diazepine, 700 ml of dichloromethane and 350 ml of pyridine was cooled in an ice bath and nitrosyl chloride was bubbled in for 20 minutes with stirring. After 1 hour it was bubbled in for 5 minutes more and then 600 ml of water was added slowly. The dichloromethane layer was separated, washed with 200 ml of water, dried over anhydrous sodium sulfate and evaporated to dryness. The oil was dissolved in dichloromethane and filtered through 400 g of Florisil. This was eluted with dichloromethane, and then ether. Crystallization of the dichloromethane fraction from a mixture of ether and petroleum ether gave 7 - chloro - 5 - (2 - chlorophenyl) - 2 - (N - nitrosomethylamino) - 3H - thieno[2,3-e][1,4]diazepine and more product was obtained from the ether fraction. A sample was recrystallized for analysis from a mixture of ether and petroleum ether to give yellow prisms, m.p. 104—107°.

A mixture of 3.4 g (0.03 m) of potassium t-butoxide, 7 ml of dimethylmalonate and 20 ml of dimethylformamide was stirred for 5 minutes under an atmosphere of nitrogen. Following the addition of 3.55 g (0.01 m) of 7 - chloro - 5 - (2 - chlorophenyl) - 2 - (N - nitrosomethylamino) - 3H - thieno[2,3-e][1,4]diazepine, the mixture was stirred and heated on the steambath for 5 minutes, was acidified by addition of 3 ml of acetic acid and crystallized by slow addition of water. The precipitated material was collected, washed with water and methanol and dissolved in methylene chloride. The solution was dried and evaporated and the residue was crystallized from ethanol to yield 7 - chloro - 5 - (2 - chlorophenyl) - 1,3 - dihydro - 2 - dimethoxymalonylidene - 2H - thieno[2,3-e][1,4]diazepine as pinkish crystals which were recrystallized from ethanol for analysis, m.p. 158—160°.

A mixture of 2.15 g (5 mmol) of 7 - chloro - 5 - (2 - chlorophenyl) - 1,3-dihydro - 2 - dimethoxymalonylidene - 2H - thieno[2,3-e][1,4]diazepine, 50 ml of methanol and 0.7 g (1.25 mmol) of potassium hydroxide was heated to reflux under nitrogen for 3 hours. The solution was partially evaporated and the residue was partitioned between methylene chloride and saturated sodium bicarbonate solution. The organic phase was dried and evaporated. The crude 7 - chloro - 5 - (2 - chlorophenyl) - 2,3 - dihydro - 2 - (methoxycarbonylmethylene) - 2H - thieno[2,3-e][1,4]diazepine obtained was dissolved in 20 ml of glacial acetic acid. Sodium nitrite (0.5 g) was added and the mixture was stirred for 15 minutes at room temperature, diluted with water and extracted with methylene chloride. The extracts were washed with water and sodium bicarbonate solution, dried and evaporated. Crystallization of the residue from methylene chloride/ether and recrystallization from tetrahydrofuran/methanol gave 7 - chloro - 5 - (2 - chlorophenyl) - alpha - hydroxyimino - 3H - thieno[2,3-e][1,4]diazepine - 2 - acetic acid methyl ester as yellow crystals, m.p. 242—245° (dec.).

7 - Chloro - 5 - (2 - chlorophenyl) - alpha - hydroxyimino - 3H - thieno[3,2-f][1,4]diazepine - 2 - acetic acid methyl ester (0.4 g, 1 mmol) was dissolved by warming in 30 ml of tetrahydrofuran and 20 ml of ethanol. Following the addition of Raney nickel (1/2 teaspoonful) the mixture was hydrogenated for 45 minutes at atmospheric pressure. The catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in 10 ml of methanol and treated with 0.4 ml of triethyl orthoacetate and 3 drops of ethanolic hydrogen chloride. After heating to reflux for 10 minutes the solvent

was evaporated and the residue was partitioned between methylene chloride and sodium bicarbonate solution. The organic layer was dried and evaporated. Chromatography of the residue over 10 g of silica gel using methylene chloride/ethyl acetate 3:5 (v/v) and crystallization of the residue obtained after removal of the eluent from ethanol yielded

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methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a]thieno[3,2-f][1,4]diazepine - 3 - carboxylate, m.p. 211—212°.

Example 77.

To 20 ml of ether under nitrogen was added 38 mg (0.001 m) of lithium aluminum hydride. The reaction was cooled in an ice bath and 0.2 g (0.000493 m) of methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a]thieno[3,2-f][1,4]diazepine - 3 - carboxylate was dissolved in 20 ml of dry tetrahydrofuran and added dropwise with stirring to the reaction. After one hour, 5 ml of ethyl acetate was added followed by 3 ml of a saturated solution of sodium bicarbonate. The reaction was filtered through Celite, which was then washed with dichloromethane and the combined filtrates were evaporated and crystallized from a mixture of dichloromethane and ether yielding 8 - chloro - 6 - (2 - chlorophenyl) - 3 - hydroxymethyl - 1 - methyl - 4H - imidazo[1,5-a]thieno[3,2-f][1,4]diazepine. Recrystallization from the same solvents gave off-white prisms, m.p. 100—110° resets, m.p. 190—194°.

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Example 78.

To 10 ml of methanol and 1 ml of water was added 0.1 g (0.000247 m) of methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a]thieno[3,2-f][1,4]diazepine - 3 - carboxylate and 0.028 g (0.000493 m) of potassium hydroxide. The reaction was refluxed for 2 hours and evaporated. The residue was dissolved in 10 ml of water, washed with 10 ml of ether and then acidified with acetic acid. This was extracted with 30 ml of dichloromethane, which was dried over anhydrous sodium sulfate, concentrated, cooled and filtered. Recrystallization of the precipitate from a mixture of dichloromethane and ether gave 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a]thieno[3,2-f][1,4]diazepine - 3 - carboxylic acid as a white prisms, m.p. 242—247°.

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Example 79.

To 0.8 g (0.00204 m) of 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a]thieno[3,2-f][1,4]diazepine - 3 - carboxylic acid in 100 ml of dry dichloromethane in an ice bath was added 0.46 g (0.0022 m) of phosphorus pentachloride. After 30 minutes ammonia was bubbled in for 5 minutes with stirring. After 2 hours 75 ml of water was added and the product was filtered off. The dichloromethane was separated, dried and evaporated. The product obtained by crystallization of the residue from ethanol was combined with the first precipitate and recrystallized from a mixture of chloroform and ethanol to give 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a]thieno[3,2-f][1,4]diazepine - 3 - carboxamide as white rods, m.p. 300—305°.

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Example 80.

A solution of 6.8 g (0.0255 m) of 6,8 - dihydro - 3 - ethyl - 1 - methyl - 4 - phenylpyrazolo[3,4-e][1,4]diazepin - 7(1H) - one in 125 ml of dry tetrahydrofuran and 50 ml of dry benzene was cooled in an ice bath and methylamine was bubbled in until the solution was saturated. A solution of 6.3 g (0.0331 m) of titanium tetrachloride in 20 ml of benzene was then added dropwise with stirring and after 18 hr at room temperature the mixture was refluxed for 30 minutes. The solution was cooled, and treated with 4 g of ice. The reaction mixture was filtered and the precipitate was washed with tetrahydrofuran and then with dichloromethane. The combined filtrates were evaporated to dryness and the residue was crystallized from a mixture of methanol and ether, and recrystallized from a mixture of dichloromethane and ether to give 3 - ethyl - 1,6 - dihydro - 1 - methyl - 7 - methylamino - 4 - phenylpyrazolo[3,4-e][1,4]diazepine as off-white prisms, mp. 218—221°.

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A solution of 5.6 g (0.0199 m) of 3 - ethyl - 1,6 - dihydro - 1 - methyl - 7 - methylamino - 4 - phenylpyrazolo[3,4-e][1,4]diazepine in 100 ml of dichloromethane and 50 ml of pyridine was stirred in an ice bath and nitrosyl chloride was bubbled in for 10 min. After 2 hr at room temperature, nitrosyl chloride was bubbled in for an additional 5 min. The mixture was allowed to stand for 30 min when it was poured into 200 ml of ice water. The organic layer was separated, washed with 100 ml of water, dried over anhydrous sodium sulfate, and filtered through 100 g of Florisil. The Florisil was thoroughly washed with ether, and the combined filtrates were evaporated.

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ated to dryness. The intermediate N-nitroso derivative was not further purified but was used in the next step as follows.

A mixture of 14 ml of dimethyl malonate and 35 ml of N,N-dimethylformamide was treated with 6.5 g (0.0580 m) of potassium tertiary butoxide and after stirring for 5 min a solution of the N-nitroso compound prepared as described above in 10 ml of N,N-dimethylformamide was added. The resulting mixture was heated on the steam bath for 5 min, cooled, and 6 ml of glacial acetic acid was added. The reaction mixture was next poured into 300 ml of cold water, and after 15 min the solution was decanted. The remaining oil was dissolved in 75 ml of dichloromethane which was washed with 50 ml of dilute ammonium hydroxide, dried over anhydrous sodium sulfate and chromatographed through Florisil. The column was eluted first with dichloromethane, then with ether and finally with ethyl acetate. The ether and ethyl acetate fractions were combined and evaporated. The residue was crystallized and recrystallized from methanol to give (3-ethyl-6,8-dihydro-1-methyl-4-phenylpyrazolo[3,4-e][1,4]diazepin-7(1H)-ylidene)-malonic acid dimethyl ester as off-white rods, mp. 145—148°.

A solution of 1.7 g (0.00445 m) of (3-ethyl-6,8-dihydro-1-methyl-4-phenylpyrazolo[3,4-e][1,4]diazepin-7(1H)-ylidene) malonic acid dimethyl ester in 40 ml of methanol was treated with a 0.56 g (0.01 m) of potassium hydroxide, and the solution was refluxed for 2.5 hr. The solvent was evaporated, and the residue was partitioned between 50 ml of dichloromethane and 30 ml of water. The water layer was first acidified with hydrochloric acid then made basic with ammonium hydroxide and extracted with 75 ml of dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate and filtered through Florisil. The Florisil was eluted with ether, and then with ethyl acetate. The eluents were combined and evaporated to give the crude monoester as an oil. This product was not further purified but was dissolved in 10 ml of glacial acetic acid and treated with 0.35 g (0.005 m) of sodium nitrite while stirring. After 45 min the reaction mixture was poured into 100 ml of water, which was extracted with 75 ml of dichloromethane. The organic layer was washed with 50 ml of dilute sodium bicarbonate solution, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was crystallized from a mixture of ethyl acetate and ether. Recrystallization from a mixture of dichloromethane and ether gave (3-ethyl-1,6-dihydro- α -hydroxyimino-1-methyl-4-phenylpyrazolo[3,4-e][1,4]diazepin-7-acetic acid methyl ester as off-white rods, mp. 225—227°.

A solution of 0.35 g (0.000986 m) of (3-ethyl-1,6-dihydro- α -hydroxyimino-1-methyl-4-phenylpyrazolo[3,4-e][1,4]diazepin-7-acetic acid methyl ester in 20 ml of dry tetrahydrofuran, and 25 ml of methanol was treated with 2 ml (0.0109 m) of triethylorthoacetate and 1 spatula of Raney nickel. The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 2.5 hr. The catalyst was removed by filtration and the spent nickel was washed with methanol. The combined filtrates were evaporated and the residue was dissolved in 50 ml of dichloromethane. The solution was washed with 40 ml of dilute ammonium hydroxide, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was refluxed for 20 min. in a solution of 50 ml of methanol, containing 2 ml (0.109 m) of triethylorthoacetate and 0.2 ml (0.00114 m) of 5.7 N ethanolic hydrogen chloride. Solvents were removed by evaporation under reduced pressure and the residue was dissolved in dichloromethane, which was then washed with dilute ammonium hydroxide, dried over anhydrous sodium sulfate and evaporated. The crude product, obtained as an oil, was developed on three silica gel thick layer plates in a mixture of 5% methanol in ethyl acetate. The product which had an R_f of 0.5 was scraped off, stirred with methanol and filtered. The solution was evaporated, and the residue was crystallized from ether to give (3-ethyl-1,6-dihydro-1,9-dimethyl-4-phenylimidazo[1,5-a]-pyrazolo[4,3-f][1,4]diazepin-7-carboxylic acid methyl ester as white prisms, mp. 181—184°.

Example 81.

A mixture of 31 g (0.075 m) of 7-chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2H-1,4-benzodiazepine 4-oxide, 4 g (0.095 m) of sodium hydroxide, 300 ml of methanol and 5 ml of water was heated to reflux for 3 hours. After cooling, the mixture was diluted with water. The precipitated crystals are collected and recrystallized from methanol to yield 7-chloro-1,3-dihydro-2-(methoxycarbonylmethylene)-5-phenyl-2H-1,4-benzodiazepine 4-oxide, m.p. 215—216°.

Sodium nitrite (1.4 g, 0.02 m) was added to a solution of 6.8 g (0.02 m) of 7-chloro-1,3-dihydro-2-(methoxycarbonylmethylene)-5-phenyl-2H-1,4-benzodiazepine 4-oxide in 100 ml of glacial acetic acid. After stirring for 15 minutes

at room temperature the reaction mixture was diluted with 100 ml of water. The crystals were collected, washed with water and dried to leave 7 - chloro - alpha-hydroxyimino - 5 - phenyl - 3H - 1,4 - benzodiazepine - 2 - acetic acid methyl ester 4-oxide as a yellow product m.p. 237—239° (dec.). The analytical sample was recrystallized from dimethylformamide/methanol and had the same melting point.

Example 82.

To a solution of 10 g (0.0264 m) of 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7-iodo - 2H - 1,4 - benzodiazepin - 2 - one in 140 ml of dry tetrahydrofuran was added 1.8 g (0.039 m) of 54% of sodium hydride under argon with stirring. The reaction was refluxed for 1 hour, cooled to 0°, and 10.8 g (0.0422 m) of phosphorodimorpholide chloride was added. After 18 hours the solution was filtered, concentrated to a small volume and ether was added. The solid was filtered and recrystallized from a mixture of dichloromethane and ether to give 5 - (2 - fluorophenyl) - 7 - iodo - 2-bis(morpholino) - phosphinyloxy - 3H - 1,4 - benzodiazepine as white plates, m.p. 104—112°.

Example 83.

A stirred suspension of 54% sodium hydride in mineral oil dispersion (3.35 g, 0.075 m) in 267 ml of dimethylformamide was treated under argon with 17.5 g (0.08 m) of diethyl acetamidomalonate in several portions. The mixture was stirred at room temperature 30 minutes longer and then treated with 26.7 g (0.05 m) of 7-bromo - 2 - [bis(morpholino)phosphinyloxy] - 5 - (2 - pyridyl) - 3H - 1,4 - benzodiazepine in one portion. Stirring under argon at room temperature was continued for 7 hours. The dark mixture was poured over ice-acetic acid and diluted with water to give a greenish yellow solid. The solid was filtered, washed with water and air dried on the funnel. About 7 g of the solid was chromatographed over silica gel and eluted with ethyl acetate to give amorphous solid which showed one spot on tlc (ethyl acetate); Rf 0.5. When stirred with a small amount of isopropanol, the solid crystallized. Recrystallization of a sample from isopropanol gave acetylamino[7 - bromo - 5 - (2-pyridyl) - 3H - 1,4 - benzodiazepin - 2 - yl]malonic acid diethyl ester as light tan plates, m.p. 178—180°.

Example 84.

Phosphorous pentachloride, 0.46 g (2.2 mmol), was added to a suspension of 0.785 g (2 mmol) of 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo-[1,5-a]thieno[3,2-f][1,4]diazepine - 3 - carboxylic acid in 50 ml of methylene chloride. After stirring under nitrogen in an ice bath for 30 min., dimethylamine was introduced until the reaction mixture was alkaline. It was stirred for 30 min. at room temperature and washed with saturated sodium bicarbonate solution, dried and evaporated. Crystallization of the residue from ethyl acetate/ether gave 8 - chloro - 6 - (2 - chlorophenyl) - 1,N,N - trimethyl - 4H - imidazo[1,5-a]thieno[3,2-f][1,4]diazepine - 3-carboxamide as off white crystals which were recrystallized from ethyl acetate for analysis, m.p. 197—200°.

Example 85.

A solution of 4.15 g (20.1 mmol) of ethyl 2 - [(phenylmethylene)amino]acetate* N-oxide in 200 ml of tetrahydrofuran was cooled to -73° and 13.2 ml (21.2 mmol) of n-butyl lithium in hexane was added slowly dropwise to give a light orange solution. After 15 min., a solution of 10.15 g (20 mmol) of 7 - chloro - 2 - di(morpholino)-phosphinyloxy - 5 - (2 - fluorophenyl) - 3H - 1,4 - benzodiazepine in 225 ml of tetrahydrofuran was added slowly dropwise and the resulting dark brown suspension was allowed to warm to room temperature and stir overnight. The mixture was quenched with 3 ml of water and the solvent was removed in vacuo. The residue was diluted with 300 ml of water and extracted repeatedly with ether. The combined organic layers were washed twice with water, once with brine, dried with anhydrous magnesium sulfate and concentrated in vacuo to give the crude product as a light yellow solid. Recrystallization from aqueous acetone gave ethyl 8 - chloro - 6 - (2 - fluorophenyl) - 1 - phenyl - 4H-imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate as a white crystalline solid. Concentration of the mother liquor gave a further yield of final product.

* E. Buehler and G. B. Brown, J. Org. Chem., 32, 265 (1967).

Example 86.

A mixture of 375 mg. of 2 - [(amino)methoxycarbonylmethylene] - 7 - chloro - 5 - (2 - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepine, 20 ml. of toluene and 0.5 ml. of benzaldehyde was heated to reflux for 10 minutes over molecular sieves 5A. Following the addition of 1 g. of activated manganese dioxide refluxing was con-

tinued for another 10 minutes. The mixture was filtered over Celite and the filtrate was evaporated. The crystalline residue was collected with ether and recrystallized from ethyl acetate/hexane to yield off-white crystals of methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate with m.p. 272—275°C.

Example 87.

A solution of 94.6 g (0.3 m) of 5 - (2 - chlorophenyl) - 1,3 - dihydro - 7 - nitro - 2H - 1,4 - benzodiazepin - 2 - one in 2 l of tetrahydrofuran and 300 ml of benzene was cooled in ice-water and saturated with methylamine. A solution of 40.2 ml (0.36 m) of titaniumtetrachloride in 300 ml of benzene was added through a dropping funnel. After addition the mixture was stirred and refluxed for 3 hours. Water (300 ml) was added slowly to the cooled reaction mixture. The inorganic solids were separated by filtration and washed well with tetrahydrofuran. The water was separated from the filtrate and the organic phase was dried over sodiumsulfate and evaporated. The residue was chromatographed over 500 g of silica gel using 10% (v/v) ethanol in methylene chloride. Crystallization of the clean fractions from methylene chloride/ethanol yielded 5 - (2 - chlorophenyl) - 7 - nitro - 2 - methylamino - 3H - 1,4 - benzodiazepine as a yellow product with m.p. 219—221°.

Sodium nitrite (8.63 g, 0.125 m) was added in three portions over a 15 minute period to a solution of 33.9 g (0.1 m) of 5 - (2 - chlorophenyl) - 7 - nitro - 2 - methylamino - 3H - 1,4 - benzodiazepine in 200 ml of glacial acetic acid. After addition stirring was continued for 1 1/2 hours at room temperature and the product was precipitated by addition of water. The yellow solids were collected, washed with water, sucked dry and recrystallized from ethanol to yield 5 - (2 - chlorophenyl) - 7 - nitro - 2 - (N - nitrosomethylamino) - 3H - 1,4 - benzodiazepine as yellow crystals with m.p. 164—166°. The analytical sample was recrystallized from methylene chloride/ethanol, m.p. 167—169°.

Example 88.

A solution of 23.6 g (0.10 mole) of 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one in 1 liter of tetrahydrofuran (containing about 20 moles of monomethylamine) was chilled in an ice bath. To this mixture was added 14 ml. (d = 1.73, 0.125 mole) of titanium tetrachloride in 200 ml of benzene.

This mixture was stirred at room temperature for two days. The titanium complex was destroyed with 20 ml of water. The inorganic salts that precipitated, were removed by filtration. The solvent was evaporated in vacuo, the residue was partitioned between methylene chloride and water. A colorless amorphous solid mp. 227—229° was removed by filtration. An additional sample, mp. 226—228° of a colorless solid was obtained from the methylene chloride mother liquors after drying over anhydrous sodium sulfate, evaporation to dryness, and crystallization from ethyl acetate.

An analytical sample was prepared by recrystallization from dimethylformamide to yield colorless prisms, mp. 227—229°C.

To a cooled (10°), stirred solution of 10.0 g (0.04 m) of 2 - methylamino - 5 - phenyl - 3H - 1,4 - benzodiazepine in 100 ml of pyridine was added 100 ml of a saturated solution of nitrosyl chloride in acetic anhydride. The solution was stirred for 3.5 hr. during which time it was allowed to warm to ambient temperature. The solution was poured into 300 ml of ice-water, and the aqueous solution was extracted with five 150 ml portions of methylene chloride. The combined organic extracts were washed with water and brine, dried (CaSO₄), and the solvent removed under reduced pressure affording a dark semi-solid. Chromatography on 500 g of silica gel (chloroform elution) afforded the 2 - (N - nitrosomethylamino) - 5 - phenyl - 3H - 1,4 - benzodiazepine, mp. 192—199° (dec.).

Example 89.

To a stirred solution of 6 g (0.02 m) of 7 - chloro - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 3 - methyl - 2H - 1,4 - benzodiazepin - 2 - one in 100 ml of dry tetrahydrofuran was added 1.05 g (0.25 m) of 57% sodium hydride dispersion in mineral oil. The mixture was placed under argon and refluxed for 1 hr. After cooling to room temperature, the mixture was treated with 7.4 g (0.03 m) of dimorpholinophosphinic chloride and stirring under argon was continued at room temperature for 2 hrs. The mixture was filtered and evaporated at reduced pressure to give a gummy residue. Stirring the gum with 100 ml of anhydrous ether gave white crystals which were collected by filtration, washed with a little ether and air dried. 7 - Chloro - 2 - di - (morpholino) - phosphinyloxy - 5 - (2 - fluorophenyl) - 3 - methyl - 3H - 1,4 - benzodiazepine thus obtained had a mp. of 90—95°.

Example 90.

A solution of 19.3 g (0.06 m) of 1,3 - dihydro - 7 - (2 - methyl - 1,3 - dioxolan - 2 - yl) - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one in 300 ml of dry tetrahydrofuran was treated under an atmosphere of argon with 3.1 g (0.075 m) of a 57% suspension of sodium hydride in mineral oil. The mixture was heated under reflux for 1 hr., cooled to room temperature when 22.2 g (0.087 m) of dimorpholinophosphinic chloride was added. The mixture was allowed to stir at room temperature for 2 hr. and then stand overnight. Sodium chloride was removed by filtration and the crude 7 - (2 - methyl - 1,3 - dioxolan - 2 - yl) - 2 - [bis(morpholino)phosphinyloxy] - 5 - phenyl - 3H - 1,4 - benzodiazepine was obtained by removal of the solvent and crystallization of the residue from ether.

Example 91.

A solution of 56.4 g (0.20 mole) of 1,3 - dihydro - 7 - ethyl - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepin - 2 - one in 2.0 l of tetrahydrofuran containing 4 moles of monomethylamine was chilled in an ice bath. To this was added 33.0 ml (0.30 mole) of titanium tetrachloride in 350 ml of benzene. The mixture was stirred at room temperature for three days.

The titanium tetrachloride was decomposed with 100 ml of water. The inorganic salts were removed by filtration. The filtrate was evaporated to dryness in vacuo. The residue was partitioned between methylene chloride and water. The methylene chloride layer was dried over anhydrous sodium sulfate, evaporated to dryness in vacuo. The residue on crystallization from acetonitrile yielded 7 - ethyl - 5 - (2 - fluorophenyl) - 2 - methylamino - 3H - 1,4 - benzodiazepine as light yellow prisms, m.p. 172—174°.

An analytical sample was prepared by recrystallization from acetonitrile to give light yellow prisms, m.p. 172—174°.

Sodium nitrite (8.6 g, 0.125 m) was added in three portions over a 1/2 hour period to a solution of 29.5 g (0.1 m) of 7 - ethyl - 5 - (2 - fluorophenyl) - 2 - methylamino - 3H - 1,4 - benzodiazepine in 100 ml of glacial acetic acid. After stirring for another 1/2 hour at room temperature, the mixture was diluted with ice-water and extracted with methylene chloride. The extracts were washed with water and aqueous bicarbonate, dried over sodium sulfate and evaporated to leave crude 7 - ethyl - 5 - (2 - fluorophenyl) - 2 - (N - nitrosomethylamino) - 3H - 1,4 - benzodiazepine as a yellow oil.

Example 92.

Method A: Preparation of 7 - Ethyl - 1,9 - dimethyl - 6 - phenyl - 4H,9H - imidazo[1,5-a]pyrazolo[4,3-f][1,4]diazepin - 3 - carboxylic acid, methyl ester

A solution of 0.35 g (0.000986 M) of 3 - ethyl - 1,6 - dihydro - α - hydroxyimino - 1 - methyl - 4 - phenylpyrazolo[3,4-e][1,4]diazepin - 7 - acetic acid, methyl ester in 20 ml of dry tetrahydrofuran, and 25 ml of methanol was treated with 2 ml (0.0109 M) of triethylorthoacetate and 1 spatula of Raney nickel. The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 2.5 hr. The catalyst was removed by filtration and the spent nickel was washed with methanol. The combined filtrates were evaporated and the residue was dissolved in 50 ml of dichloromethane. The solution was washed with 40 ml of dilute ammonium hydroxide, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was refluxed for 20 min in a solution of 50 ml of methanol, containing 2 ml (0.109 M) of triethylorthoacetate and 0.2 ml (0.00114 M) of 5.7 N ethanolic hydrogen chloride. Solvents were removed by evaporation under reduced pressure and the residue was dissolved in dichloromethane, which was then washed with dilute ammonium hydroxide, dried over anhydrous sodium sulfate and evaporated. The crude product, obtained in an oil was developed on three silica gel thick layer plates in a mixture of 5% methanol in ethyl acetate. The product which had an R_f of 0.5 was scraped off, stirred with methanol and filtered. The solution was evaporated, and the residue was crystallized from ether to give the pure product as white prisms, mp. 186—189°.

Method B: 7 - Ethyl - 1,9 - dimethyl - 6 - phenyl - 4H,9H - imidazo[1,5-a]pyrazolo[4,3-f][1,4]diazepine - 3 - carboxylic acid, methyl ester

A stirred solution of 0.2 g (0.000567 M) of 3 - ethyl - 1,6 - dihydro - α - hydroxyimino - 1 - methyl - 4 - phenylpyrazolo[3,4-e]diazepin - 7 - acetic acid, methyl ester in 10 ml of dichloromethane and 0.35 ml of acetic acid was treated with 0.4 g (0.0061 M) of zinc dust and stirring was continued for 5 min. The mixture was filtered, and the zinc was washed with dichloromethane and tetrahydrofuran. The combined filtrates were next treated with 0.3 ml (0.00164 M) of triethylorthoacetate. The mixture was evaporated under reduced pressure and the residue was heated under reflux for 1 min in a solution of 15 ml of ethyl acetate which contained 0.3 ml of tri-

ethylorthoacetate. The solution was evaporated and developed on 2 thick layer silica gel plates in a solution of ethyl acetate containing methanol (10%). The area having an R_f of 0.2—0.4 was scraped off and washed with methanol. The methanol solution was filtered and evaporated. Crystallization of the residue from ethyl acetate and recrystallization from a mixture of ethyl acetate and ether gave final product as white rods, m.p. 186—189°.

Example 93.

Methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - (2 - pyridyl) - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxylate

A mixture of 8.5 g (0.02 m) of 2 - [(amino)methoxycarbonylmethylene] - 7-chloro - 5 - (2 - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepine ethanolate 200 ml of toluene, 4 ml of pyridine-2-carboxaldehyde and 15 g of molecular sieves 5A was heated to reflux for 10 min. Following addition of 20 g of activated manganese dioxide heating and stirring was continued for another 10 min. The mixture was filtered over Celite and the filtrate was evaporated. Crystallization of the residue from ethylacetate/ether yielded off-white crystals with mp. 282—285°. The analytical sample was recrystallized from methylene chloride/ethylacetate, mp. 283—285°.

Example 94.

Methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - propyl - 4H - imidazo[1,5-a][1,4]-benzodiazepine - 3 - carboxylate

A mixture of 4.5 g (0.0107 m) of 2 - [(amino)methoxycarbonylmethylene] - 7-chloro - 5 - (2 - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepine ethanolate, 100 ml of methylene chloride, 2 ml of butylaldehyde and 5 g of molecular sieves 5A was stirred at room temperature for 15 min. Activated manganese dioxide, 10 g, was then added and stirring was continued for additional 15 min. The mixture was filtered over Celite and the filtrate was evaporated. Crystallization of the residue from ether yielded a final product with mp. 196—198°. The analytical sample was recrystallized from ethylacetate/tetrahydrofuran/hexane, mp. 197—198°.

Example 95.

Methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - isopropyl - 4H - imidazo[1,5-a][1,4]-benzodiazepine - 3 - carboxylate

Following the procedure of Example 99, but substituting butylaldehyde by isobutylaldehyde gave a final product, crystallized from ether. For analysis it was recrystallized from ethylacetate/tetrahydrofuran/hexane, mp. 234—235°.

Example 96.

Methyl 8 - chloro - 1 - chloromethyl - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxylate

A solution of chloroacetaldehyde, 5 ml, which was prepared by heating a mixture of 50 ml 2N hydrochloric acid and 50 ml of chloroacetaldehyde dimethylacetal for 30 min to reflux, was added to a solution of 4.5 g (0.0107 mol) of 2 - [(amino)methoxycarbonylmethylene] - 7 - chloro - 5 - (2 - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepine ethanolate in 200 ml of methylene chloride. After stirring for 15 min, the reaction mixture was partitioned between methylene chloride and saturated aqueous sodium bicarbonate solution. The organic phase was dried and treated with 12 g of activated manganese dioxide. After stirring for 15 min at room temperature, the MnO_2 was separated by filtration over Celite and the filtrate was evaporated. Crystallization of the residue from methylene chloride/ether yielded the final product. The analytical sample was purified by chromatography over 30 fold amount of silica gel using methylene chloride/ethylacetate 7:3 (v/v). The pure product was crystallized from ether, mp. 237—239° dec.

Example 97.

Methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - (2 - dimethylaminoethyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate

Dimethylamine, 5 ml, and 2 ml of acrolein were added to a solution of 4.5 g (0.0107 mol) of 2 - [(amino)methoxycarbonylmethylene] - 7 - chloro - 5 - (2 - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepine ethanolate in 100 ml of methylene chloride. After stirring for 10 min at room temperature, 12 g of activated manganese dioxide was added and stirring was continued for 15 min. The MnO_2 was removed by filtration over Celite and the filtrate was evaporated. Crystallization of the residue from ethanol/ether yielded final product which was recrystallized from ethylacetate/methanol/hexane for analysis, mp. 203—204°.

Example 98.

8 - chloro - 6 - (2 - chlorophenyl) - 1 - (2 - pyridyl) - 4H - imidazo[1,5-a][1,4]-benzodiazepine - 3 - carboxylic acid

A mixture of 4.3 g (0.009 mol) of methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - (2 - pyridyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate, 200 ml of methanol, 10 ml of water and 1.7 g (0.03 m) of potassium hydroxide was heated to reflux for 4 hrs. After partial evaporation of the solvent, the residue was acidified with glacial acetic acid and diluted with water. The precipitated product was collected, washed with water and dried to leave crystalline material which for analysis was recrystallized from methylene chloride/methanol/ethylacetate, mp. 262—265° dec.

Example 99.

8 - chloro - 6 - (2 - chlorophenyl) - 1 - (2 - pyridyl) - 4H - imidazo[1,5-a][1,4]-benzodiazepine - 3 - carboxamide

Phosphorus pentachloride, 3 g (0.0145 mol) was added to a suspension of 4 g (0.0089 mol) of 8 - chloro - 6 - (2 - chlorophenyl) - 1 - (2 - pyridyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylic acid in 250 ml of methylene chloride cooled by ice/water. After stirring for 30 min over ice/water, ammonia gas was introduced until the mixture showed alkaline reaction. Aqueous ammonia, 20 ml, and 200 ml of methylene chloride were then added and stirring was continued for 15 min. The organic layer was separated, dried over sodium sulfate and passed over a pad of silica gel using 5% (v/v) of ethanol in methylene chloride. The solution was evaporated and the residue was crystallized from ethanol/ethylacetate to yield off-white crystals which were recrystallized for analysis from methylene chloride/ethylacetate, mp. 255—257°, reset and melted again at 275—278°.

Example 100.

8 - chloro - 6 - (2 - chlorophenyl) - 1 - propyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide

Reaction of 1.5 g (3.5 mmol) of methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - propyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate with 20 ml of methanolic ammonia yielded, under the conditions described in Example 106, a final product, crystallized from methylene chloride/ethanol, mp. 298—300°.

Example 101.

8 - chloro - 6 - (2 - chlorophenyl) - 1 - isopropyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide

A mixture of 1.3 g (3 mmol) of methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - isopropyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate and 20 ml of methanol containing 20% of weight of ammonia was heated in an autoclave at 130° for 20 hrs. The solvent was evaporated and the residue was crystallized from methylene chloride/ethanol to give the final product with mp. 328—330°. The analytical sample was recrystallized from the same solvents.

Example 102.

8 - chloro - 6 - (2 - chlorophenyl) - 1 - (2 - dimethylaminoethyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide

A mixture of 0.46 g of methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - (2 - dimethylaminoethyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate and 10 ml of methanol containing 20% of ammonia was heated in the bomb for 20 hours at 130°. The solvent was evaporated and the residue was chromatographed over silica gel (7 g) using 20% of ethanol in methylene chloride. Crystallization of the clean fractions from 2-propanol gave pure product with mp. 249—251°.

Example 103.

8 - chloro - 6 - (2 - chlorophenyl) - N - methyl - 1 - methylaminomethyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide

A solution of methylamine in tetrahydrofuran, 75 ml containing 20% methylamine, was added to a solution of 3 g (6.9 mmol) of methyl 8 - chloro - 1 - chloromethyl - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate in 50 ml of tetrahydrofuran. The mixture was heated to 100° for 18 hrs. in a sealed vessel. The solvent was evaporated and the residue was crystallized from ethanol to yield final product which was purified by chromatography over 50 g of silica gel using 5% (v/v) of ethanol in methylene chloride. The combined clean fractions gave

after evaporation and crystallization from methylene chloride/ethanol, product with mp. 270—273°.

Example 104.

Methyl 1 - Aminomethyl - 8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxylate, hydrochloride

A solution of 2.4 g (5.4 mmol) of methyl 1 - azido - methyl - 8 - chloro - 6 - (2-chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate in 50 ml of tetrahydrofuran and 50 ml of ethanol was hydrogenated for 2 hrs at atmospheric pressure with Raney nickel as catalyst. The catalyst was removed by filtration and the filtrate was evaporated. The residue was dissolved in 2-propanol and the solution was treated with 5 mmol of ethanolic hydrogen chloride. The precipitated hydrochloride was collected and recrystallized from 2-propanol/methanol to yield product with mp. 265—270° dec. The analytical sample was recrystallized from the same solvents, mp. 270—275° dec.

Example 105.

Methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - dimethylaminomethyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate

A mixture of 0.435 g (1 mmol) of methyl 8 - chloro - 1 - chloromethyl - 6 - (2-chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate, 15 ml of tetrahydrofuran and 1.5 ml of dimethylamine was heated in a sealed tube at 100° for 3 hrs. The solvent was evaporated and the residue was partitioned between methylene chloride and aqueous sodium bicarbonate solution. The organic phase was dried and evaporated and the residue was crystallized from ether to yield final product. The analytical sample was recrystallized from ethylacetate/hexane mp. 181—183°.

Example 106.

Methyl 1 - azidomethyl - 8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxylate

A mixture of 2.18 g (5 mmol) of methyl 8 - chloro - 1 - chloromethyl - 6 - (2-chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate, 0.65 g (10 mmol) of sodium azide and 30 ml of dimethylformamide was heated to reflux for 5 min. The product was precipitated by addition of water, was collected and dissolved in methylene chloride. The solution was dried and evaporated. Crystallization from ethylacetate/ether yielded colorless crystals with mp. 187—189°. The analytical sample was recrystallized from ethylacetate/hexane, mp. 188—190°.

Example 107.

Methyl 1 - acetoxymethyl - 8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxylate

A mixture of 0.435 g (1 mmol) of methyl 8 - chloro - 1 - chloromethyl - 6 - (2-chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate, 0.5 g of sodium acetate and 20 ml of dimethyl formamide was heated to reflux for 10 min under an atmosphere of nitrogen. The solvent was removed under reduced pressure and the residue was partitioned between water and methylene chloride. The methylene chloride layer was dried and evaporated and the residue was chromatographed over 7 g of silica gel using 30% (v/v) of ethylacetate in methylene chloride. Crystallization of the combined clean fractions from ether yielded final product with mp. 186—188°. For analysis it was recrystallized from methylene chloride/ether/hexane.

Example 108.

1 - Aminomethyl - 8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide hydrochloride hemihydrate hemiisopropanolate

A solution of 2 g (4.65 mmol) of 7 - azidomethyl - 8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide in 150 ml of tetrahydrofuran and 75 ml of ethanol was hydrogenated for 1 1/2 hours at atmospheric pressure with Raney nickel as catalyst. The catalyst was separated by filtration and the filtrate was evaporated. Crystallization from ethanol/ether yielded final product with mp. 230—235° which was converted to the hydrochloride as follows: 1.2 g of the above base was dissolved in a mixture of hot ethanol and methanol. Ethanolic hydrogen chloride (3 mmol) was added. The mixture was concentrated and the hydrochloride was crystallized by addition of isopropanol and cooling. The crystals were collected, washed with 2-propanol and ether to leave product with mp. 250—260°. The analytical sample was recrystallized from methanol/2-propanol to give crystals which analyzed for a hemihydrate hemiisopropanolate, mp. 250—260° undefined.

Example 109.

8 - chloro - 6 - (2 - chlorophenyl) - 1 - dimethylaminoethyl - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxamide

A mixture of 0.44 g (1 mmol) of methyl 8 - chloro - 6 - (2 - chlorophenyl) - 1 - dimethylaminomethyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate and 15 ml of methanol containing 20% of ammonia was heated for 16 hrs at 130° in an autoclave. The solvent was evaporated and the residue was crystallized from ethanol/ether yield final product. The analytical sample was purified by passing over silica gel using methylene chloride/ethylacetate 1:1 (v/v) and crystallization from ethylacetate, mp. 242—245°.

Example 110.

1 - Azidomethyl - 8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide

A mixture of 4.4 g (0.01 mol) of methyl 1 - azidomethyl - 8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate 200 ml of methanol, 10 ml of water and 1.7 g (0.03 mol) of potassium hydroxide was heated to reflux for 3 hrs. After partial evaporation the mixture was acidified with glacial acetic acid and diluted with water. The precipitated product was collected and dissolved in methylene chloride. The solution was dried and evaporated and the residue was crystallized from methylene chloride/ethylacetate/hexane to yield 1 - azidomethyl - 8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylic acid which was converted to the amide as follows: Phosphorus pentachloride 2.1 g (0.01 mol) was added to a suspension of the above material in 200 ml of methylene chloride and the mixture was stirred in ice-water for 20 min. A stream of ammonia was then introduced until the reaction mixture was alkaline. After stirring for an additional 15 min, aqueous ammonia was added and stirring was continued for 1 hr at room temperature. The mixture was diluted with methylene chloride and washed with saturated sodium chloride solution. The organic phase was dried and evaporated. The residue was chromatographed over 120 g of silica gel using 2.5% (v/v) of ethanol in methylene chloride. The clean fractions were combined and evaporated and the residue was crystallized from ethanol to yield final product with mp. 258—260° dec. The analytical sample was recrystallized from methylene chloride/ethylacetate.

Example 111.

Methyl 8 - chloro - 6 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate

Raney nickel, 2 teaspoonsful, was added to a solution of 10 g (0.028 mol) of 7 - chloro - alpha - hydroximino - 5 - phenyl - 3H - 1,4 - benzodiazepine - 2 - acetic acid, methyl ester in a mixture of 200 ml of methanol and 200 ml of tetrahydrofuran. The mixture was hydrogenated at atmospheric pressure for 5 hrs. The catalyst was separated by filtration over Celite and the filtrate was evaporated to dryness. The residue was dissolved in 100 ml of methanol and the solution was treated with 10 ml of triethyl orthoformate and 5 ml of ethanolic hydrogen chloride. After refluxing the mixture for 10 min the solvent was evaporated under reduced pressure and the residue was partitioned between methylene chloride and saturated aqueous sodium bicarbonate solution. The organic phase was dried and evaporated. Crystallization of the residue from ether yielded final product which was recrystallized from methylene chloride/ether for analysis mp. 235—236°.

Example 112.

Methyl 8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate

A mixture of 9 g of 2 - [(amino)methoxycarbonyl methylene] - 7 - chloro - 5 - (2 - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepine ethanolate, 100 ml of toluene and 20 ml of triethyl orthoformate was heated to reflux for 15 min. The solvent was evaporated under reduced pressure and the crystalline residue was collected with ether and recrystallized from ethylacetate/methanol to yield final product with mp. 206—208°.

Example 113.

8 - chloro - 6 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide

A mixture of 5 g of methyl 8 - chloro - 6 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate and 100 ml of methanol containing 20% of ammonia was heated to 130° in an autoclave for 8 hrs. The precipitated crystals were collected and recrystallized from tetrahydrofuran/methanol to yield final product with mp.

295—296°. The analytical sample was recrystallized from dimethylformamide/ether, mp. 296—297°.

Example 114.

8 - chloro - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3-carboxamide

Phosphorus pentachloride, 2.6 g (0.0125 m) was added to a suspension of 3.55 g (0.01 m) of 8 - chloro - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylic acid in 200 ml of methylene chloride cooled with ice/water. After stirring for 30 min ammonia gas was introduced until the reaction mixture was alkaline. After additional 15 min aqueous ammonia was added and stirring was continued for 30 min. The reaction mixture was then partitioned between water and methylene chloride containing 10% (v/v) of ethanol. The organic phase was dried and passed over a pad of silica gel. The solution was evaporated and the solid residue was recrystallized from ethanol to yield the final product. The analytical sample was recrystallized from tetrahydrofuran/ethanol, mp. 292—294°.

Example 115.

8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3-carboxamide

A mixture of 5 g (0.013 mol) of methyl 8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate and 75 ml of methanol containing 20% of ammonia was heated in an autoclave at 130° for 18 hrs. The reaction mixture from which the product had crystallized was heated in methanol/methylene chloride until solution was complete. Filtration and concentration yielded the final product with mp. >300°. The analytical sample was recrystallized from methylene chloride/ethanol.

Example 116.

8 - chloro - N,N - dimethyl - 6 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide

A mixture of 5 g (0.014 mol) of methyl 8 - chloro - 6 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate, 2.4 g (0.043 mol) of potassium hydroxide, 10 ml of water and 140 ml of methanol heated to reflux for 6 hrs. The solvent was evaporated and the residue was dissolved in water. The solution was filtered and acidified with glacial acetic acid. The precipitated crystals were collected and crystallized from methylene chloride/ethanol to give 8 - chloro - 6 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylic acid with mp. 268—270°.

1 g of this acid was stirred with 1.3 g of phosphorus pentachloride and 100 ml of methylene chloride at room temperature for 2 hrs. Dimethylamine was bubbled into the mixture with cooling until a clear solution with basic pH resulted. The solution was then washed with sodium chloride solution and water. The methylene chloride layer was dried and evaporated.

Crystallization of the residue from ether yielded the final product which was recrystallized from methylene chloride/ethylacetate for analysis, mp. 231—233°.

Example 117.

8 - chloro - 6 - (2 - chlorophenyl) - N,N - dimethyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide

A mixture of 2 g of methyl 8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate, 15 ml of hexamethyl phosphoric triamide and 1.5 g of lithium chloride was heated to 225°. The cooled reaction mixture was partitioned between water and methylene chloride/ether. The organic phase was washed with aqueous bicarbonate solution, was dried and evaporated. Crystallization from ether yielded the final product which was recrystallized from ethylacetate/methanol for analysis, mp. 240—242°.

Example 118.

8 - chloro - 6 - (2 - chlorophenyl) - 3 - hydroxymethyl - 4H - imidazo[1,5-a][1,4]benzodiazepine isopropanolate

A solution of 25 g (0.065 mol) of methyl 8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylate in 250 ml of tetrahydrofuran was added at -10° to a suspension of 5 g of lithium aluminum hydride in 200 ml of ether. After addition the mixture was stirred between -5° and 0° for 15 min. The mixture was then hydrolyzed by addition of 25 ml of water. The inorganic material was separated by filtration over Celite and the filtrate was dried and evaporated. Crystallization of the residue from methylene chloride/ether/ethylacetate yielded the solvated product.

Recrystallization from 2-propanol/ether gave a solvate with mp. 103—105° dec. which according to analytical and spectral data contained 1 mol of isopropanol.

Example 119.

8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxaldehyde

A mixture of 0.5 g of 8 - chloro - 6 - (2 - chlorophenyl) - 3 - hydroxymethyl - 4H - imidazo[1,5-a][1,4]benzodiazepine isopropanolate, 40 ml of methylene chloride and 2.5 g of activated manganese dioxide was stirred at room temperature for 2 hrs. The MnO₂ was removed by filtration over Celite and the filtrate was evaporated. Crystallization of the residue from ether gave the final product with mp. 213—215°.

Example 120.

8 - chloro - 3 - chloromethyl - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine

Crude 8 - chloro - 6 - (2 - chlorophenyl) - 3 - hydroxymethyl - 4H - imidazo[1,5-a][1,4]benzodiazepine, 6 g, was added slowly to 30 ml of thionyl chloride. Following addition the mixture was stirred for 15 min at room temperature and then gradually diluted with 100 ml of ethylacetate. The precipitate crystals were collected after 15 min and partitioned between methylene chloride and saturated aqueous sodium bicarbonate solution. The methylene chloride/ether yielded the final product. The analytical sample was purified by passing over silica gel using 10% (v/v) of ethylacetate in methylene chloride followed by crystallization from ether, mp. ca. 165°. The crystals do not melt upon slow heating but on immersion at about 165°.

Example 121.

3 - acetyl - 8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine

A solution of 2.8 g (7.8 mmol) of 8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxaldehyde in 150 ml of tetrahydrofuran was added to 50 ml of a 1 molar solution of methyl magnesium iodide in ether. After stirring for 15 min at room temperature the reaction mixture was hydrolysed by addition of water, diluted with tetrahydrofuran dried over sodium sulfate and filtered over Celite. The filtrate was evaporated and the residue was chromatographed over 60 g of silica gel using 5% (v/v) of ethanol in methylene chloride. The clean fractions containing 8 - chloro - 6 - (2 - chlorophenyl) - 3 - (1 - hydroxyethyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine were combined and evaporated. The residue was dissolved in 100 ml of methylene chloride and stirred for 2 hrs at room temperature after addition of 15 g of activated manganese dioxide. The MnO₂ was removed by filtration over Celite and the filtrate was evaporated. The residue was again purified by chromatography over 30 g of silica gel using 10% (v/v) of ethylacetate in methylene chloride. Crystallization of the combined clean fractions from ethylacetate/hexane gave the final product with mp. 214—216°.

Example 122.

8 - chloro - 6 - (2 - chlorophenyl) - 3 - methoxymethyl - 4H - imidazo[1,5-a][1,4]benzodiazepine

A mixture of 2.7 g (7.15 mmol) of 8 - chloro - 3 - chloromethyl - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine, 50 ml of methanol and 3 ml of triethylamine was heated to reflux for 20 min. The solvent was evaporated and the residue was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The methylene chloride layer was dried and evaporated and the residue was dissolved in 2-propanol and treated with ethanolic hydrogen chloride. The crystalline dihydrochloride with mp. >230° dec. which precipitated was collected and partitioned between methylene chloride and aqueous sodium carbonate solution. The organic phase was dried and evaporated and the residue was crystallized from ether/hexane to yield final product with mp. 126—130°. The analytical sample was recrystallized from ether.

Example 123.

8 - chloro - 6 - phenyl - 1,N,N - trimethyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide

A mixture of 1.5 g (4.2 mmol) of 8 - chloro - 1 - methyl - 6 - phenyl - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxylic acid, 1.7 g (8 mmol) of phosphorus pentachloride and 100 ml of methylene chloride was stirred under argon for 3 hrs. Dimethylamine was introduced at room temperature until a clear solution with basic pH resulted. The solution was washed with water, dried and evaporated. Crystal-

lization of the residue from ethylacetate/ether/hexane and recrystallization from ether gave final product with mp. 173—175°.

Example 124.

8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - N - phenyl - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxamide

Phosphorus pentachloride, 1.3 g (6.25 mmol) was added to a suspension of 1.9 g (5 mmol) of 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxylic acid in 100 ml of methylene chloride. After stirring for 30 min with cooling over ice/water, 7 ml of aniline was added and stirring was continued for 30 min at room temperature. The reaction mixture was partitioned between 10% aqueous sodium carbonate solution and methylene chloride. The organic layer was dried and evaporated. Crystallization of the residue from ether and recrystallization from methylene chloride/ethanol gave a final product which was recrystallized from tetrahydrofuran/ethanol for analysis, mp. 228—288°.

Example 125.

8 - chloro - N - cyclopropyl - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxamide

Phosphorus pentachloride, 1.3 g (6.25 mmol) was added to a suspension of 1.9 g (5.1 mmol) of 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxylic acid in 100 ml of methylene chloride. After stirring for 30 min over ice/water 3 ml of cyclopropylamine was added and stirring was continued for 10 min. The reaction mixture was washed with aqueous sodium carbonate solution, dried and evaporated. The residue was passed over a pad of silica gel using 10% (v/v) of ethanol in methylene chloride. Crystallization of the product from ethylacetate/hexane yielded final product as crystals with mp. 196—197°.

Example 126.

8 - chloro - 6 - (2 - chlorophenyl) - 1,1,N - trimethyl - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxamide

A stirred suspension of 3.6 g (0.0093 mole) of 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxylic acid in 75 ml of dichloromethane was cooled in an ice bath and treated with 2.1 g (0.01 mole) of phosphorus pentachloride in portions. The reaction was protected by a drying tube and stirring in the cold was continued 30 min. longer. With continued cooling dimethylamine was bubbled into the solution for 5 minutes and stirring was continued for an additional 30 min. The mixture was evaporated at reduced pressure to dryness. The gummy residue was stirred with water and basified with ammonium hydroxide. Extraction with methylene chloride followed by drying and evaporation *in vacuo* gave a tan foam. The foam was dissolved in 600 ml of boiling ether and filtered to remove some insoluble material. After concentrating the filtrate on a steam bath to about 250 ml, it was filtered again. Further concentration to about 100 ml with occasional scratching initiated crystallization. The flask was removed from the heat and cooled at room temperature overnight. The off-white prisms were filtered, washed with ether and air dried on the funnel to final product with mp. 225—230°. Recrystallization of a sample from benzene-ether raised the melting point to 228—232°.

Example 127.

8 - chloro - 5,6 - dihydro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxylic acid, 2,2 - dimethylhydrazide

A mixture of 1.2 g (2.9 mmol) of 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxylic acid, 2,2 - dimethylhydrazide, 50 ml of methylene chloride, 5 ml of glacial acetic acid and 2.5 g of zinc dust was stirred at room temperature for 2 hrs. The inorganic material was separated. The filtrate was washed with sodium carbonate solution, dried and evaporated. The residue was crystallized from ethylacetate/ether to yield a final product which was recrystallized from ethylacetate for analysis, mp. 218—219°.

Example 128.

8 - chloro - 6 - (2 - chlorophenyl) - 5,6 - dihydro - 1 - methyl - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxamide

A stirred solution of 7 g (0.018 mole) of 8 - chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxamide in 70 ml of glacial acetic acid treated with 5.6 g (0.087 g. atm) of zinc dust in portions. The

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stirred mixture was heated under argon in an oil bath at 110° for 5 hrs. After cooling to room temperature the mixture was filtered and the solid was washed with methylene chloride. The filtrate was concentrated at reduced pressure at 60° to remove methylene chloride and the residue was poured into cold water and basified with ice cold ammonia. The resulting white solid was filtered, washed with water and partially dried on the funnel. Treatment on the damp solid with 200 ml of 1N hydrochloric acid with stirring for 5 min and then filtering gave about 3 g of unreacted material as a white solid. When the filtrate was basified with cold, dilute ammonium hydroxide a white solid separated which was collected by filtration, washed with water and air dried on the funnel to give final product. Recrystallization from ethanol-methylene chloride gave white plates, m.p. 298—305° dec.

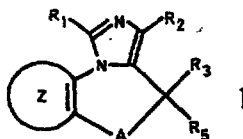
Example 129.

8 - chloro - 6 - (2 - chlorophenyl) - 5,6 - dihydro - 1 - methyl - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxamide hydrochloride 1 1/3 hydrate

A suspension of 1.3 g (0.0034 mole) of the base of Example 133 in 75 ml of 95% ethanol was treated with 10 ml of a 5.7N solution of hydrogen chloride in ethanol and boiled on a steam bath to give a clear solution. The solution was filtered and kept at room temperature overnight. White needles had separated. The product was filtered, washed with ethanol and air dried to give final product, mp. 310—315° dec. after changing to prisms at ca. 250°. Another amount of product, mp. 305—310° dec. was obtained by concentrating the mother liquor.

WHAT WE CLAIM IS:—

1. A process for the preparation of imidazo[1,5-a][1,4]diazepine compounds of the general formula



wherein A represents $-\text{C}(\text{R}_6)=\text{N}-$; R_1 represents hydrogen, lower alkyl, hydroxy lower alkyl, acyloxy lower alkyl, phenyl, alkoxy lower alkyl, halo lower alkyl, amino lower alkyl, substituted amino lower alkyl, substituted phenyl, pyridyl, aralkyl or the group $-\text{COR}_{10}$ (wherein R_{10} represents hydrogen or lower alkyl) or $-\text{COOR}$ (wherein R represents lower alkyl); R_2 represents chloro, bromo, iodo, hydroxy lower alkyl, acyloxy lower alkyl, alkoxy lower alkyl, halo lower alkyl, amino lower alkyl, cyano, cyano lower alkyl, acylamino, lower alkoxy carbonylamino, aralkyloxy carbonylamino, substituted amino lower alkyl, the group $-\text{COOR}_{10}$ (wherein R_{10} represents hydrogen or lower alkyl), the group $-\text{COR}_{10}$ (wherein R_{10} represents hydrogen or lower alkyl) or a derivative thereof, i.e., a) the group $-\text{C}(\text{R}_{10})=\text{N}-\text{R}_{11}$ wherein R_{11} represents hydrogen, lower alkyl, hydroxy, alkoxy, amino, mono or dialkylamino or arylamino and R_{10} represents hydrogen or lower alkyl; b) the group $-\text{CONR}_{12}\text{R}_{13}$, wherein R_{12} and R_{13} represent individually hydrogen, lower alkyl, hydroxy lower alkyl, lower alkenyl, aryl or the group $-(\text{CH}_2)_n\text{NR}_{14}\text{R}_{15}$ (wherein R_{14} and R_{15} represent individually hydrogen, lower alkyl, hydroxy lower alkyl or lower alkenyl, or R_{14} and R_{15} together form a part of a heterocyclic ring, and n is 1 to 4) or R_{12} and R_{13} together form a part of a heterocyclic ring; or c) the group $-\text{CON}(\text{R}_{16})\text{NR}_{17}\text{R}_{18}$, wherein one of R_{16} , R_{17} and R_{18} represents hydrogen or lower alkyl or the group $-(\text{CH}_2)_n\text{NR}_{14}\text{R}_{15}$ (wherein n is 1 to 4 and R_{14} and R_{15} represent individually hydrogen, lower alkyl, hydroxy lower alkyl or lower alkenyl or R_{14} and R_{15} together form a part of a heterocyclic ring) and the remaining R_{16} , R_{17} and R_{18} represent hydrogen or lower alkyl; and R_3 represents additionally hydrogen or lower alkyl in the case where R_1 represents hydroxy lower alkyl, acyloxy lower alkyl, halo lower alkyl, amino lower alkyl, substituted amino lower alkyl, the group $-\text{COR}_{10}$ (wherein R_{10} represents hydrogen or lower alkyl) or $-\text{COOR}$ (wherein R represents lower alkyl); R_5 represents hydrogen or lower alkyl; R_6 represents phenyl, mono-substituted phenyl, di-substituted phenyl, pyridyl or mono-substituted pyridyl; and



represents the group



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stirred mixture was heated under argon in an oil bath at 110° for 5 hrs. After cooling to room temperature the mixture was filtered and the solid was washed with methylene chloride. The filtrate was concentrated at reduced pressure at 60° to remove methylene chloride and the residue was poured into cold water and basified with ice cold ammonia. The resulting white solid was filtered, washed with water and partially dried on the funnel. Treatment on the damp solid with 200 ml of 1N hydrochloric acid with stirring for 5 min and then filtering gave about 3 g of unreacted material as a white solid. When the filtrate was basified with cold, dilute ammonium hydroxide a white solid separated which was collected by filtration, washed with water and air dried on the funnel to give final product. Recrystallization from ethanol-methylene chloride gave white plates, m.p. 298—305° dec.

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Example 129.

8 - chloro - 6 - (2 - chlorophenyl) - 5,6 - dihydro - 1 - methyl - 4H - imidazo[1,5-a]-[1,4]benzodiazepine - 3 - carboxamide hydrochloride 1 1/3 hydrate

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A suspension of 1.3 g (0.0034 mole) of the base of Example 133 in 75 ml of 95% ethanol was treated with 10 ml of a 5.7N solution of hydrogen chloride in ethanol and boiled on a steam bath to give a clear solution. The solution was filtered and kept at room temperature overnight. White needles had separated. The product was filtered, washed with ethanol and air dried to give final product, mp. 310—315° dec. after changing to prisms at ca. 250°. Another amount of product, mp. 305—310° dec. was obtained by concentrating the mother liquor.

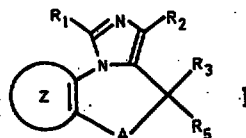
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WHAT WE CLAIM IS:—

1. A process for the preparation of imidazo[1,5-a][1,4]diazepine compounds of the general formula

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wherein A represents $-\text{C}(\text{R}_6)=\text{N}-$; R_1 represents hydrogen, lower alkyl, hydroxy lower alkyl, acyloxy lower alkyl, phenyl, alkoxy lower alkyl, halo lower alkyl, amino lower alkyl, substituted amino lower alkyl, substituted phenyl, pyridyl, aralkyl or the group $-\text{COR}_{10}$ (wherein R_{10} represents hydrogen or lower alkyl) or $-\text{COOR}$ (wherein R represents lower alkyl); R_2 represents chloro, bromo, iodo, hydroxy lower alkyl, acyloxy lower alkyl, alkoxy lower alkyl, halo lower alkyl, amino lower alkyl, cyano, cyano lower alkyl, acylamino, lower alkoxy carbonylamino, aralkyloxy carbonylamino, substituted amino lower alkyl, the group $-\text{COOR}_{10}$ (wherein R_{10} represents hydrogen or lower alkyl), the group $-\text{COR}_{10}$ (wherein R_{10} represents hydrogen or lower alkyl) or a derivative thereof, i.e., a) the group $-\text{C}(\text{R}_{10})=\text{N}-\text{R}_{11}$ wherein R_{11} represents hydrogen, lower alkyl, hydroxy, alkoxy, amino, mono or dialkylamino or arylamino and R_{10} represents hydrogen or lower alkyl; b) the group $-\text{CONR}_{12}\text{R}_{13}$, wherein R_{12} and R_{13} represent individually hydrogen, lower alkyl, hydroxy lower alkyl, lower alkenyl, aryl or the group $-(\text{CH}_2)_n\text{NR}_{14}\text{R}_{15}$ (wherein R_{14} and R_{15} represent individually hydrogen, lower alkyl, hydroxy lower alkyl or lower alkenyl, or R_{14} and R_{15} together form a part of a heterocyclic ring, and n is 1 to 4) or R_{12} and R_{13} together form a part of a heterocyclic ring; or c) the group $-\text{CON}(\text{R}_{16})\text{NR}_{17}\text{R}_{18}$, wherein one of R_{16} , R_{17} and R_{18} represents hydrogen or lower alkyl or the group $-(\text{CH}_2)_n\text{NR}_{14}\text{R}_{15}$ (wherein n is 1 to 4 and R_{14} and R_{15} represent individually hydrogen, lower alkyl, hydroxy lower alkyl or lower alkenyl or R_{14} and R_{15} together form a part of a heterocyclic ring) and the remaining R_{16} , R_{17} and R_{18} represent hydrogen or lower alkyl; and R_3 represents additionally hydrogen or lower alkyl in the case where R_1 represents hydroxy lower alkyl, acyloxy lower alkyl, halo lower alkyl, amino lower alkyl, substituted amino lower alkyl, the group $-\text{COR}_{10}$ (wherein R_{10} represents hydrogen or lower alkyl) or $-\text{COOR}$ (wherein R represents lower alkyl); R_4 represents hydrogen or lower alkyl; R_5 represents phenyl, mono-substituted phenyl, di-substituted phenyl, pyridyl or mono-substituted pyridyl; and

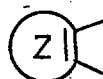
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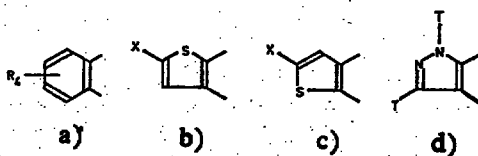
represents the group

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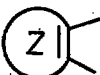
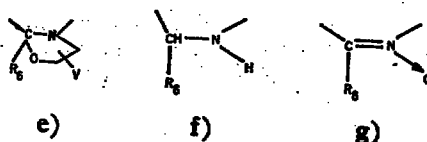
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wherein X is hydrogen, chlorine, bromine or iodine; T is hydrogen or lower alkyl, R₄ represents hydrogen, halogen, nitro, cyano, trifluoromethyl, lower alkyl, substituted amino, amino, hydroxy lower alkyl or lower alkanoyl and R₅ represents hydrogen and additionally alkanoyloxy or hydroxy in the case where



represents the group a), b) or c) above, analogs thereof corresponding to formula I but, wherein A represents the group

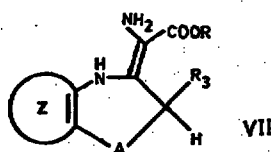


represents the group a), b) or c) above, R₅ is hydrogen, R₁, R₂, R₃ and R₆ are as in formula I above, and V represents hydrogen or lower alkyl, and pharmaceutically acceptable acid addition salts of these compounds which in the case of compounds of formula I wherein



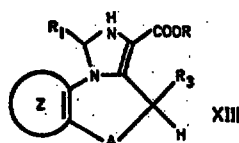
is R₄-phenyl, A is —C(R₆)=N— and R₅ is hydrogen, have a structure in which the diazepine ring is opened by cleavage of the C/N-double bond in the 5,6-position, which process comprises

a) reacting a compound of formula



or an N-oxide thereof with an alkanolic acid ortho ester of the formula R₁C(OR)₂, wherein R is lower alkyl and R₁ is hydrogen, lower alkyl, alkoxy lower alkyl or halo lower alkyl, or with a technical equivalent thereof to obtain directly a corresponding compound of formula I, any amino or alkylamino group being present in a protected form during this reaction, or

b) oxidizing a compound of formula



or an N-oxide thereof to a corresponding compound of formula I, or
c) dehydrating with concurrent cyclization a compound of formula



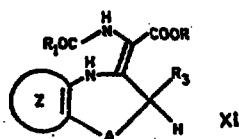
* C L M S *

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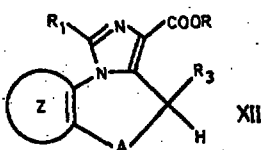
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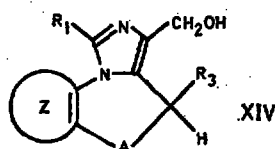


wherein R_1 is hydrogen, lower alkyl, phenyl, alkoxy lower alkyl, substituted phenyl, pyridyl or aralkyl, or an N-oxide thereof to a corresponding compound of formula I, or
d) hydrolyzing a compound of formula



to the corresponding free acid, or

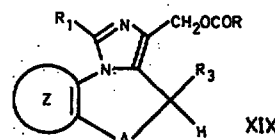
e) reducing a compound of formula XII to the corresponding compound of formula



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or,

f) acylating a compound of formula XIV to a corresponding compound of formula

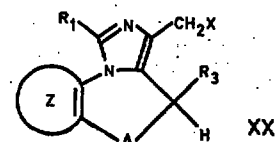


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any substituent liable to undesirable acylation being present in protected form during this reaction, or

g) substituting the hydroxy group in the 3-substituent of a compound of formula XIV with a halogen, or

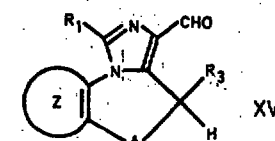
h) nucleophilically displacing the halogen in the 3-position substituent of a compound of formula



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wherein X is halogen, by an amine, alkoxide or cyanide, any R_1 haloalkyl substituent being produced subsequent to the above nucleophilic reaction, and any hydroxy alkyl substituent being in a protected form during reaction with an alkoxide, or

i) reacting the 3-position aldehyde group of a compound of formula



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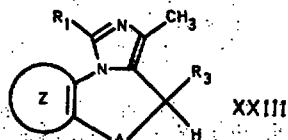
with a lower alkyl, Grignard or lithium reagent, any R_1/R_2 hydroxy alkyl substituent being present in a protected form during this reaction, or

j) reductively dehalogenating the 3-position substituent of a compound of

25



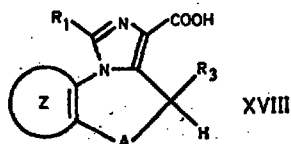
formula XX to the corresponding compound of formula



any nitro, cyano and R_1 haloalkyl substituent being formed subsequent to the production of compound of formula XXIII, or

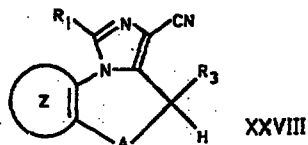
k) subjecting a compound of formula XII to ammonolysis with an amino compound of the formula H_2NR_{12} wherein R_{12} is hydrogen, lower alkyl, hydroxy lower alkyl, lower alkenyl, aryl or the group $-(CH_2)_nNR_{14}R_{15}$, wherein R_{14} and R_{15} are hydrogen, lower alkyl, hydroxy lower alkyl or lower alkenyl or taken together form a part of a heterocyclic ring and n is 1 to 4, any haloalkyl or ROOC-substituent being produced subsequent to the above ammonolysis, or

l) reacting an acid chloride of a compound of formula



with an amino compound of the formula $HNR_{12}R_{13}$, wherein R_{12} and R_{13} have the meaning indicated in formula I above, any haloalkyl or ROOC-substituent being produced subsequent to the above amination, or

m) for the preparation of a nitrile of formula



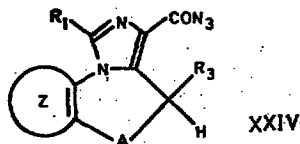
dehydrating a corresponding $-CONH_2$ compound, or

n) subjecting a compound of formula XII to direct hydrazinolysis with a hydrazine of the formula $HN(R_{16})NR_{17}R_{18}$, wherein R_{16} , R_{17} , and R_{18} have the meaning indicated in formula I above, any haloalkyl or ROOC-substituent being produced subsequent to the above hydrazinolysis, or

o) treating an acid chloride of a compound of formula XVIII with a hydrazine of the formula $HN(R_{16})NR_{17}R_{18}$, wherein R_{16} , R_{17} , and R_{18} have the meaning indicated in formula I above, any haloalkyl or ROOC-substituent being produced subsequent to the above treatment with the hydrazine, or

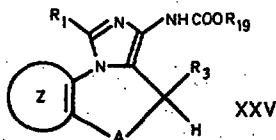
p) decarboxylating a compound of formula XVIII, or

q) heating a compound of formula



with an alkanol or an aralkanol, any haloalkyl substituent being formed subsequent to the Curtius type reaction, or

r) hydrogenating a compound of formula

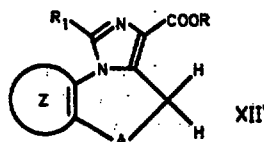




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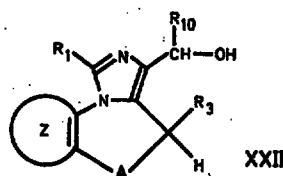
wherein R_{10} is benzyl, into the corresponding free amine and alkanoylating the compound thus obtained, any haloalkyl, nitro or cyano substituent being formed subsequent to the above hydrogenation, or

s) alkylating a compound of formula

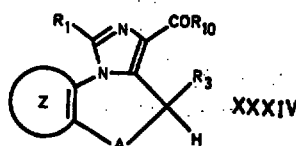


in the 4-position, no substituent with active hydrogen being present in case alkylation of such a substituent is undesirable and no haloalkyl substituent being present, or

t) oxidizing an alcohol of formula



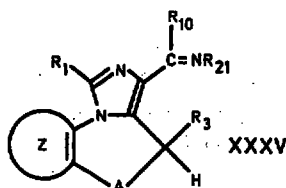
wherein R_{10} is hydrogen or lower alkyl, to the corresponding acyl derivative of the formula



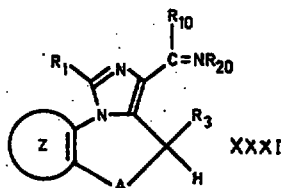
wherein R_{10} has the meaning as in formula XXII, any hydroxyalkyl substituent being present in a protected form during the above oxidation, or

u) treating a compound of formula XXXIV with a hydrazine of formula H_2NNR_{20} , wherein R_{20} is amino, mono- or dialkylamino or arylamino or with ammonia, hydroxyl amine, a lower alkylamino or a lower alkoxy amine, any R_1/R_4 acyl group being present in a protected form during the above reaction and any haloalkyl substituent being produced subsequent to the above reaction, or

v) reducing a compound of formula



wherein R_{21} is hydrogen, hydroxy, lower alkyl or lower alkoxy and R_{10} is hydrogen or lower alkyl, or a compound of formula



wherein R_{20} is amino, mono- or dialkyl amino or arylamino and R_{10} is hydrogen or lower alkyl, to the corresponding amino compound, any halo alkyl, nitro or cyano substituent being produced subsequent to the above reduction, or

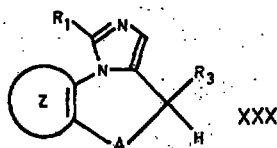
w) introducing into the 3-position of a compound of formula



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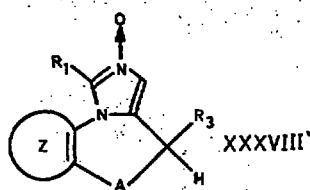
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a chloro, bromo or iodo substituent; any hydroxyalkyl or aminoalkyl substituent being present in protected form during the above halogenation and any halogenated compound wherein R₁ is hydrogen being produced subsequent to the above halogenation step, or

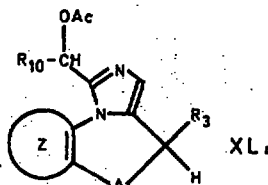
x) converting a compound of formula



wherein A is $\text{—C(R}_6\text{)=N—}$ or $\text{—C(R}_6\text{)=N(→O)—}$,



is group a), b) or c) in formula I, R₁ is lower alkyl and R₆ is phenyl or mono- or disubstituted phenyl, into a corresponding compound of formula

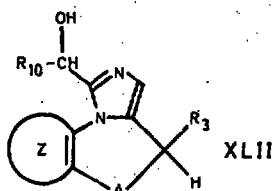


wherein R₁₀ is hydrogen or lower alkyl and A,



and R₆ are as in formula XXXVIII', and R₁-hydroxyalkyl substituent being present in protected form during the above conversion, or

y) converting a compound of formula XLI into a corresponding compound of formula

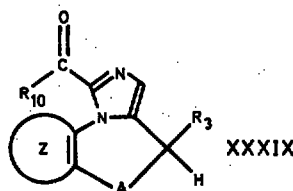


wherein A,



R₁₀ and R₆ are as in formula XLI, or

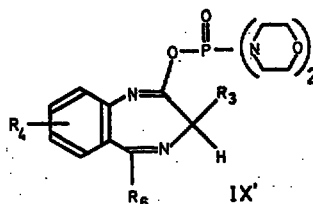
aa) oxidizing a compound of formula XLII to a corresponding compound of formula



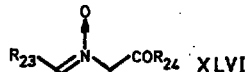
wherein A,



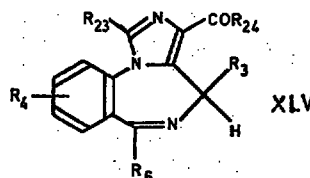
5 R_{10} and R_3 are as in formula XLII, any hydroxyalkyl substituent being present in a protected form during the above oxidation, or
bb) reacting a compound of formula



with a nitron of the formula



10 wherein R_{23} is phenyl, substituted phenyl or pyridyl and R_{24} is lower alkoxy or dilower alkylamino, yielding a compound of formula



wherein R_{23} and R_{24} are as in formula XLVI, or

cc) homologating the R_2 substituent in the meaning of aminomethyl, substituted aminomethyl, cyanomethyl, halomethyl, methyl, acyloxymethyl or alkoxyethyl in compounds of formula I above to higher homologs, or

dd) preparing compounds of formula I above with an R_2 substituent being an isomer to α -hydroxy lower alkyl, or

ee) reducing one compound of formula I to another compound of formula I, or

ff) converting an amino substituent present in a compound of formula I above or in an analog thereof corresponding to formula I but wherein A represents the group e), f) or g) above,



25 represents the group a), b) or c) above, R_3 is hydrogen and V represents hydrogen or lower alkyl, except that in formula I with A being structure f), R_3 is not nitro and R_6 is not nitro substituted, into the corresponding nitro, cyano, chloro or bromo substituent by means of a Sandmeyer reaction, or

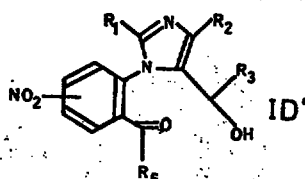
gg) cyclizing a compound of formula



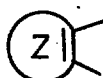
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to a corresponding cyclized compound, or
hh) converting a compound of formula I above wherein



5 is group a), b) or c) above and R_5 is hydrogen, into the corresponding N-oxide thereof, 5
or

ii) converting an N-oxide of a compound of formula I above wherein



10 is the group a), b) or c) above and R_5 is hydrogen into a corresponding compound 10
of formula I wherein R_5 is alkanoyloxy, or

jj) converting a compound of formula I above, wherein



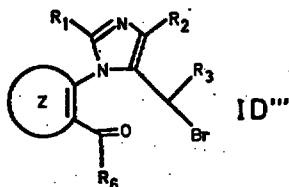
is the group a), b) or c) above and R_5 is alkanoyloxy into the corresponding compound 15
of formula I above wherein R_5 is hydroxy, or

kk) converting a compound of formula I above, but wherein A is 15
—CH(R_6)—N(R_7)— in which R_7 is hydroxy, acyl or an aromatic or aliphatic sulfonyl
group, into the corresponding compound of formula I above, or

ll) converting an analog of a compound of formula I above, wherein A is the 20
group f) above into the corresponding compound of formula I above, or

mm) reacting a compound of formula I above with ethylene oxide or propylene 20
oxide in the presence of a Lewis acid catalyst, or

nn) reacting a compound of the formula



with ethanol-amine or a 1- or 2-alkyl substituted ethanolamine, or

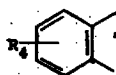
oo) resolving a racemic compound of formula I above or an analog thereof as 25
defined above into its optical enantiomers, or

pp) converting a compound of formula I above or an analog thereof as defined 25
above into a pharmaceutically acceptable acid addition salt by reaction with a suitable
acid, any R being lower alkyl.

2. A process as claimed in claim 1 wherein there is prepared a compound of 30
formula I wherein R_1 is hydrogen or lower alkyl,



is



R_4 is hydrogen, nitro or halogen, R_5 is phenyl or halo, nitro or lower alkyl substituted
phenyl and R_3 and R_5 are hydrogen.



3. A process as claimed in Claim 1 or 2, wherein R_4 is 8-halo and R_6 is 2-halophenyl.

4. A process as claimed in Claim 3, wherein R_4 is 8-chloro and R_6 is 2-chloro- or 2-fluorophenyl.

5. A process as claimed in any one of Claims 1 to 4, wherein R_1 is methyl.

6. A process as claimed in Claim 1, 3, 4 or 5, wherein R_3 is methyl.

7. A process as claimed in any one of Claims 1 to 6, wherein R_2 is hydroxy lower alkyl, carboxylic acid hydrazide or carboxamide.

8. A process as claimed in Claim 7, wherein R_2 is hydroxymethyl or the $-\text{CONHNH}_2$ or $-\text{CONH}_2$ group.

9. A process as claimed in any one of Claims 1, 3 or 4, wherein there is prepared a compound of formula I wherein

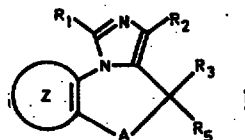


is an 8-chlorophenyl or an 8-chlorothiemo[3,2-f] group, R_1 is hydrogen or methyl, R_2 is acetyl, carboxamido or dimethylcarboxamido, R_6 is 2'-fluoro- or 2'-chlorophenyl and R_3 and R_5 are hydrogen.

10. A process according to claim 1 for the preparation of imidazo[1,5-a][1,4]-diazepine compounds as hereinbefore particularly described, especially with reference to any one of the foregoing Examples.

11. Imidazo[1,5-a][1,4]diazepine compounds of the general formula I as defined in Claim 1, analogs thereof as defined in Claim 1 and pharmaceutically acceptable acid addition salts thereof as defined in claim 1 whenever prepared according to the process claimed in any one of Claims 1 to 10.

12. Imidazo[1,5-a][1,4]diazepine compounds of the general formula



wherein A represents $-\text{C}(\text{R}_6)=\text{N}-$; R_1 represents hydrogen, lower alkyl, hydroxy lower alkyl, acyloxy lower alkyl, phenyl, alkoxy lower alkyl, halo lower alkyl, amino lower alkyl, substituted amino lower alkyl, substituted phenyl, pyridyl, aralkyl or the group $-\text{COR}_{10}$ (wherein R_{10} represents hydrogen or lower alkyl) or $-\text{COOR}$ (wherein R represents lower alkyl); R_2 represents chloro, bromo, iodo, hydroxy lower alkyl, acyloxy lower alkyl, alkoxy lower alkyl, halo lower alkyl, amino lower alkyl, cyano, cyano lower alkyl, acylamino, lower alkoxy carbonylamino, aralkyloxy carbonylamino, substituted amino lower alkyl, the group $-\text{COOR}_{10}$ (wherein R_{10} represents hydrogen or lower alkyl), the group $-\text{COR}_{10}$ (wherein R_{10} represents hydrogen or lower alkyl) or a derivative thereof, i.e., a) the group $-\text{C}(\text{R}_{10})=\text{N}-\text{R}_{11}$, wherein R_{11} represents hydrogen, lower alkyl, hydroxy, alkoxy, amino, mono or di-alkylamino or arylamino and R_{10} represents hydrogen or lower alkyl; b) the group $-\text{CONR}_{12}\text{R}_{13}$, wherein R_{12} and R_{13} represent individually hydrogen, lower alkyl, hydroxy lower alkyl, lower alkenyl, aryl or the group $-(\text{CH}_2)_n\text{NR}_{14}\text{R}_{15}$ (wherein R_{14} and R_{15} represent individually hydrogen, lower alkyl, hydroxy lower alkyl or lower alkenyl, or R_{14} and R_{15} together form a part of a heterocyclic ring, and n is 1 to 4) or R_{12} and R_{13} together form a part of a heterocyclic ring; or c) the group $-\text{CON}(\text{R}_{16})\text{N}(\text{R}_{17}, \text{R}_{18})$, wherein one of R_{16} , R_{17} and R_{18} represents hydrogen or lower alkyl or the group $-(\text{CH}_2)_n\text{N}(\text{R}_{14}, \text{R}_{15})$ (wherein n is 1 to 4 and R_{14} and R_{15} represent individually hydrogen, lower alkyl, hydroxy lower alkyl or lower alkenyl or R_{14} and R_{15} together form a part of a heterocyclic ring) and the remaining R_{16} , R_{17} and R_{18} represent hydrogen or lower alkyl; and R_3 represents additionally hydrogen or lower alkyl in the case where R_1 represents hydroxy lower alkyl, acyloxy lower alkyl, halo lower alkyl, amino lower alkyl, substituted amino lower alkyl, the group $-\text{COR}_{10}$ (wherein R_{10} represents hydrogen or lower alkyl) or $-\text{COOR}$ (wherein R represents lower alkyl); R_5 represents hydrogen or lower alkyl; R_6 represents phenyl, mono-substituted phenyl, di-substituted phenyl, pyridyl or mono-substituted pyridyl; and



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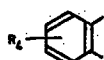
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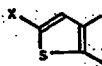
represents the group



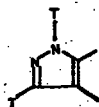
a)



b)



c)



d)

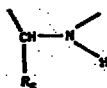
wherein X is hydrogen, chlorine, bromine or iodine, T is hydrogen or lower alkyl, R_4 represents hydrogen, halogen, nitro, cyano, trifluoromethyl, lower alkyl, substituted amino, amino, hydroxy lower alkyl or lower alkanoyl and R_5 represents hydrogen and additionally alkanoyloxy or hydroxy in the case where



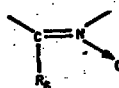
represents the group a), b) or c) above, analogs thereof corresponding to formula I but, wherein A represents the group



e)



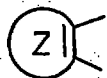
f)



g)



represents the group a), b) or c) above, R_5 is hydrogen, R_1 , R_2 , R_3 and R_6 are as in formula I above, and V represents hydrogen or lower alkyl, and pharmaceutically acceptable acid addition salts of these compounds which in the case of compounds of formula I wherein



is R_4 -phenyl, A is $-\text{C}(\text{R}_5)=\text{N}-$ and R_5 is hydrogen, have a structure in which the diazepine ring is opened by cleavage of the C/N-double bond in the 5,6-position.

13. Compounds as claimed in Claim 12 corresponding to formula I wherein R_1 is hydrogen or lower alkyl.



is



R_4 is hydrogen, nitro or halogen, R_6 is phenyl or halo, nitro or lower alkyl substituted phenyl and R_1 and R_2 are hydrogen.

14. Compounds as claimed in Claim 12 or 13, wherein R_4 is 8-halo and R_6 is 2-halophenyl.

15. Compounds as claimed in Claim 14, wherein R_4 is 8-chloro and R_6 is 2-chloro- or 2-fluorophenyl.

16. Compounds as claimed in any one of Claims 12 to 15, wherein R_1 is methyl.

17. Compounds as claimed in Claim 12, 14, 15 or 16, wherein R_3 is methyl.

18. Compounds as claimed in any one of Claims 12 to 17, wherein R_2 is hydroxy lower alkyl, carboxylic acid hydrazide or carboxamide.

19. Compounds as claimed in Claim 18, wherein R_2 is hydroxymethyl or the $-\text{CONHNH}_2$ or $-\text{CONH}_2$ group.

20. Compounds as claimed in any one of Claims 12, 14 or 15 corresponding to formula I wherein



(Z)

is an 8-chlorophenyl or an 8-chlorothieno[3,2-f] group, R₁ is hydrogen or methyl, R₂ is acetyl, carboxamido or dimethylcarboxamido, R₃ is 2'-fluoro- or 2'-chlorophenyl and R₄ and R₅ are hydrogen.

- 5 21. 8 - Chloro - 6 - (2 - fluorophenyl) - 3 - hydroxymethyl - 1 - methyl - 4H - imidazo[1,5-a][1,4]benzodiazepine. 5
22. 8 - Chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4] - benzodiazepine - 3 - carboxylic acid hydrazide.
- 10 23. 8 - Chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5-a][1,4] - benzodiazepine - 3 - carboxamide. 10
24. 8 - Chloro - 6 - (2 - chlorophenyl) - 1 - methyl - 4H - imidazo[1,5-a] - thieno[3,2-f][1,4]diazepine - 3 - carboxamide.
- 25 25. 8 - Chloro - 6 - (2 - chlorophenyl) - 1,N,N - trimethyl - 4H - imidazo - [1,5-a]thieno[3,2-f][1,4]diazepine - 3 - carboxamide. 15
- 15 26. 3 - Acetyl - 8 - chloro - 6 - (2 - chlorophenyl) - 4H - imidazo[1,5-a][1,4] - benzodiazepine. 15
27. 8 - Chloro - 6 - (2 - chlorophenyl) - N,N - dimethyl - 4H - imidazo[1,5-a] - [1,4]benzodiazepine - 3 - carboxamide.
- 20 28. 8 - Chloro - 6 - (2 - chlorophenyl) - 1,N,N - trimethyl - 4H - imidazo - [1,5-a][1,4]benzodiazepine - 3 - carboxamide. 20
29. 8 - Chloro - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5-a][1,4]benzodiazepine - 3 - carboxamide.
30. A compound as claimed in claim 12 or an analog or pharmaceutically accept- able salt thereof as claimed in claim 12 as hereinbefore described specifically.
- 25 31. A composition having muscle relaxant, sedative or anti-convulsant properties comprising a compound as claimed in any one of claims 11 to 30 or an analog or pharmaceutically acceptable acid addition salt thereof as claimed in claim 11, 12 or 30 and a therapeutically compatible carrier or excipient. 25
32. A composition as claimed in claim 31, wherein the carrier or excipient is a non-toxic, inert solid.
- 30 33. A composition as claimed in claim 31, wherein the carrier or excipient is a non-toxic, inert liquid. 30

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