

1 527 131

PATENT SPECIFICATION

(11) 1 527 131

- (21) Application No. 37252/75 (22) Filed 10 Sept. 1975
 (31) Convention Application No. 504924
 (32) Filed 11 Sept. 1974 in
 (33) United States of America (US)
 (44) Complete Specification published 4 Oct. 1978
 (51) INT CL² C07D 487/04 A61K 31/55 C07D 405/04 498/14
 513/14/233/56 239/74 243/16 487/04 513/04 C07F 9/58
 9/65 (C07D 405/04 233/64 317/12) (C07D 487/04 243/16)
 (C07D 498/14 263/04) (C07D 513/14 333/36)



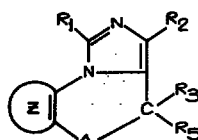
(52) Index at acceptance

C2C 140X 1410 142X 1492 151X 1604 1746 200 213 214 215 220
 226 22Y 246 247 250 251 252 253 255 256 25Y 271 281
 282 28X 29X 29Y 304 305 30Y 311 313 314 315 31Y 321
 322 323 32Y 332 333 334 337 338 339 342 346 34Y 351
 355 35X 35Y 360 362 366 368 36Y 37X 386 407 40Y 43X
 450 453 45Y 470 471 475 490 491 503 509 50Y 55X 579
 584 601 611 616 618 620 621 623 625 628 62X 630 631
 650 651 652 658 65X 660 661 665 670 671 672 675 678
 679 67X 681 695 697 698 699 69Y 701 708 709 719 776
 777 77Y 790 79Y BC KF KG KS LL LP LW LY MJ
 ML MM MV NF NL NM UK WC YX ZB ZF
 C2P 1L1 1L2 1L3 2E13 2E18C 2E24 2E25B 2E26C 2E26D 7

(54) BENZO OR HETEROCYCLIC FUSED IMIDAZODIAZEPINES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

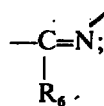
(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIEN-
 GESELLSCHAFT, a Swiss Company of 124-184 Grenzacherstrasse,
 Basle, Switzerland, do hereby declare the invention, for which we pray that a
 patent may be granted to us, and the method by which it is to be performed, to be
 particularly described in and by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

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



(I)

wherein A is

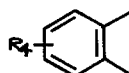


R₁ is hydrogen, lower alkyl, phenyl, alkoxy lower alkyl, substituted phenyl, pyridyl
 or aralkyl; R₂ is hydrogen or lower alkyl; R₃ is hydrogen or lower alkyl; R₄ is
 hydrogen, alkanoyloxy or hydroxy; R₅ is phenyl, mono-substituted phenyl, di-
 substituted phenyl, pyridyl or mono-substituted pyridyl; and

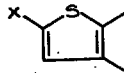


is selected from the group consisting of

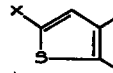
(a)



(b)

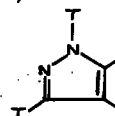


(c)



and

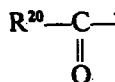
(d)



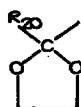
3

and branched chain (C_1-C_7) carbon-hydrogen radicals, preferably C_1-C_4 carbon-hydrogen radicals such as methyl, ethyl, propyl, isopropyl and butyl.

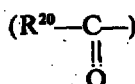
By the term "lower alkanoyl" or "acyl" as utilized herein, an acyl moiety of a C_1-C_7 , preferably a C_1-C_4 , alkanoyl acid is intended, e.g. acetyl, propionyl, butyryl, i.e., moieties of the formula



wherein R^{20} is C_1-C_6 aliphatic hydrocarbyl or hydrogen. Also as utilized herein, the term "lower alkanoyl" comprehends a protected aldehyde or ketone such as an acetal or ketal having 2 to 7 carbon atoms, e.g. a group of the formula



wherein R^{20} is C_1-C_6 aliphatic hydrocarbyl or hydrogen. The ketal or acetal 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" comprehend compounds of the formula SO_2X' wherein X' is a branched or straight chain C_1-C_7 , preferably C_1-C_4 , aliphatic hydrocarbyl group, e.g., methyl, or a substituted or unsubstituted aromatic group such as a phenyl or substituted phenyl group, e.g., tolyl.

The phenyl moiety R_6 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. When the phenyl ring is mono-substituted the substituent is preferably halogen or nitro and preferably the substituent is in the 2-position of the phenyl moiety. When the phenyl ring is di-substituted the substituents are preferably 2,6 or 2,5 di-halogen or 2,6 or 2,5 halogen-nitro. In the case of mono-substituted pyridyl, the preferred substituents are halogen and nitro.

In the case of compounds of formula I in which substituents R_3 and R_4 are not identical, 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 and tolyl.

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

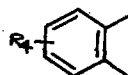
By the term "substituted amino" herein is meant an $-NH_2$ group which may be mono or disubstituted by lower alkyl, e.g. methylamino or dimethylamino groups, and an acyl amino group e.g., acetylamino which may also be substituted on the nitrogen atom by lower alkyl or aryl e.g., methyl, phenyl or tolyl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

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 or tolyl.

Preferred compounds are those wherein R_1 is hydrogen or lower alkyl, preferably methyl R_3 and R_4 are hydrogen;



is



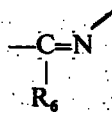
wherein R_4 is located preferably in the 8-position of the imidazobenzodiazepine molecule and is hydrogen, nitro or halogen, preferably chlorine; A is

14

4

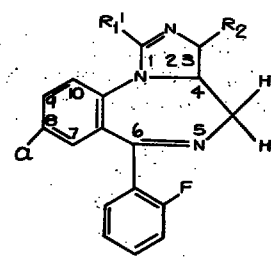
1,527,131

4



wherein R_6 is phenyl or halo, nitro, or lower alkyl substituted phenyl, preferably halo e.g., fluoro, with the fluoro substituted in the 2-position of the phenyl moiety e.g. compounds of the formula

5

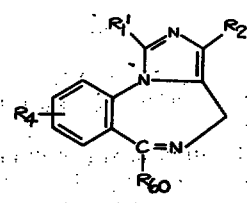


(IB)

5

wherein R_1 and R_2 are as defined in formula IB' below.

Thus an especially preferred genus included within the pervue of the present invention comprises compounds of the formula



(IB')

10

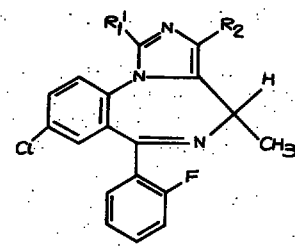
wherein R_1 is hydrogen or lower alkyl preferably methyl, R_4 is hydrogen, nitro or halogen, most preferably chlorine, and in a most preferred embodiment R_4 is positioned in the 8-position of the imidazobenzodiazepine, R_6 is phenyl or halo-, nitro-, or lower alkyl-substituted phenyl, preferably halo-substituted phenyl, with fluorine being the preferred halogen. Preferably the substituted fluoro is positioned in the 2-position of the phenyl moiety. R_2 is hydrogen or lower alkyl.

10

15

Another preferred class of compounds falling within the scope of formula I are those wherein R_1 , R_2 , R_4 , R_3 , R_6 and A are as in Formula IB' above and R_3 is lower alkyl, preferably methyl, e.g., compounds of the formula

15



(IC)

20

Compounds of formula IC and their pharmaceutically acceptable salts exhibit optical isomerism. Such compounds have been resolved into their optical enantiomers by a procedure similar to the one generally outlined in *Advanced Organic Chemistry*, L. Fieser and M. Fieser, 1961, pp. 85—88, Reinholt Publishing Co. Both the optical isomers and the racemic forms of compounds 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.

20

25

25

30

30

The expression "pharmaceutically acceptable salts", is used to include salts with both inorganic and organic pharmaceutically acceptable acids such as

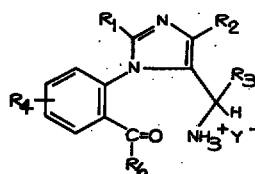
hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulfonic acid and para toluene-sulfonic acid. Such salts can be formed quite readily by those skilled in the art, with the prior art and the nature of the compound to be placed in salt form, in view.

The most preferred pharmaceutically acceptable acid addition salts of the compounds of formula IC and ID respectively are:

8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo [1,5 - a] [1,4]benzodiazepine maleate;

8 - chloro - 1,4 - dimethyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a] [1,4]benzodiazepine maleate.

It has been found that certain compounds of formula I in solution open to compounds of formula ID,

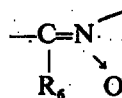


(ID)

wherein Y^- 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. 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, which are also part of the invention, exhibit pharmacological activity comparable to their corresponding closed ring parents.

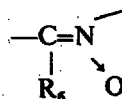
The imidazo [1,5-a][1,4] diazepine compounds of the formula I, their analogs of formula IA and the pharmaceutically acceptable acid addition salts of these compounds can be prepared by the various process embodiments defined in Claim 1, hereinbelow.

Compounds of the formula IA where A is



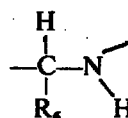
are formed by the conversion of corresponding formula I compounds into the N-oxides thereof. This conversion may be effected for example by oxidizing a formula I compound with an organic peracid. A conventional organic peracid, such as peracetic acid, perpropionic acid or *m*-chloroperbenzoic acid can be utilized in carrying out this reaction. The oxidation can be effected at room temperature, or above or below room temperature.

Compounds of the Formula IA where A is

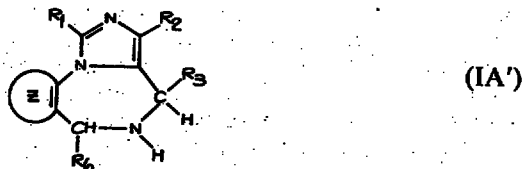


may be then utilized to produce compounds of Formula I wherein R_3 is alkanoyloxy or hydroxy by methods known in the art, such as, for example, a Polonovski rearrangement utilizing an acid anhydride to form the alkanoyloxy radical which may be converted to the hydroxy radical by treatment with an alkali metal hydroxide such as sodium hydroxide. An example of such a Polonovski rearrangement is found in U.S. Patent No. 3,296,249 issued January 3, 1967 to S. C. Bell.

Compounds of the formula IA where A is



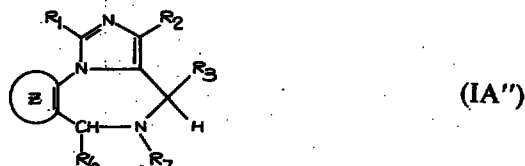
are formed by the reduction of corresponding formula I compounds to compounds of the formula



wherein R_1 , R_2 , R_3 and



are as in Formula I and R_4 is as in Formula I but is not nitro and R_5 is as in Formula I but not nitro substituted phenyl or nitro substituted pyridyl (since nitro substituents may be reduced to amino under the reaction conditions) which may then be converted to other compounds of the formula



wherein R_1 , R_2 , R_3 , R_4 and R_5 are as in formula IA' and R_7 is hydroxyl, acyl or an aromatic or aliphatic sulfonyl group.

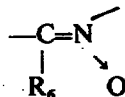
These compounds of formula IA'' form the subject of our Divisional Application No. 12689/78 (Serial No. 1,527,133).

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. These compounds (IA') may be converted to IA'' compounds having an R_7 -radical other than hydroxyl by reaction with an alkyl or aryl sulfonyl halide, e.g. tosyl chloride, mesyl chloride, or lower alkanoyl group providing agent, e.g. acetyl chloride.

This process is conveniently effected in the presence of an inert organic solvent such as an alkanol, e.g., ethanol and methanol, an ether such as diethyl ether and tetrahydrofuran or dimethylformamide. Suitably, an acid acceptor is provided 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. Preferred acid acceptors are tertiary amines, e.g., triethylamine and pyridine.

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 at room temperature and above for the conversion of compounds IA' and IA'' bearing an R_7 -radical other than hydrogen.

Reduction of IA compounds wherein A is



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/puridine mixture. No 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 acetyl, mesyl or tosyl may be

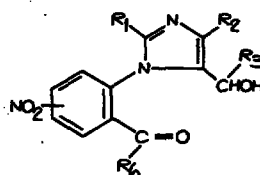
converted to the corresponding formula I unsaturated imine by treatment of the IA'' compound with a non-aqueous base, e.g., potassium tertiary butoxide, in the presence of an inert solvent e.g., THF or DMF. Such a reaction and the conditions at which it is run are well known in the art; see, for example U.S. Patent No. 3,625,957 issued December 7, 1971 to Fryer et al.

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 issued May 30, 1967 to Fryer et al.

Conversion of compounds of formula I wherein R₄ is amino to compounds wherein R₄ is nitro may be suitably effected 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 nitride 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



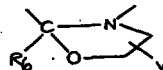
(XXIII')

wherein R₁, R₂, R₃ and R₆ 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 XXIII' 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.

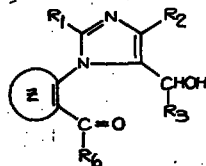
The Sandmeyer reaction has been found to also be applicable in producing compounds which contain a cyano, chloro or bromo group in place of a nitro group. Corresponding compounds of formula XXIII' can be converted to their ring closed analogs in the same manner as described above for nitro compounds.

It is obvious to one skilled in the art that certain other substituents may also be attacked during the above reactions, 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



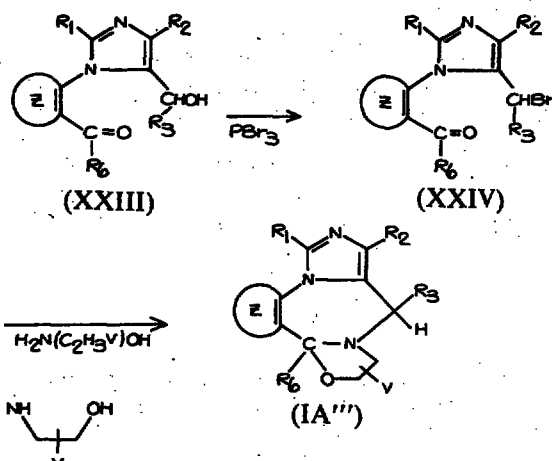
(XXIII)

wherein R₁, R₂, R₃,



and R₆ are as in Formula I (except that R₄ is not amino or substituted amino) with

phosphorus tribromide and subsequent treatment of the intermediate (XXIV) with ethanolamine, a 1-alkyl substituted ethanolamine or a 2-alkyl substituted ethanolamine as shown in the following reaction scheme:



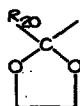
V is hydrogen or lower alkyl

The compounds of formula XXIII may be formed by the reaction of a compound of the formula ID with sodium nitride 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 XXIII compounds with phosphorus tribromide is effected as illustrated above, 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 XXIV with ethanolamine or 1-alkyl or 2-alkyl substituted ethanolamine is effected *in situ* in the presence of an inert solvent such as dichloromethane, at a temperature in the range of -10°C to reflux, preferably about room temperature.

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

In compounds of formula I and their analogs wherein the ketal group e.g.

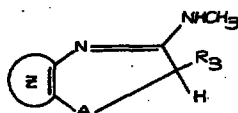


is present as a 8-position substituent in an imidazobenzodiazepine, such ketal group may be converted to an 8-position ketone by subjecting the ketal group to a mild acid hydrolysis. The 8-ketone can then be converted to a 8-position secondary or tertiary alcohol which is racemic in nature. The reaction conditions for the above two steps, are found in U.S. Patent No. 3,846,410 issued November 5, 1974.

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 issued February 25, 1975 to Fryer et al.

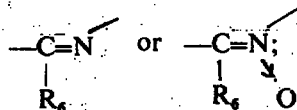
The compounds of formula I above can be prepared according to the following novel process aspects which form a part of the present invention.

In one of the aforementioned novel process aspects of this invention, the compounds of formula I above may be prepared by the nitrosation of a compound of the formula



(II)

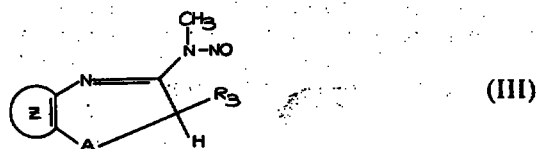
wherein A is



R₃ is hydrogen or lower alkyl and



and R₆ are as described in formula I, to produce a compound of the formula



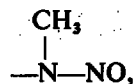
wherein A, R₃ and



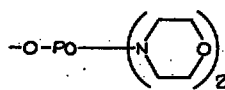
are as described in Formula II.

Such a nitrosation may be effected by "in situ formed" nitrous acid. Reagents which may be employed include (1) alkali metal nitrites, e.g., sodium nitrite, in the presence of organic or inorganic acids, e.g., glacial acetic acid, and aqueous or non-aqueous solvents; (2) alkyl nitrites, e.g., methyl nitrite, in the presence of an inert solvent such as an alcohol or a chlorinated hydrocarbon or, for example, dimethyl formamide; 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 affected at around or below room temperature, i.e., in the range of -20°C. to 25°C.

The 2-position nitrosoalkylamine, e.g.,

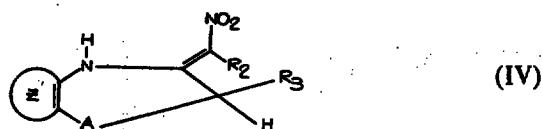


represents a "leaving group". Equivalent leaving groups which may be utilized as 2-position substituents include groups such as alkoxide, e.g., -OCH₃; alkylthio, e.g., -SCH₃; halo, e.g., chloro; cyano, and phosphate e.g.



Reactions which form the alkoxide and alkylthio 2-position substituents are well known in the art; see, for example, G. A. Archer and L. H. Sternbach, *Journal of Organic Chemistry*, 29, 231 (1964) and U.S. Patent No. 3,681,341, issued August 1, 1972 to Fryer et al.

Compounds of formula III may then be condensed with a nitroalkane to form a novel intermediate of the formula



wherein R₂ is hydrogen or lower alkyl, and A, R₃ and



are as described in Formula II.

20

10

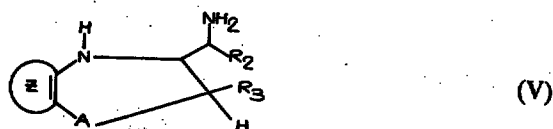
1,527,131

10

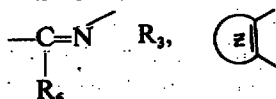
The condensation reaction is effected with a nitroalkane, ($R_2-CH_2-NO_2$), e.g. nitromethane or nitroethane, in the presence of a base which is strong enough to generate the nitroalkane anion. Suitable bases include the alkali metal or alkaline earth metal alkoxides, e.g., potassium tertiary butoxide, amides, e.g., lithium amide or hydrides, e.g., sodium hydride. The reaction is preferably carried out in an inert solvent, such as dimethylformamide, dimethylsulfoxide, or an ether, e.g. THF, at temperatures below or above room temperature, i.e., in the range of -50°C. to 150°C. , preferably at about room temperature.

The novel compounds of formula IV and formula V below, besides being major intermediates in the synthesis of compounds of formula I, also exhibit activity as central nervous system depressants.

Compounds of formula IV may then be catalytically hydrogenated, for example, with Raney nickel in the presence of hydrogen or by other reductants such as lithium aluminum hydride (with limitation that A is not N-oxide) to produce a compound of the formula



wherein A is



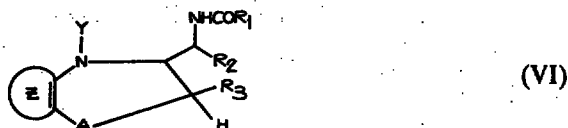
and R_6 are as in Formula II, except that R_4 is not nitro or cyano, and R_6 is not nitro substituted, and R_2 is hydrogen or lower alkyl.

The exclusion of nitro and cyano from the substituent groups present results from the conversion of nitro into amino and cyano into methylamino under the reaction conditions employed in the step IV $\rightarrow$ V.

Solvents suitable for hydrogenation with Raney nickel include alcohols, e.g., ethanol, ethers, e.g. THF and diethylether, hydrocarbon solvents, e.g. toluene and dimethylformamide. The reaction temperature may be above or below room temperature (i.e., -50°C. to 150°C.) and the reaction may be carried out with or without pressure, i.e. at a pressure of one atmosphere or higher.

Solvents suitable for hydrogenation employing a reductant such as lithium aluminum hydride include ethers, e.g., THF, dioxane, diethylether and mixtures of ethers and hydrocarbon solvents, e.g., THF and benzene. The reaction may be carried out from below room temperature to reflux temperature, i.e., preferably in the range of -50°C. to 60°C.

The compounds of formula V may then be acylated with an acylating agent such as an acid halide or acid anhydride, i.e., a group of the formula R_1COCl or $(R_1CO)_2O$ wherein R_1 is as defined in formula I, e.g. acetic anhydride and acetyl chloride, to produce a compound of the formula



wherein A, R_2 , R_3 and

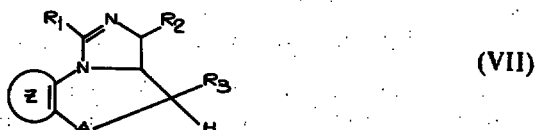


are as described in Formula V, R_1 is as in formula I and Y is hydrogen or $-COR_1$.

In acylating the compounds of formula V to compounds of formula VI, there may be obtained a mixture consisting predominantly of the monoacylated product, i.e., wherein the NH_2 group of V (position 2) is converted to $NHCOR_1$, and the diacylated product wherein both the NH_2 of V (position 2) and 1-position nitrogen are acylated. The yield of diacylated product may be increased by

subjecting the compounds of formula V to more rigorous conditions, i.e., excess of acylating agent and increased reaction time.

The acylation is preferably carried out in the presence of an aqueous or non-aqueous solvent e.g., water, methylene chloride, benzene or chloroform, and preferably with an acid acceptor such as an organic or inorganic base such as triethylamine, pyridine or an alkali metal carbonate. The compounds of formula VI may then be cyclized to novel compounds of the formula



wherein A, R₁, R₂, R₃ and

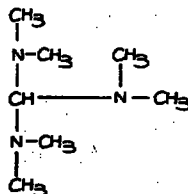


are as described in Formula VI.

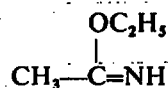
The cyclization reaction is effected with a dehydrating agent such as phosphorus pentoxide, polyphosphoric acid or other acid catalysts, i.e., organic or inorganic acids e.g., conc. H₂SO₄. A solvent is not essential but a solvent such as an aromatic hydrocarbon solvent, e.g., toluene, xylene, may be employed. The reaction is carried out at a temperature in the range of from about 100°C to 200°C.

These compounds of formula VII form the subject of our divisional application No. 12688/78 (Serial No. 1,527,132).

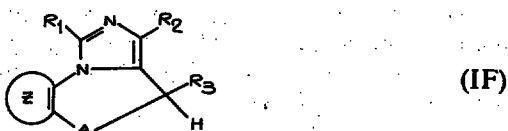
The compounds of formula V may also be reacted with an acylating agent such as an orthoester, e.g., triethylorthoacetate, an orthoamide, e.g., the dimethylacetal of N,N-dimethylformamide, or a compound of the formula



optionally in the presence of an acid catalyst, e.g., an organic or inorganic acid, e.g., *p*-toluene sulfonic acid or phosphoric acid, and at room temperature or above, i.e., 25°C. to 150°C., in which instance the cyclization to compound VII occurs spontaneously. Other useful acylating agents include esters, e.g., methyl acetate; amidines, e.g., acetamidine; nitriles, e.g., acetonitrile and ester imidates, e.g., a compound of the formula



The compounds of formula VII may then be dehydrogenated to yield compounds of the formula



wherein A, R₁, R₂, R₃ and



are as described in formula VI.

Preferred reactants for the dehydrogenation include manganese dioxide and palladium on carbon although potassium permanganate may also be utilized. Solvents which may be utilized include chlorinated hydrocarbon solvents, aromatic hydrocarbons and dimethylformamide. The dehydrogenation is carried out at room temperature or above, i.e., in the range of about 25°C. to 200°C.

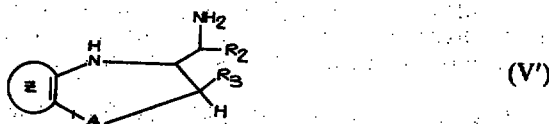
The novel compounds of formula VII also exhibit activity as central nervous depressants.

The above novel process may proceed, if desired, from intermediate compounds IV or V to compounds of formula IF without the requirement of isolating any formed intermediate compounds before proceeding to the next process step.

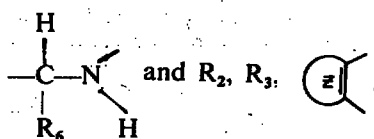
It should be noted that, in acylating the compounds of Formula V to the compounds of Formula VI when R₄ is amino, the amino substituent R₄ may also be acylated to acylamino. The acylamino may be converted back to amino by subjecting the compounds of Formula VII or Formula I to a mild hydrolysis.

Also it has been found that compounds of the formulas IV, V, VI and VII may exhibit both optical and geometric isomerism.

The reaction of a compound of the formula V with acetic acid and zinc or any other suitable reductants, e.g., hydrogen in the presence of a catalyst e.g., platinum in dilute acetic acid solution, produces a compound of the formula



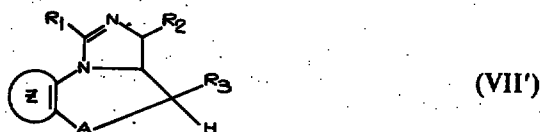
wherein A is



and R₆ are as in formula V.

Depending on the above method of reduction chosen, formula V' when R₂ is hydrogen can be isolated as a racemic mixture of either of the two possible diastereomers.

A compound of the formula V' may be converted to the dihydroimidazo derivative of the formula



wherein



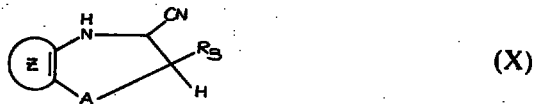
A, R₂ and R₃ are as in formula V' and R₁ is hydrogen or lower alkyl, with retention of stereochemistry, by utilizing the direct reaction set forth above i.e. the reaction of formula V compounds with an acylating agent such as an orthoester e.g., triethylorthoacetate and maintaining the reaction parameters set forth above for such a reaction.

Compounds of formula VII' can also be prepared by reduction of a compound of formula VII by utilizing reductants as mentioned above e.g., acetic acid and zinc or H₂/platinum catalyst in dilute acetic acid, with the particular stereoisomer produced dependent on the reductant chosen.

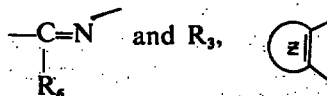
Compounds of the formula VII' can, if desired, be oxidized directly to analogous compounds of the formula I using an oxidant such as manganese dioxide in toluene or benzene solution. Reaction conditions utilized and various

alternate useful oxidants are found in U.S. Patent No. 3,322,753 issued May 30, 1967 to Fryer et al.

Another process to produce the novel intermediates of formula V where R_4 and R_5 are other than nitro or cyano and R_2 is hydrogen consists of the reduction of compounds of the formula



wherein A is

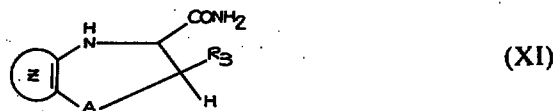


and R_5 are as described in formula II except that R_4 is not nitro or cyano and R_5 is not nitro-substituted.

The reduction comprises the reaction of the compounds of formula X with a known reductant such as Raney nickel in the presence of hydrogen or by other reductants such as lithium aluminum hydride. Solvents suitable for hydrogenation with Raney nickel include alcohols e.g., ethanol, ethers e.g., THF, hydrocarbon solvents e.g., toluene, and dimethylformamide. The reaction temperature may be above or below room temperature (i.e., -50°C . to 150°C .) and the reaction may be carried out with or without pressure, i.e. at a pressure of one atmosphere or higher.

Solvents suitable for hydrogenation employing a reductant, such as lithium aluminum hydride include ethers, such as dioxane, diethyl ether and THF. The reaction may be carried out from below room temperature to reflux temperature, preferably in the range of -50°C to 60°C .

A variation of the above process comprises a mild acid hydrolysis of the compounds of formula X to produce compounds of the formula



wherein A, R_5 and

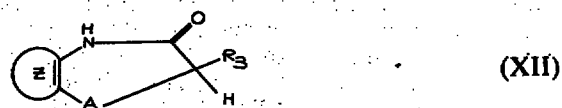


are as in formula X.

The mild acid hydrolysis is suitably effected by a dilute mineral acid, e.g., aqueous H_2SO_4 in aqueous alcohol. The reaction temperature may range from room temperature, i.e., about 25°C ., to above room temperature, i.e., about 60°C .. The compounds of formula XI may then be reduced to the novel intermediates of Formula V.

Another process, although it does not form a part of the present invention, is useful in producing novel intermediates of formulas IV and V. The following process is included in this specification for the sake of unity.

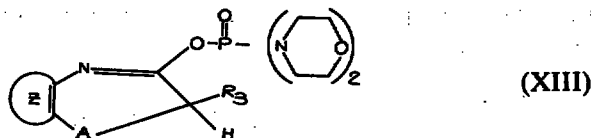
Compounds of formula IV above may be produced by the successive reaction of the compounds of the formula



wherein A,



and R_3 are as in formula II, except that R_4 is not amino or substituted amino, with dimorpholinophosphinic chloride to produce compounds of the formula



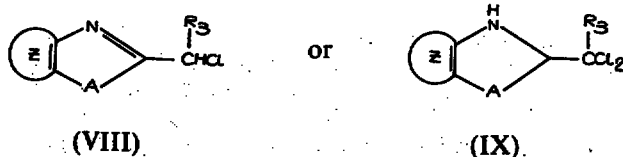
wherein A,



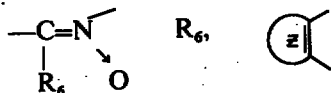
and R_3 are as in formula XII; which imino phosphates are then displaced by the anion of a nitroalkane to produce the novel intermediates IV.

The displacement reaction is effected with a nitroalkane, e.g. nitromethane or nitroethane, in the presence of a base which is strong enough to generate the nitroalkane anion. Suitable bases include the alkali metal or alkaline earth metal alkoxides, hydrides, amides or hydroxides. The reaction is preferably carried out in an inert solvent, such as dimethylformamide, dimethylsulfoxide, or an ether, at temperatures below or above room temperature, i.e., in the range of -50°C . to 150°C .

Another process to produce intermediates of formula IV wherein R_2 is hydrogen and A is an N-oxide comprises the ring expansion of compounds of the formula



wherein A is



and R_3 are as described in formula II except that R_4 is not amino.

The ring expansion comprises the reaction of the compounds of formulae VIII or IX with nitromethane in the presence of a base strong enough to generate the nitromethane anion. Suitable bases include the alkali metal and alkaline earth metal alkoxides, e.g., potassium tertiary butoxides, amides e.g., lithium amide or hydrides e.g., sodium hydride. The reaction may be preferably be carried out in an inert solvent such as anhydrous ether e.g., THF, dimethylformamide or dimethylsulfoxide, and at a temperature in the range of about -20°C to 25°C .

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. 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 and vegetable oils to provide tablets, elixirs, capsules, solutions and emulsions according to acceptable pharmaceutical practices; and according to another aspect of the invention a process for the manufacture of preparations having muscle relaxant, sedative and anti-convulsant properties comprises mixing a compound of formula I or an analog thereof or a

pharmaceutically acceptable acid addition salt, as active substance, with a non-toxic, inert, therapeutically compatible solid or liquid carrier commonly used in such preparations, and/or an excipient.

The following Examples are illustrative but not limitative of the present invention. All temperatures are stated in degrees Centigrade.

Example 1

A solution of 200 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 sodium sulfate 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°.

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.

This material was dissolved in 100 ml of dimethylformamide and added to a mixture of 200 ml of dimethylformamide, 50 ml of nitromethane and 11.1 g (0.1 m) of potassium t-butoxide which had been stirred under nitrogen for 15 minutes.

After stirring for 1 hour at room temperature, the reaction mixture was acidified by addition of glacial acetic acid, was diluted with water and extracted with methylene chloride. The extracts were washed with water, dried over sodium sulfate and evaporated.

Crystallization of the residue from ether yielded 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2-nitromethylene-2H-1,4-benzodiazepine, m.p. 170—172°. The analytical sample was recrystallized from methylene chloride/ethanol, m.p. 174—176°.

A solution of 16.5 g (0.05 m) of 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2-nitromethylene-2H-1,4-benzodiazepine in 500 ml of tetrahydrofuran and 250 ml of methanol was hydrogenated with 5 teaspoons of Raney nickel for 2-1/2 hours at atmospheric pressure. Separation of the catalyst and evaporation of the solvent left crude 2-aminomethyl-7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1H-1,4-benzodiazepine.

Propionic anhydride (20 ml) was added to a solution of 12 g of the above material in 300 ml of methylene chloride. The solution was added to 300 ml of 10% aqueous sodium carbonate and the two phase mixture was stirred at room temperature for 30 minutes. The organic layer was separated, washed with sodium carbonate solution and dried over sodium sulfate. Evaporation yielded crude 7-chloro-2,3-dihydro-5-(2-fluorophenyl)-2-propionylaminomethyl-1H-1,4-benzodiazepine.

This material was heated in 50 g of polyphosphoric acid at 150—170° for 10 minutes. The reaction mixture was cooled, dissolved in water and made alkaline with concentrated ammonia and ice. The base was extracted with methylene chloride and the extracts were dried over sodium sulfate and evaporated. The residue was chromatographed over 300 g of silica gel using 20% methanol in methylene chloride. The clean fractions were combined, evaporated and the residue was crystallized from ether to yield 8-chloro-3a,4-dihydro-1-ethyl-6-(2-fluorophenyl)-3H-imidazo[1,5-a][1,4]benzodiazepine m.p. 131—133°.

A mixture of 3.4 g of 8-chloro-3a,4-dihydro-1-ethyl-6-(2-fluorophenyl)-4H-imidazo[1,5-a][1,4]benzodiazepine, 400 ml toluene and 30 g activated manganese dioxide was refluxed with separation of water in a Dean-Stark trap for 2 hours. The manganese dioxide was separated by filtration over Celite (Trade Mark) and the filtrate was evaporated. Crystallization of the residue

from ether yielded 8 - chloro - 1 - ethyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine, m.p. 140—143°. For analysis it was recrystallized from ether, m.p. 143—145°.

Example 2

Acetic anhydride (7 ml) was added to a solution of 6.16 g of crude 2 - aminomethyl - 7 - chloro - 2,3 - dihydro - 5 - (2 - fluorophenyl) - 1H - 1,4 - benzodiazepine in 200 ml of methylene chloride. The solution was added to 200 ml of saturated aqueous sodium bicarbonate and the mixture was stirred for 20 minutes. The organic layer was separated, washed with sodium bicarbonate, dried over sodium sulfate and evaporated to leave resinous 2 - acetylaminomethyl - 7 - chloro - 2,3 - dihydro - 5 - (2 - fluorophenyl) - 1H - 1,4 - benzodiazepine. This material was heated with 40 g of polyphosphoric acid at 150° for 10 minutes. The cooled reaction mixture was dissolved in water, made alkaline with ammonia and ice and extracted with methylene chloride. The extracts were dried and evaporated and the residue was chromatographed over 120 g of silica gel using 20% methanol in methylene chloride. The clean fractions were combined and evaporated to yield resinous 8 - chloro - 3a,4 - dihydro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine. A mixture of this material was 500 ml of toluene and 30 g of manganese dioxide was heated to reflux for 1-1/2 hours. The manganese dioxide was separated by filtration over Celite. The filtrate was evaporated and the residue was crystallized from ether to yield 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine, m.p. 152—154°. The analytical sample was recrystallized from methylene chloride/hexane.

Example 3

Reaction as in the first paragraph of Example 1 of 152.5 g (0.5 m) of 7 - chloro - 5 - (2 - chlorophenyl) - 1,3 dihydro - 2H - 1,4 - benzodiazepin - 2 - one saturated with methylamine with 133 g (0.7 m) of titanium tetrachloride in 2-1 of tetrahydrofuran and 400 ml of benzene yielded 7 - chloro - 5 - (2 - chlorophenyl) - 2 - methylamino - 3H - 1,4 - benzodiazepine, m.p. 216—219°. The analytical sample was recrystallized from methylene chloride/ethanol and had m.p. 217—219°.

Sodium nitrite (10 g, 0.145 m) was added in portions over 45 minutes to a solution of 22.4 g (0.07 m) of 7 - chloro - 5 - (2 - chlorophenyl) - 2 - methylamino - 3H - 1,4 - benzodiazepin 150 ml of glacial acetic acid. After addition stirring was continued for 20 minutes under nitrogen. The product was precipitated by addition of ice-water, collected and dissolved in toluene. The solution was washed with saturated aqueous sodium bicarbonate, dried and evaporated under reduced pressure. The yellow viscous oil consisted according to thin layer chromatogram mainly of the desired nitrosamine. This material was dissolved in 100 ml of dimethylformamide and was added to a mixture of 30 ml of nitromethane, 100 ml of dimethylformamide and 10 g of potassium t-butoxide. The reaction mixture was slowly heated up to 85° with stirring under a nitrogen stream. After 5 minutes, the reaction mixture was cooled, and then acidified by addition of 10 ml of glacial acetic acid. The product was crystallized by gradual addition of water with seeding (seeds were obtained by chromatography over silica gel using 10% ethyl acetate in methylene chloride). The separated crystals were collected, washed with water and recrystallized from methylene chloride/ethanol to yield 7 - chloro - 5 - (2 - chlorophenyl) - 1,3 - dihydro - 2 - nitromethylene - 2H - 1,4 - benzodiazepine, m.p. 182—185°.

Hydrogenation of 7 g of 7 - chloro - 5 - (2 - chlorophenyl) - 1,3 - dihydro - 2 - nitromethylene - 2H - 1,4 - benzodiazepine in 300 ml of tetrahydrofuran and 150 ml of methanol in the presence of Raney nickel (5 teaspoonsful) for 1 hour yielded crude 2 - aminomethyl - 7 - chloro - 5 - (2 - chlorophenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepine. This material was acetylated in the usual fashion to produce oily 2 - acetylaminomethyl - 7 - chloro - 5 - (2 - chlorophenyl) - 2,3 - dihydro - 1H - 1,4 - benzodiazepine which was heated in 15 g of polyphosphoric acid for 10 minutes at 140—150°. The usual workup afforded a yellow resin which was chromatographed over 250 g of silica gel using 20% methanol in methylene chloride.

The clean fractions left resinous 8 - chloro - 6 - (2 - chlorophenyl) - 3a,4 - dihydro - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine. This material was oxidized with 10 g of manganese dioxide in 200 ml of toluene. After heating to reflux for 1-1/2 hour, the manganese dioxide was separated and the filtrate was

evaporated. Crystallization of the residue from ether yielded 8-chloro-6-(2-chlorophenyl)-1-methyl-4H-imidazo-[1,5-a][1,4]benzodiazepine, m.p. 140—144°. For analysis it was recrystallized from methylene chloride/hexane, m.p. 142—144°.

Example 4

A solution of 94.6 g (0.3 m) of 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepine-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 titanium tetrachloride 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 sodium sulfate and evaporated. The residue was chromatographed over 500 g of silica gel using 10% (v/v) ethanol in methylene chloride. Crystallization of 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°.

A mixture of 3.58 g (0.01 m) of 5-(2-chlorophenyl)-7-nitro-2-(N-nitrosomethylamino)-3H-1,4-benzodiazepine, 20 ml of dimethylformamide, 5 ml of nitromethane and 1.3 g (0.0115 m) of potassium t-butoxide was stirred at room temperature for 15 minutes under nitrogen. After addition of 2 ml of glacial acetic acid the reaction mixture was partitioned between methylene chloride and water. The organic phase was washed with water, dried over sodium sulfate and evaporated. The residue was chromatographed over 80 g of silica gel using 10% (v/v) ethyl acetate in methylene chloride. Crystallization of the clean fractions from methylene chloride/ethanol yielded straw colored crystals of 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2-nitromethylene-2H-1,4-benzodiazepine with m.p. 240—243° (dec.).

Example 5

A solution of 33 g (0.1 m) of 7-chloro-2-(N-nitrosomethylamino)-5-phenyl-3H-1,4-benzodiazepine 4-oxide in 100 ml of dimethylformamide was added to a mixture of 50 ml of nitromethane, 12.5 g (0.11 m) of potassium t-butoxide and 100 ml of dimethylformamide. The reaction mixture was stirred under a stream of nitrogen for 1 hour. After addition of 10 ml of glacial acetic acid, the product was crystallized by gradual addition of 250 ml of water. The precipitated yellow material was collected, washed with water, methanol and ether to leave 7-chloro-1,3-dihydro-2-nitromethylene-5-phenyl-2H-1,4-benzodiazepine 4-oxide, m.p. 253—255° (dec.). The analytical sample was recrystallized from methylene chloride and showed the same melting point.

Raney nickel (5 teaspoons) was added to a solution of 16.5 g (0.05 m) of 7-chloro-1,3-dihydro-2-nitromethylene-5-phenyl-2H-1,4-benzodiazepine 4-oxide in 500 ml of tetrahydrofuran and 250 ml of methanol. The mixture was hydrogenated for 5 hours at atmospheric pressure. The catalyst was removed by filtration and the filtrate was evaporated. The residue was dissolved in 2-propanol and the solution was made strongly acidic with ethanolic hydrogen chloride. The dihydrochloride of the product crystallized upon evaporation of part of the solvent. The orange crystals were collected to leave 2-aminomethyl-7-chloro-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine dihydrochloride, m.p. 230—240°.

Acetic anhydride (10 ml) was added to a solution of 10 g of the above dihydrochloride in 50 ml of water and 50 ml of methanol. A 10% aqueous solution of sodium carbonate (100 ml) was added with stirring over a period of 5 minutes. After addition the mixture was stirred for an additional ten minutes and was then extracted with methylene chloride. The extracts were washed with sodium

carbonate solution, dried over sodium sulfate and evaporated, at the end azeotropically with toluene. 2 - Acetaminomethyl - 7 - chloro - 2,3 - dihydro - 5 - phenyl - 1H - 1,4 - benzodiazepine was obtained as a yellow resin.

The above material was heated in 50 g of polyphosphoric acid to 135—140° for 10 minutes. The initially orange color of the reaction mixture faded to a light yellow. The cooled reaction mixture was dissolved in water, made alkaline with concentrated ammonia and ice and extracted with methylene chloride. The extracts were dried and evaporated. The yellow resin was dissolved in 2-propanol and treated with ethanolic hydrogen chloride whereupon the colorless dihydrochloride of the product crystallized. Melting point was 240—245°.

This hydrochloride was partitioned between methylene chloride and aqueous ammonia. The organic phase was dried and evaporated. Crystallization of the residue from ether yielded 8 - chloro - 3a,4 - dihydro - 1 - methyl - 6 - phenyl - 3H - imidazo[1,5 - a][1,4]benzodiazepine as a colorless product with m.p. 116—118°.

A mixture of 3.1 g (0.01 m) of 8 - chloro - 3a,4 - dihydro - 1 - methyl - 6 - phenyl - 3H - imidazo[1,5 - a][1,4]benzodiazepine, 20 g of activated manganese dioxide and 150 ml of toluene was refluxed for 1 hour. The manganese dioxide was removed by filtration over Celite and was washed well with methylene chloride. The filtrate was evaporated and the residue was crystallized from ether to yield 8 - chloro - 1 - methyl - 6 - phenyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine as colorless crystals with m.p. 187—188°.

Example 6

A mixture of 11.2 g (0.1 m) of potassium tert.butoxide, 50 ml of nitroethane and 200 ml of dimethylformamide was stirred at room temperature for 15 min. A solution of 29 g (0.088 m) of crude 7 - chloro - 5 - (2 - fluorophenyl) - 2 - (N - nitrosomethylamino) - 3H - 1,4 - benzodiazepine in 100 ml of dimethylformamide was then added and stirring under nitrogen was continued for 6 hrs. The reaction mixture was neutralized by addition of glacial acetic acid and diluted with water. The product was extracted with ether. The extracts were washed with saturated aqueous sodiumbicarbonate solution, dried over sodium sulfate and evaporated. Crystallization from ether yielded 7 - chloro - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2 - (1 - nitroethylene) - 2H - 1,4 - benzodiazepine as yellow crystals with m.p. 136—142°.

Raney nickel (5 teaspoonsful) was added to a solution of 17.3 g (0.05 m) of 7 - chloro - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2 - (1 - nitroethylene) - 2H - 1,4 - benzodiazepine in 750 ml of tetrahydrofuran. The mixture was hydrogenated at atmospheric pressure for 4 hrs. The catalyst was removed by filtration over Celite and was washed well with methanol. The filtrate was evaporated to leave crude 2 - (1 - aminoethyl) - 7 - chloro - 2,3 - dihydro - 5 - (2 - fluorophenyl) - 1H - 1,4 - benzodiazepine as a reddish oil.

This material was dissolved in 300 ml of methylene chloride. Following, the addition of 14 ml of acetic anhydride, 300 ml of saturated aqueous sodium bicarbonate solution was added and the two-phase mixture was stirred at room temperature for 1 hr. The methylene chloride layer was separated, washed with bicarbonate, dried over sodium sulfate and evaporated. The residue was heated with 40 g of polyphosphoric acid for 10 minutes at 160—170°. The cool reaction mixture was diluted with water, made alkaline with ammonia and extracted with methylene chloride. The extracts were washed with water, dried and evaporated to leave a brown residue which was chromatographed on 250 g of silica gel using 20% (v/v) methanol in methylene chloride. The thin layer chromatographically homogeneous fractions were combined to yield a resin which was subjected to the following oxidation.

A mixture of the above material, 20 g of activated manganese dioxide and 300 ml of toluene was heated to reflux for 3 hrs using a Dean-Stark trap to remove the water. The manganese dioxide was separated by filtration over Celite and was washed well with methylene chloride. The filtrate was evaporated and the residue was chromatographed with pressure over 150 g of silica gel H using 3% ethanol in methylene chloride. The first eluted major component was 8 - chloro - 1,4 - dimethyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine.

It was converted to a crystalline dihydrochloride by treatment with ethanolic hydrogen chloride in ether, mp. 247—250° (dec.).

The more polar component could be crystallized from methylene chloride/ether/hexane to yield 8 - chloro - 1,3 - dimethyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine with mp. 178—180°.

19

Example 7

A mixture of 3.1 g (0.01 m) of 8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine, 2.15 g (0.0125 m) of *m*-chloroperbenzoic acid and 100 ml of methylene chloride was stirred for 48 hrs. at room temperature. It was then washed with 10% aqueous sodium carbonate solution and water. The residue was chromatographed over 80 g of silica gel using 10% (v/v) of ethanol in methylene chloride. The Tlc-homogeneous fractions were combined and evaporated. Crystallization of the residue from methylene chloride/ether yielded 8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 5-oxide mp. 260—261°.

Example 8

A solution of 1 g of 8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine 5-oxide in 20 ml of acetic anhydride was heated on the steam bath for 24 hrs. The reagent was evaporated under reduced pressure and the residue was crystallized from ether to yield 4-acetoxy-8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine, mp. 200—201°.

Example 9

Sodium methoxide (0.54 g) was added to a solution of 0.73 g (2 mmol) of 4-acetoxy-8-chloro-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine in 20 ml of methanol. After sitting at room temperature for 30 min, the solvent was evaporated under reduced pressure after neutralization with acetic acid. The residue was partitioned between methylene chloride and sodium bicarbonate solution. The organic layer was dried over sodium sulfate and evaporated. Crystallization of the residue from ether yielded 8-chloro-4-hydroxy-1-methyl-6-phenyl-4H-imidazo[1,5-a][1,4]benzodiazepine, mp. 173—174°.

Example 10

A warm solution of 6.5 g (0.02 m) of 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine in 30 ml of ethanol was combined with a warm solution of 2.6 g (0.022 m) of maleic acid in 20 ml of ethanol. The mixture was diluted with 150 ml of ether and heated on the steam bath for 3 min. After cooling, the crystals were collected, washed with ether and dried in vacuo to yield 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine maleate, mp. 148—151°.

Example 11

A mixture of 17.4 g (0.05 m) of 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2-(1-nitromethylene)-2H-1,4-benzodiazepine 4-oxide, 500 ml of tetrahydrofuran, 200 ml of methanol and 5 teaspoonsful of Raney nickel was hydrogenated at atmospheric pressure for 5 hrs. The catalyst was removed by filtration and the filtrate was evaporated, at the end azeotropically with xylene to leave crude 2-aminomethyl-7-chloro-5-(2-fluorophenyl)-2,3-dihydro-1H-1,4-benzodiazepine.

This material was dissolved in 200 ml of methanol and the solution was heated to reflux for 2 hrs. after addition of 14 ml of triethylorthoacetate and 2.8 g of *p*-toluenesulfonic acid. The solvent was evaporated under reduced pressure and the residue was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The organic layer was dried and evaporated to yield oily 8-chloro-3a,4-dihydro-6-(2-fluorophenyl)-1-methyl-3H-imidazo[1,5-a][1,4]benzodiazepine. This crude product was dissolved in 500 ml of xylene. After addition of 50 g of activated manganese dioxide, the mixture was stirred and heated to reflux for 1-1/2 hrs with separation of water in a Dean-Stark trap. The inorganic material was removed by filtration and the filtrate was evaporated to leave 10 g of brown oil.

A warm solution of 4.65 g (0.04 m) of maleic acid in 50 ml of ethanol was added to this residue. After the solution was complete, the product was crystallized by addition of ether. It was collected and washed with ether to leave 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine maleate, mp. 112—115°. Heating under vacuum at 90° to 100° converts this product to the higher melting form with mp. 148—151°.

Example 12

A solution of 0.32 g (1 mmol) of 8-chloro-6-(2-fluorophenyl)-1-methyl-

30

20

1,527,131

20

4H - imidazo[1,5 - a][1,4]benzodiazepine in 5 ml of ethanol was treated with excess ethanolic hydrogen chloride. The salt was crystallized by addition of 2-propanol and ether. The colorless crystals were collected, washed with ether and dried to leave 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine dihydrochloride, mp. 290—295°.

5

5

Example 13

A solution of 0.325 g (1 mmol) of 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine in 3 ml of ethanol was combined with a suspension of 0.4 g (1 mmol) of the dihydrochloride of the same compound in 5 ml of ethanol. After filtration, the solution was treated with ether and heated on the steam bath for 5 min to crystallize. The crystals were collected, washed with ether and dried to leave 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine hydrochloride, mp. 295—297°.

10

10

Example 14

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.

15

15

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 evaporated in vacuo, and the residue partitioned between methylene chloride and water. A colorless amorphous solid mp. 227—229° was removed by filtration. An additional sample, mp. 226—228° of the colorless solid was obtained from the methylene chloride mother liquors after drying over anhydrous sodium sulfate, evaporation to dryness, and crystallization from ethyl acetate.

20

20

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

25

25

To a cooled (10°), stirred solution of 10.0 g (0.04 m) of the product, 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.). This material was used in the following step:

30

30

The conjugate base of nitromethane was prepared by treatment of 50 ml of nitromethane in 200 ml of dimethylformamide with 5.7 g (0.05 m) of potassium *tert*-butoxide. The resultant stirred yellow suspension was treated with 10.9 g of crude 2 - (N - nitrosomethylamino) - 5 - phenyl - 3H - 1,4 - benzodiazepine in 100 ml of dimethylformamide. The dark mixture thus obtained was stirred for 2 hrs. at 25° and for 1 hr at 85° and then cooled to 25° and poured into 1 l of water. After acidification with acetic acid, the aqueous solution was extracted with four 250 ml portions of methylene chloride, and the combined organic extracts were then washed with water and brine, dried (CaSO₄), and concentrated in vacuo to give a dark oil which was purified by chromatography over 1 kg of silica gel (CHCl₃ elution) to afford crude 1,3 - dihydro - 2 - nitromethylene - 5 - phenyl - 2H - 1,4 - benzodiazepine, mp. 131—142°.

35

35

40

40

45

45

50

50

An analytical sample, mp 141—142°, was prepared by recrystallization from ethanol.

A mixture of 8.4 g (0.03 m) of 1,3 - dihydro - 2 - nitromethylene - 5 - phenyl - 2H - 1,4 - benzodiazepine, 75 ml of tetrahydrofuran, 75 ml of methanol and 2 teaspoonsful of Raney nickel was hydrogenated at atmospheric pressure for 6 hrs. The catalyst was removed by filtration and the filtrate was evaporated to leave crude 2 - aminomethyl - 2,3 - dihydro - 5 - phenyl - 1H - 1,4 - benzodiazepine.

55

55

This material was dissolved in 50 ml of methylene chloride and was treated with 6 ml of acetic anhydride and 200 ml of saturated aqueous sodium bicarbonate solution for 15 min. with stirring. The methylene chloride layer was separated, washed with bicarbonate solution, dried and evaporated. The residue was treated with 25 g of polyphosphoric acid to 130—150° for 15 min. The cooled reaction

60

60

mixture was partitioned between water and ether. The aqueous phase was made alkaline with ammonia and was extracted with methylene chloride. The extracts were dried and evaporated. Chromatography of the residue over 70 g of silica gel with 20% (v/v) ethanol in methylene chloride yielded 3a,4 dihydro - 1 - methyl - 6 - phenyl - 3H - imidazo[1,5 - a][1,4]benzodiazepine as a light yellow resin.

This material was heated in 50 ml of toluene with 7 g of activated manganese dioxide to reflux for 1-1/2 hrs. The inorganic material was filtered off and the filtrate was evaporated. The residue was purified by chromatography over 30 g of silica gel using 10% ethanol in methylene chloride. The clean fractions were combined and evaporated. Crystallization of the residue from ether yielded 1 - methyl - 6 - phenyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine.

Example 15

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°.

A stirred solution of 2.4 g (0.04 m) of nitromethane in 50 ml of dry dimethylformamide was treated with 1 g (0.024 m) of 57% sodium hydride dispersion in mineral oil at room temperature under argon. After stirring for 1 hr. at room temperature, the mixture was treated with 5.2 g (0.01 m) of 7 - chloro - 2 - di - (morpholino) - phosphinyloxy - 5 - (2 - fluorophenyl) - 3 - methyl - 3H - 1,4 - benzodiazepine in one portion and stirring under argon was continued at room temperature for 24 hrs. The dark mixture was poured over a mixture of ice and glacial acetic acid with stirring to give a yellow solid. Stirring was continued until the ice had melted. The solid was filtered, washed with water and air dried on the funnel to yield 7 - chloro - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 3 - methyl - 2 - nitromethylene - 2H - 1,4 - benzodiazepine having mp of 215° (dec.). Recrystallization of a sample from 1:1 methanol/methylene chloride gave yellow needles, mp. 219—221° (dec.).

A solution of 5.2 g (0.015 m) of 7 - chloro - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 3 - methyl - 2 - nitromethylene - 2H - 1,4 - benzodiazepine in 450 ml of 2:1 tetrahydrofuran methanol was hydrogenated for 3 hrs. using a Parr apparatus, Raney nickel catalyst (3 teaspoonsful) and an initial pressure of 18 psi. The mixture was filtrated and evaporated at reduced pressure to give crude 2 - aminomethyl - 7 - chloro - 2,3 - dihydro - 5 - (2 - fluorophenyl) - 3 - methyl - 1H - 1,4 - benzodiazepine as a yellow oil.

The crude aminomethyl compound was mixed with 5 ml of triethyl orthoacetate and 0.5 g of p-toluenesulfonic acid monohydrate in 100 ml of ethanol. After heating under reflux for 2 hrs, the solution was evaporated at reduced pressure. The residue was cooled to room temperature, treated with a mixture of ice and concentrated ammonium hydroxide and extracted with methylenechloride. Evaporation of the dried extracts in vacuo gave crude 8 - chloro - 3a,4 - dihydro - 1,4 - dimethyl - 6 - (2 - fluorophenyl) - 3H - imidazo[1,5 - a][1,4]benzodiazepine as a gum.

The crude dihydroimidazobenzodiazepine was mixed with 20 g of activated manganese dioxide and 200 ml of toluene and heated under reflux for 2 hrs. The mixture was filtered and the manganese dioxide was washed with methylene chloride. Evaporation of the combined filtrate and washings at reduced pressure gave a brown gum. The dihydrochloride of 8 - chloro - 1,4 - dimethyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine was obtained as a white powder by stirring the gum with ethanolic hydrogen chloride for a few minutes. The salt melted at 247—250°.

Example 16

Zinc dust, 3 g, was added to a solution of 2.8 g of 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine in 75 ml of

(32)

22

1,527,131

22

methylene chloride and 75 ml of glacial acetic acid. After stirring at room temperature for 2 hrs, the inorganic material was filtered off and washed with methylene chloride and water.

The filtrate was diluted with 100 ml of methylene chloride and 200 ml of water and was made alkaline with ammonia. The methylene chloride layer was separated, dried and evaporated. Crystallization of the residue from ether/hexane yielded 8 - chloro - 5,6 - dihydro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine, m.p. 200—203°.

Example 17

A mixture of 100 g (0.8 m) of chloroacetaldehyde dimethylacetal and 100 ml of 1.5 N hydrochloric acid was heated under reflux for 15 min. and then cooled and added to a solution of 130 g (0.5 m) of 2 - amino-2' - fluoro - 5 - nitrobenzophenone and 46 g (0.28 m) of hydroxylamine sulfate and 1 l of ethanol. The mixture was stirred at room temperature for 2 hr. and then heated to reflux for 1.5 hr. The mixture was cooled and the product obtained by filtration. Recrystallization from a mixture of chloroform and methanol gave pure 2 - chloromethyl - 4 - (2 - fluorophenyl) - 6 - nitro - 1,2 - dihydroquinazoline 3-oxide as yellow prisms, mp. 220—224°.

A solution of 142 g (0.423 m) of 2 - chloromethyl - 4 - (2 - fluorophenyl) - 6 - nitro - 1,2 - dihydroquinazoline 3-oxide in 2.3 l of dichloromethane was treated with 400 g of manganese dioxide, and after stirring for 18 hr. the solution was filtered. The manganese dioxide was washed with 600 ml of tetrahydrofuran and 800 ml of dichloromethane. The combined filtrates were concentrated to 400 ml and 1 l of ether was added. This was cooled and filtered to give 2 - chloromethyl - 4 - (2 - fluorophenyl) - 6 - nitroquinazoline 3-oxide. A sample was recrystallized from a mixture of dichloromethane and methanol to give the pure product as pale yellow prisms, mp. 127—130°.

To 500 ml of dimethylsulfoxide and 75 ml (1.4 m) of nitromethane was added with stirring under nitrogen 15.6 g (0.678 m) of lithium amide. After 30 minutes the solution was cooled to 5° and 104 g (0.31 m) of 3 - chloromethyl - 4 - (2 - fluorophenyl) - 6 - nitroquinazoline 3-oxide was added slowly, keeping the temperature below 8°. After 68 hr. at room temperature the reaction mixture was poured into a mixture of 2.5 l of ice and water and 25 ml of acetic acid, and the solution was filtered. The gummy precipitate was dissolved in 1 l of dichloromethane which was washed with dilute ammonium hydroxide, dried over anhydrous sodium sulfate and evaporated. The residue was crystallized from ethyl acetate to give 1,3 - dihydro - 5 - (2 - fluorophenyl) - 7 - nitro - 2 - nitromethylene - 2H - 1,4 - benzodiazepine 4-oxide, and the filtrates were evaporated, dissolved in dichloromethane and filtered through a sintered glass funnel containing 200 g of Florisil (Trade Mark). The Florisil was eluted with dichloromethane (600 ml), ether (600 ml) and ethyl acetate (1.2 l). The ether and ethyl acetate fractions were combined and concentrated to give additional final product. A sample was recrystallized from a mixture of tetrahydrofuran and hexane to give the pure product as yellow prisms, mp. 216—220°.

A suspension of 25 g (0.0698 m) of 1,3 - dihydro - 5 - (2 - fluorophenyl) - 7 - nitro - 2 - nitromethylene - 2H - 1,4 - benzodiazepine 4-oxide in 1.3 l of absolute ethanol was treated with 10 teaspoons of Raney nickel and hydrogenated at atmospheric pressure and room temperature for 9 hr. The mixture was filtered through Celite and the filtrate was evaporated to dryness. A sample of the oil was crystallized from tetrahydrofuran to give the intermediate 7 - amino - 2 - aminomethyl - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepine as yellow prisms which melted with decomposition at 185—192°.

Without further purification, the oil obtained from the reduction was heated under reflux for 2 hr. in a solution of 300 ml of absolute ethanol, containing 4.5 ml (0.0257 m) of ethanolic hydrogen chloride and 50 g (0.309 m) of triethylorthoacetate. The mixture was then evaporated to dryness and the residue was dissolved in 150 ml of dichloromethane which was washed with 100 ml of dilute ammonium hydroxide, dried over anhydrous sodium sulfate and evaporated to dryness.

The residual oil, which was crude 8 - acetylamino - 3a,4 - dihydro - 6 - (2 - fluorophenyl) - 1 - methyl - 3H - imidazo[1,5 - a][1,4]benzodiazepine, was dissolved in 500 ml of benzene and treated with 100 g of activated manganese dioxide. The mixture was refluxed and stirred for 9 hr. using a Dean Stark trap. An

additional 25 g of activated manganese dioxide was added and after 4 hr. of refluxing the manganese dioxide was removed by filtration and was washed with 500 ml of tetrahydrofuran. The filtrates were combined and evaporated to dryness. The residual oil, which was 8 - acetylamino - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo - [1,5 - a][1,4]benzodiazepine, was dissolved in 75 ml of methanol and an excess of ethanolic hydrogen chloride was added. After 10 min, 100 ml of water was added, and after an additional 20 min, during which time the 8-acetyl group was hydrolyzed, a mixture of ice and dilute ammonium hydroxide was added until the solution was basic. The reaction was filtered and the precipitate and filtrates were extracted separately with dichloromethane. The extracts were dried, and evaporated. The extract from the filtrates were crystallized from isopropanol to give 8 - amino - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo - [1,5 - a][1,4]benzodiazepine isopropanol and the extract from the precipitate was chromatographed through Florisil, first with dichloromethane and then with ether and ethyl acetate containing 10% (v/v) of methanol gave, after evaporation and crystallization from isopropanol, additional product. Recrystallization of the combined products from isopropanol gave the product as white rods, m.p. 135—145°.

Example 18

A mixture of 17 g (0.05 m) of racemic 8 - chloro - 1,4 - dimethyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine which had been obtained from its dihydrochloride by partitioning between methylene chloride and aqueous ammonia, 18.8 g (0.05 m) of O,O' - dibenzoyl - d - tartaric acid hydrate and 170 ml of ethanol was boiled until solution was complete. For crystallization the solution was allowed to sit overnight. The separated crystals were collected, washed with ethanol and ether to yield the O,O' - dibenzoyl - d - tartrate with m.p. 140—142°. Recrystallization from ethanol/ether yielded a product with m.p. 141—142° and $[\alpha]_D^{25} - 43.39$ (c=1% in methanol).

A solution of 1.6 g (0.0106 m) of 1-tartaric acid in 11 ml of ethanol was added to a solution of 3.5 g of the levo-rotatory base liberated from the above O,O' - dibenzoyl - d - tartrate in 11 ml of ethanol. The crystals obtained were collected and washed with ethanol and ether to yield (+) - 8 - chloro - 1,4 - dimethyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine 1-tartrate, m.p. 178—180°. Recrystallization from ethanol gave product with m.p. 183—185° and $[\alpha]_D^{25} + 25.69$ (c=1.012% in methanol). The amorphous base liberated from this salt showed a rotation of $[\alpha]_D^{25} - 36.74$ (c=0.939% in methylene chloride).

Example 19

The mother liquor left after separation of the crystalline salt with O,O' - benzoyl - d - tartaric acid described in the preceding Example was evaporated and reconverted to the base by partitioning between aqueous ammonia and methylene chloride. The methylene chloride solution was dried over sodium sulfate and evaporated to yield partly resolved base.

A solution of 9.7 g (0.029 m) of this material in 15 ml of ethanol was treated with a solution of 4.4 g of d-tartaric acid in 14 ml of ethanol. The crystals which separated after several hours were collected to yield (–) - 8 - chloro - 1,4 - dimethyl - 6 - (1 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine d-tartrate, m.p. 176—178°. Recrystallization from ethanol gave a product with m.p. 182—184° and $[\alpha]_D^{25} - 24.96$ (0.9616% in methanol). The amorphous base liberated from this salt showed a rotation of $[\alpha]_D^{25} + 37.6$ (c=1.0% in methylene chloride).

Example 20

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.

A mixture of 100 ml of dry N,N - dimethylformamide and 6.8 g of

nitromethane was treated under an atmosphere of argon with 2.8 g (0.066 m) of a 57% suspension of sodium hydride in mineral oil. The mixture was stirred for 1 hr. at room temperature when a solution of 18 g (0.033 m) of crude 7 - (2 - methyl - 1,3 - dioxolan - 2 - yl) - 2[bis(morpholino)phosphinyloxy] - 5 - phenyl - 3H - 1,4 - benzodiazepine in 50 ml of dry N,N - dimethylformamide was added. The reaction mixture was allowed to stand at room temperature for 15 hrs. when the dark viscous liquid was poured over a mixture of ice and dilute acetic acid. The bright yellow precipitate was removed by filtration, dissolved in dichloromethane which was washed with dilute ammonium hydroxide and water, dried over anhydrous sodium sulfate and evaporated. The original filtrate was extracted with dichloromethane which was washed, dried and evaporated as above. The two crude residues were combined and chromatographed over Florisil. Using dichloromethane, 10% (v/v) ether as the eluent and monitoring the fractions by tlc, several fractions containing the product were collected and evaporated. Crystallization and recrystallization from a mixture of dichloromethane and hexane gave the pure 2,3 - dihydro - 7 - (2 - methyl - 1,3 - dioxolan - 2 - yl) - 2 - nitromethylene - 5 - phenyl - 1H - 1,4 - benzodiazepine as pale yellow prisms, m.p. 158—161°.

Hydrogenation of 5 g (0.0137 m) of 2,3 - dihydro - 7 - (1 - methyl - 1,3 - dioxolan - 2 - yl) - 2 - nitromethylene - 5 - phenyl - 1H - 1,4 - benzodiazepine in 250 ml of absolute ethanol in the presence of 1 teaspoon of Raney nickel for 3.5 hours yielded crude 2 - aminomethyl - 2,3 - dihydro - 7 - (1 - methyl - 1,3 - dioxolan - 2 - yl) - 5 - phenyl - 1H - 1,4 - benzodiazepine. To a solution of 4 g (0.0119 m) of this compound in 75 ml of absolute ethanol was added 0.7 g (0.0037 m) of *p*-toluene sulfonic acid and 6 g (0.037 m) of triethyl orthoacetate. The mixture was refluxed for 2 hours; evaporated to dryness and the residue was dissolved in 50 ml of dichloromethane. This was washed with 25 ml of dilute ammonium hydroxide, dried over anhydrous sodium sulfate and evaporated to give crude 3a,4 - dihydro - 1 - methyl - 8 - (1 - methyl - 2,3 - dioxolan - 2 - yl) - 6 - phenyl - 3H - imidazo[1,5 - a][1,4]benzodiazepine as an oil.

A solution containing 3.8 g (0.0105 m) of this crude oil, and 18 g of activated manganese dioxide in 100 ml of toluene was refluxed and stirred for 2 hours using a Dean Stark trap. The mixture was filtered and washed with a mixture of 250 ml of dichloromethane and 250 ml of tetrahydrofuran. The filtrates were evaporated and dissolved in a small amount of isopropanol and treated with 1.4 g (0.0121 m) of maleic acid in ethanol. Ether was added and the precipitate was filtered and recrystallized from a mixture of methanol and ether to give 1 - methyl - 8 - (2 - methyl - 1,3 - dioxolan - 2 - yl) - 6 - phenyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate methanol (2/1) as off white prisms, m.p. 179—182°.

Example 21

A solution of 0.3 g (0.1000607 m) of 1 - methyl - 8 - (2 - methyl - 1,3 - dioxolan - 2 - yl) - 6 - phenyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate methanol (2/1) in 10 ml (0.01 m) of 1N hydrochloric acid was allowed to stand for 18 hours. A small amount of charcoal was added and the reaction mixture was filtered. The solution was made basic with ammonium hydroxide, extracted with 25 ml of dichloromethane, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was dissolved in isopropanol and 0.35 g (0.10015 m) of picric acid in 5 ml of ethanol was added. The solution was evaporated and the residue was crystallized from methanol. Recrystallization from a mixture of tetrahydrofuran and isopropanol gave 8 - acetyl - 1 - methyl - 6 - phenyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine dipicrate as yellow prisms m.p. 225—230°.

Example 22

A solution of 1 g (0.00317 m) of 8 - acetyl - 1 - methyl - 6 - phenyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine dipicrate in 75 ml of absolute ethanol was treated with 0.78 g (0.0205 m) of sodium borohydride and after 18 hours the solution was evaporated to dryness. The residue was acidified with dilute acetic acid, made basic with ammonium hydroxide and the mixture was extracted with 75 ml of dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate and evaporated to dryness. The oil thus obtained was dissolved in isopropanol and 1.6 g (0.007 m) of picric acid in 20 ml of ethanol was added. The precipitated salt was filtered and recrystallized twice from methanol to give 8 - (1 - hydroxyethyl) - 1 - methyl - 6 - phenyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine dipicrate as yellow rods, m.p. 223—225°.

Example 23

The filtrates from the reaction of Example 22 were concentrated and the crude product was filtered off. Recrystallization twice from a mixture of tetrahydrofuran and methanol gave pure 8 - (1 - hydroxyethyl) - 1 - methyl - 6 - phenyl - 5,6 - dihydro - 4H - imidazo[1,5 - a][1,4]benzodiazepine dipicrate as yellow rods, m.p. 143—145°.

Example 24

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 - (nitrosomethylamino) - 3H - 1,4 - benzodiazepine as a yellow oil.

The material prepared above was dissolved in 100 ml of dimethylformamide and the solution was added to a mixture of 100 ml of dimethylformamide, 35 ml of nitromethane and 9.9 g of potassium t-butoxide had been stirred for 1/2 hour at room temperature. After completion of the addition, the reaction mixture was stirred for 1 hour at room temperature and for 30 minutes on the steam bath. The cooled solution was acidified with glacial acetic acid, diluted with water and extracted with methylene chloride. The extracts were washed with water, dried and evaporated. The residue was dissolved in 50 ml of ethanol and was allowed to crystallize in the refrigerator overnight after seeding. The yellow crystals were collected and recrystallized from ethanol yielding 1,3 - dihydro - 7 - ethyl - 5 - (2 - fluorophenyl) - 2 - nitromethylene - 2H - 1,4 - benzodiazepine, m.p. 138—140°. Seed crystals were obtained by chromatography of the crude product over 40-fold amount of silica gel using 5% (v/v) of ethylacetate in methylene chloride. The analytical sample was recrystallized from ether/hexane, m.p. 138—141°.

1,3 - Dihydro - 7 - ethyl - 5 - (2 - fluorophenyl) - 2 - nitromethylene - 2H - 1,4 - benzodiazepine (2.6 g) was hydrogenated for 4 hours with Raney nickel (1 teaspoonful) in 30 ml of ethanol. The catalyst was separated by filtration and the filtrate was evaporated. The residue was dissolved in ether and the amine was extracted with 10% aqueous acetic acid. The extracts were washed with ether and made alkaline with ammonia. The precipitated amine was extracted with methylene chloride. The extracts were dried and evaporated to leave 1.5 g of crude 2 - aminomethyl - 2,3 - dihydro - 7 - ethyl - 5 - (2 - fluorophenyl) - 1H - 1,4 - benzodiazepine. This material was dissolved in 50 ml of xylene. The solution was then heated to reflux for 2 hours after addition of 3 ml of triethylorthoacetate. The residue obtained after evaporation under reduced pressure was chromatographed over 50 g of silica gel using 20% methanol in methylene chloride. The homogeneous fractions were combined and evaporated to yield 3a,4 - dihydro - 8 - ethyl - 6 - (2 - fluorophenyl) - 1 - methyl - 3H - imidazo[1,5 - a][1,4]benzodiazepine. This material was dissolved in 50 ml of toluene and the solution was heated to reflux for 1 hour after addition of 5 g of activated manganese dioxide. The inorganic material was separated by filtration and the filtrate was evaporated. The residue was dissolved in ether and treated with ethanolic hydrogen chloride and acetone. The crystalline dihydrochloride (m.p. 248—255°) was collected and reconverted to the base by partitioning between methylene chloride and aqueous

ammonia. The methylene chloride layer was dried and evaporated. Crystallization of the residue from ether/hexane yielded 8 - ethyl - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine, m.p. 152—154°.

Example 25

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 completion of the addition, the mixture was stirred at room temperature for 1 hour and was then 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.

Example 26

To 5 ml of acetic anhydride was added 0.3 g (0.00082 m) of 8 - amino - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine isopropanol and the reaction mixture was heated on the steam bath for 1 hour, and then evaporated to dryness. The residue was dissolved in 25 ml of dichloromethane which was washed with 15 ml of 5% potassium carbonate solution, dried over anhydrous sodium sulfate and evaporated to dryness. The product was recrystallized twice from a mixture of methanol and ethyl acetate to give 8 - acetamido - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine as white rods, m.p. 326—331°.

Example 27

A solution of 0.8 g (0.0024 m) of 8 - acetamido - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine in 10 ml of dry N,N - dimethylformamide under nitrogen was treated with 0.13 g (0.003 m) of 55% sodium hydride in mineral oil and after 30 minutes the reaction mixture was cooled in an ice bath. To the stirred reaction 0.43 g (0.003 m) of methyl iodide was added and after 18 hours at room temperature the reaction mixture was poured into water. Filtration afforded the crude product which was recrystallized from a mixture of ethyl acetate and ether to give 6 - (2 - fluorophenyl) - 1 - methyl - 8 - (N - methylacetamido) - 4H - imidazo[1,5 - a][1,4]benzodiazepine as off white prisms, m.p. 217—223°.

Example 28

A solution of 0.3 g (0.000828 m) of 6 - (2 - fluorophenyl) - 1 - methyl - 8 - (N - methylacetamido) - 4H - imidazo[1,5 - a][1,4]benzodiazepine in 10 ml of methanol was treated with 3 ml of concentrated hydrochloric acid and refluxed for 1 hour. The solution was made basic with ammonium hydroxide and then partitioned between 50 ml of dichloromethane and 50 ml of water. The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness. The residual oil was dissolved in 10 ml of dichloromethane and filtered through Florisil. It was eluted with ether/ethyl acetate and finally ethyl acetate containing 5% methanol. This last mixture was evaporated and the residue crystallized from a mixture of ethyl acetate and ether to give 6 - (2 - fluorophenyl) - 1 - methyl - 8 - methylamino - 4H - imidazo[1,5 - a][1,4]benzodiazepine as off white prisms, m.p. 255—259°.

Example 29

A solution of 0.3 g (0.00082 m) of 8 - amino - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine isopropanol in 0.5 ml of sulfuric acid was treated with 4 g of ice followed by 0.2 g (0.0029 m) of sodium nitrite. After 5 minutes this was added to a fresh solution prepared by adding 1 g (0.00625 m) of copper sulfate in 10 ml of water to 1 g (0.00794 m) of sodium sulfite in 5 ml of water and then adding this to 8 g (0.116 m) of sodium nitrite in 40 ml of water. After 15 minutes the reaction was warmed to 35° for 5 minutes, made basic with 10% potassium carbonate solution and extracted with 100 ml of dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate, concentrated and applied to a silica gel thick layer plate. This was developed in a mixture of ethyl acetate and ethanol (10/1), and the spot having an R_f of 0.5 was scraped off. Crystallization from methanol and recrystallization from a mixture of dichloromethane and ether gave 2 - (5 - hydroxymethyl) - 2 -

methyl - 1 - imidazolyl) - 5 - nitrophenyl]methanone as off white prisms, m.p. 188—192°.

Example 30

5 A solution of 0.5 g (0.00137 m) of 8 - amino - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine isopropanol in 20 ml of formic acid and 5 ml (0.062 m) of 37% formaldehyde was heated on the steam bath for 3 hours, and then evaporated to dryness. The residue was dissolved in 50 ml of dichloromethane, which was washed with 15 ml of 10% potassium carbonate solution, dried over anhydrous sodium sulfate and concentrated. The residual oil was applied to and developed on 2 silica gel thick layer plates in a mixture of ethyl acetate and ethanol (7/1). The material having an Rf of 0.4 was scraped off, washed with methanol, filtered and evaporated. The oil was dissolved in ether and 5 ml of a 10% ethanolic solution of picric acid was added. The precipitate was filtered and recrystallized from a mixture of tetrahydrofuran and isopropanol to give (2 - fluorophenyl)[2 - (2 - methyl - 5 - dimethylamino - methyl - 1 - imidazolyl) - 5 - dimethylaminophenyl]methanone dipicrate as yellow prisms, m.p. 228—230°.

Example 31

20 A) A solution of 3 g (0.00920 m) of 8 - chloro - 6 - (2 - fluoro - phenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine in 50 ml of water and 0.5 ml (0.4092 m) of concentrated sulfuric acid was treated with 1.5 g (0.0217 m) of sodium nitrite. After 18 hours an additional 0.5 ml of sulfuric acid and 1.5 g of sodium nitrite was added, and after 10 minutes the reaction was made basic with 10N sodium hydroxide. The reaction mixture was extracted with 75 ml of dichloromethane, which was dried over anhydrous sodium sulfate and evaporated to dryness. Crystallization of the residue from a mixture of ethyl acetate and ether gave (2 - fluorophenyl) - [2 - (5 - hydroxymethyl - 2 - methyl - 1 - imidazolyl) - 5 - chlorophenyl]methanone as white prisms, m.p. 165—168°.

30 B) A solution of 1 g (0.00240 m) of 5 - aminomethyl - 1 - [4 - chloro - 2 - (2 - fluorobenzoyl) - phenyl] - 2 - methylimidazole dihydrochloride was dissolved in 20 ml of water and 1 g (0.0145 m) of sodium nitrite was added slowly with stirring in an ice bath. After 3 hours the reaction was made basic with 10N sodium hydroxide and extracted with 50 ml of dichloromethane. The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness. Crystallization from ethyl acetate gave (2 - fluorophenyl) - [2 - (5 - hydroxymethyl - 2 - methyl - 1 - imidazolyl) - 5 - chlorophenyl]methanone as white prisms, m.p. and mmp with a sample prepared as above 163—166°.

40 To a mixture of 0.1 g (0.000273 m) of 8 - amino - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine isopropanol and 5 ml of water was added 1 ml of concentrated hydrochloric acid. The reaction was cooled in an ice bath and 0.15 g (0.00217 m) of sodium nitrite was added slowly with stirring. After 1 hour the reaction mixture was poured into a solution of 0.2 g (0.00202 m) of cuprous chloride in 50 ml of water which had been heated to 70°. After 18 hours the reaction was made basic with sodium hydroxide, extracted with dichloromethane (2x50 ml) dried over anhydrous sodium sulfate and evaporated to dryness. The residue was developed on a silica gel thick layer plate in a mixture of ethyl acetate and methanol (10/1). The product which had an Rf of 0.7 was scraped off the plate, stirred with methanol and filtered. Evaporation and crystallization of the crude product from a mixture of ethyl acetate and ether gave (2 - fluorophenyl) - [2 - (5 - hydroxymethyl - 2 - methyl - 1 - imidazolyl) - 5 - chlorophenyl]methanone as white prisms, m.p. and mmp with an authentic sample 159—166°.

Example 32

55 A solution of 0.5 g (0.00145 m) of (2 - fluorophenyl) - [2 - (5 - hydroxymethyl - 2 - methyl - 1 - imidazolyl) - 5 - chlorophenyl]methanone in 25 ml of dichloromethane was treated with 0.15 ml (0.00155 m) of phosphorous tribromide in an ice bath and after 1 hour at room temperature was poured into 50 ml of liquid ammonia. After the ammonia had evaporated the reaction was partitioned between 50 ml of dichloromethane and water. The organic phase was separated and dried over anhydrous sodium sulfate. The solution was concentrated and the residue was applied to 2 silica gel thick layer plates which were developed in a mixture of ethyl acetate/10% methanol.

The compound which had an Rf of 0.6 was scraped off, stirred with methanol

and filtered. The solution was treated with 0.1 g (0.000962 m) of maleic acid and evaporated. The residual salt was crystallized from a mixture of isopropanol and ether to give the maleate of 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine as white prisms, m.p. and mmp with an authentic sample 112—115° (melting point of solvated product). The base was obtained by partitioning the salt between dichloromethane and water, adjusting the pH separating the layers and evaporating the organic phase. Crystallization of the product from ether gave white prisms, m.p. and mmp with an authentic sample 154—157°.

Example 33

A mixture of 9.75 g (0.03 m) of 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine, 200 ml of methylene chloride and 12 g (0.07 m) of *m*-chloroperbenzoic acid was stirred for 1-1/2 hours. The solution was then extracted with 3×150 ml of 1N hydrochloric acid. The extracts were washed with ether, made alkaline with ammonia and extracted with methylene chloride. The methylene chloride extracts were dried and evaporated and the residue was crystallized from ethyl acetate to leave a product which was further purified by chromatography over 100 g of silica gel using 5% (v/v) of ethanol in methylene chloride. The clean fractions were combined and evaporated. Crystallization of the residue from ethyl acetate/ether yielded 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine 5-oxide as colorless crystals, m.p. 245—246° (dec.).

Example 34

A solution of 4 g of 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine 5-oxide in 100 ml of acetic anhydride was heated on the steam bath for 24 hours. The reagent was evaporated under reduced pressure, at the end azeotropically with xylene. The residue was chromatographed over 80 g of silica gel using 20% (v/v) methylene chloride in ethyl acetate. Crystallization of the clean fractions from methylene chloride/ether yielded 4-acetoxy-8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine as colorless crystals, m.p. 201—202°.

Example 35

4-Acetoxy-8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine (0.5 g, 1.3 mmol) was added to 40 ml of methanol containing 4 mmol of sodium methoxide. After stirring under nitrogen for 1/2 hour at room temperature, the solvent was evaporated under reduced pressure. The residue was dissolved in water and the solution was acidified with acetic acid. The precipitated crystals were collected and dissolved in methylene chloride. The solution was dried and evaporated and the residue was crystallized from methylene chloride/ether to yield 8-chloro-6-(2-fluorophenyl)-4-hydroxy-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine as colorless crystals, m.p. 185—186°.

Example 36

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 37

To a solution of 1.6 g (5 mmoles) of 8-chloro-5,6-dihydro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine in 10 ml of pyridine was added 1.2 g (6 mmoles) of *p*-toluenesulfonyl chloride. After standing at room temperature for 19 hours, the reaction mixture was diluted with water and extracted with methylene chloride. The organic extract was dried and concentrated in vacuo to dryness. The residue was crystallized from a mixture of methylene chloride, ether and gave 8-chloro-6-(2-fluorophenyl)-5,6-dihydro-1-methyl-5-(4-methylphenylsulfonyl)-4H-imidazo[1,5-

al[1,4]benzodiazepine melting at 252—253°. After recrystallization from tetrahydrofuran the pure product formed yellow prisms with the same melting point.

5 To a stirred solution of 2.4 g (5 mmoles) of 8 - chloro - 6 - (2 - fluorophenyl) - 5,6 - dihydro - 1 - methyl - 5 - (4 - methylphenylsulfonyl) - 4H - imidazo[1,5 - al[1,4]benzodiazepine in 120 ml of dry tetrahydrofuran was added 1.1 g of potassium tert-butoxide. After stirring at room temperature for 2 hours the reaction mixture was poured into ice water and extracted with a 50% mixture of ether and petroleum ether. The organic extract was dried and concentrated in vacuo to dryness. The residue was crystallized from a mixture of ether, petroleum ether and gave 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - al[1,4]benzodiazepine melting at 152—153°. The mixed melting point with an authentic sample gave no depression.

Example 38

15 To a stirred solution of 1.2 g (3.5 mmoles) of 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - al[1,4]benzodiazepine 5-oxide in 120 ml of ethanol was added slowly 1.2 g (31 mmoles) of sodium borohydride. After stirring for 4.5 hours at room temperature the reaction mixture was diluted with about 175 ml of water and product melting at 246—248° was separated by filtration. After recrystallization from a mixture of methylene chloride/ether, the pure 8 - chloro - 6 - (2 - fluorophenyl) - 5,6 - dihydro - 5 - hydroxy - 1 - methyl - 4H - imidazo[1,5 - al[1,4]benzodiazepine formed colorless needles melting at 251—252°.

20 A solution of 0.3 g of 8 - chloro - 6 - (2 - fluorophenyl) - 5,6 - dihydro - 5 - hydroxy - 1 - methyl - 4H - imidazo[1,5 - al[1,4]benzodiazepine in a mixture of 10 ml of pyridine and 2 ml of acetic anhydride was left at room temperature for 19 hours. The reaction mixture was concentrated in vacuo to dryness. The residue was dissolved in 20 ml of methanol and 0.2 g of sodium methoxide added. After standing at room temperature for 45 minutes, the reaction mixture was concentrated in vacuo to dryness. The residue was partitioned between methylene chloride and water. The organic layer was separated, dried and concentrated in vacuo to dryness. The residue was crystallized from a methylene chloride/ether mixture and gave starting material melting at 255—256°. Concentration of the filtrate and crystallization of the residue from ether gave 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - al[1,4]benzodiazepine melting at 158—160°. The mixed melting point with an authentic sample gave no depression.

Example 39

40 A solution of 1.5 g of 8 - chloro - 5,6 - dihydro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - al[1,4]benzodiazepine in a mixture of 10 ml pyridine and 5 ml of acetic anhydride was left at room temperature for 18 hours. The reaction mixture was concentrated in vacuo to dryness. The residue was dissolved in methylene chloride and washed with dilute potassium hydroxide. The organic layer was separated, dried and concentrated in vacuo to dryness. The residue was crystallized from a mixture of methylene chloride, ether, petroleum ether and gave 5 - acetyl - 8 - chloro - 6 - (2 - fluorophenyl) - 5,6 - dihydro - 1 - methyl - 4H - imidazo[1,5 - al[1,4]benzodiazepine melting at 185—186°. After recrystallization from methylene chloride the pure product formed colorless prisms melting at 186—187°.

Example 40

50 To a stirred solution of 27.8 g (92 mmoles) of DL - 2 - aminomethyl - 7 - chloro - 2,3 - dihydro - 5 - (2 - fluorophenyl) - 1H - 1,4 - benzodiazepine in a mixture of 450 ml of methylene chloride and 300 ml of acetic acid was added slowly 27.8 g of zinc dust. After stirring at room temperature for 4 hours the reaction mixture was filtered over Celite. The filtrate was diluted with ice water, made alkaline with 50% potassium hydroxide solution and extracted with methylene chloride. The organic extract was separated, dried and concentrated in vacuo to dryness. The residue was crystallized from ether and gave 2 - aminomethyl - 7 - chloro - 2,3,4,5 - tetrahydro - 5 - (2 - fluorophenyl) - 1H - 1,4 - benzodiazepine melting at 119—120°. After recrystallization from ether the pure product formed slightly yellow prisms melting at 127—128°.

60 The hydrochloride was prepared by treating a solution of the base in isopropanol with an excess of concentrated hydrochloric acid. After recrystallization of the salt from a mixture of water and isopropanol the pure product formed slightly yellow needles melting at 268—271°.

39

30

1,527,131

30

A) A solution of 3 g (10 mmoles) of rac.2 - aminomethyl - 7 - chloro - 2,3,4,5 - tetrahydro - 5 - (2 - fluorophenyl) - 1H - 1,4 - benzodiazepine in a mixture of 30 ml of xylene and 10 ml of triethylorthoacetate (97%) was refluxed for 4 hours. The reaction mixture was diluted with ether and extracted with dilute ice cold hydrochloric acid. The acid extract was made alkaline with dilute potassium hydroxide and extracted with methylene chloride. The organic layer was separated, dried and concentrated in vacuo to dryness. The residue was crystallized from ether and gave 8 - chloro - 6 - (2 - fluorophenyl) - 3a,4,5,6 - tetrahydro - 1 - methyl - 3H - imidazo[1,5 - a][1,4]benzodiazepine (Isomer A) melting at 187—189°. After recrystallization from a mixture of methylene chloride and ether the pure product formed slightly yellow prisms melting at 189—190°.

B) To a stirred solution of 2.5 g of 8 - chloro - 3a,4 - dihydro - 6 - (2 - fluorophenyl) - 1 - methyl - 3H - imidazo[1,5 - a][1,4]benzodiazepine in a mixture of 100 ml methylene chloride and 25 ml of acetic acid was added slowly 2.5 g of zinc dust. After stirring at room temperature for 4 hours, the reaction mixture was filtered over Celite. The filtrate was diluted with ice water, made alkaline with 50% potassium hydroxide and extracted with methylene chloride. The organic extract was separated, dried and concentrated in vacuo to dryness. The residue was crystallized from ether and gave 8 - chloro - 6 - (2 - fluorophenyl) - 3a,4,5,6 - tetrahydro - 1 - methyl - 3H - imidazo[1,5 - a][1,4]benzodiazepine (Isomer A) which was identical with the product prepared above, m.p. and mmp 189—190°.

C) A solution of 3.2 g (10 mmoles) of 8 - chloro - 3a,4 - dihydro - 6 - (2 - fluorophenyl) - 1 - methyl - 3H - imidazo[1,5 - a][1,4]benzodiazepine in 50 ml acetic acid and 10 ml of water was hydrogenated at room temperature and atmospheric pressure in the presence of 0.4 g of prehydrogenated platinum oxide. After 15 minutes, 10 mmoles of hydrogen were absorbed. The catalyst was separated by filtration and the filtrate concentrated in vacuo to dryness. The residue was dissolved in methylene chloride and washed with an excess of ice cold dilute sodium carbonate. The organic layer was separated, dried and concentrated in vacuo to dryness. The residue was crystallized from a mixture of ether/petroleum ether and gave 8 - chloro - 6 - (2 - fluorophenyl) - 3a,4,5,6 - tetrahydro - 1 - methyl - 3H - imidazo[1,5 - a][1,4]benzodiazepine (Isomer B) melting at 108—110°. After recrystallization from ether the pure product formed colorless prisms melting at 110—112°.

A mixture of 2.9 g of 8 - chloro - 6 - (2 - fluorophenyl) - 3a,4,5,6 - tetrahydro - 1 - methyl - 3H - imidazo[1,5 - a][1,4]benzodiazepine, 90 ml of toluene and 15 g of activated manganese dioxide was stirred and refluxed for 2 hours. The reaction was filtered over Hyflo and the filtrate concentrated in vacuo to dryness. The residue was crystallized from ether and gave 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine which gave no melting point depression with an authentic sample.

Example 41

A suspension of 17 g (0.05 m) of 7 - chloro - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2 - nitromethylene - 2H - 1,4 - benzodiazepine - 4 - oxide in 200 ml of tetrahydrofuran and 100 ml of methanol was hydrogenated in the presence of 17 g of Rany nickel at an initial pressure of 155 psi for 24 hrs. The catalyst was removed by filtration and the filtrate was evaporated. The residue was dissolved in 50 ml of 2-propanol and warmed on the steambath. A warm solution of 17 g of maleic acid in 60 ml of ethanol was added and the salt was allowed to crystallize by cooling in the ice-bath. The 2 - aminomethyl - 7 - chloro - 2,3 - dihydro - 5 - (2 - fluorophenyl) - 1H - 1,4 - benzodiazepine dimaleate consisted of yellow crystals with mp. 196—198°.

2 - Aminomethyl - 7 - chloro - 2,3 - dihydro - 5 - (2 - fluorophenyl) - 1H - 1,4 - benzodiazepine dimaleate (8.0 g, 0.015 m) was partitioned between methylene chloride and aqueous ammonia. The methylene chloride solution was washed with water, dried over sodium sulfate and evaporated. The residue was dissolved in 50 ml of pyridine. After addition of 10 ml of acetic anhydride the mixture was heated on the steam bath for 4 hours. The reagents were evaporated under reduced pressure and the residue was partitioned between methylene chloride and aqueous sodium bicarbonate solution. The organic layer was dried and evaporated. Crystallization of the residue from methylene chloride/ether with seeding yielded 1 - acetyl - 2 - acetylaminomethyl - 7 - chloro - 2,3 - dihydro - 5 - (2 - fluorophenyl) - 1H - 1,4 - benzodiazepine, mp. 213—215°. Seeds were obtained by chromatography over silica gel (40 fold amount) using 10% (v/v) ethanol in

(48)

methylene chloride for elution. The analytical sample was recrystallized from ethylacetate/hexane and had a melting point of 215—217°.

5 A mixture of 0.5 g of 1 - acetyl - 2 - acetylaminomethyl - 7 - chloro - 2,3 - dihydro - 5 - (2 - fluorophenyl) - 1H - 1,4 - benzodiazepine and 10 g of polyphosphoric acid was heated to 150—170°C for 10 min. The cool reaction mixture was dissolved in ice-water and the solution was made alkaline with ammonia. The precipitated base was extracted with methylene chloride, the extracts were washed with water, dried over sodium sulfate and evaporated. The residue was chromatographed over 10 g of silica gel using 20% methanol in methylene chloride. The clean fractions were combined and evaporated. The residue was crystallized from ether to yield 8 - chloro - 3a,4 - dihydro - 6 - (2 - fluorophenyl) - 1 - methyl - 3H - imidazo[1,5 - a][1,4]benzodiazepine, mp. 142—144°.

10

Example 42

15 A solution of 2.9 g (0.00927 m) of 2,3 - dihydro - 5 - (2 - fluorophenyl) - 2 - nitromethylene - 1H - 1,4 - benzodiazepine - 4 - oxide in a mixture of 1 teaspoon of Raney nickel, 90 ml of tetrahydrofuran and 45 ml of methanol was hydrogenated at atmospheric pressure and at room temperature for 2.3 hr. The mixture was filtered, and the nickel was washed with dichloromethane. The combined filtrates were evaporated and the resulting oil was dissolved in 50 ml of dichloromethane which was washed with 50 ml of dilute ammonium hydroxide, dried over anhydrous sodium sulfate and evaporated to dryness. A solution of 2.2 g (0.019 m) of maleic acid in 15 ml of ethanol was added to the oil and after ether was added 2-aminomethyl - 2,3 - dihydro - 5 - (2 - fluorophenyl) - 1H - 1,4 - benzodiazepine dimaleate hemihydrate crystallized. Recrystallization from a mixture of methanol and ether gave a product as yellow rods, m.p. 147—150°.

20

25

A solution of 4.0 g (0.0149 m) of the base of 2 - amino - methyl - 2,3 - dihydro - 5 - (2 - fluorophenyl) - 1H - 1,4 - benzodiazepine dimaleate hemihydrate in 125 ml of absolute ethanol was treated with 4 g (0.0247 m) of triethylorthoacetate and 0.5 g (0.00263 m) of *p*-toluene sulfonic acid. After refluxing the mixture for 2 hr. the reaction mixture was evaporated to dryness. The resulting oil was dissolved in 50 ml of dichloromethane, which was washed with 50 ml of dilute ammonium hydroxide, dried over anhydrous sodium sulfate and evaporated to dryness to yield the crude 3a,4 - dihydro - 6 - (2 - fluorophenyl) - 1 - methyl - 3H - imidazo[1,5 - a][1,4]benzodiazepine as an oil.

30

35

A) The crude product from the previous paragraph was dissolved in 100 ml of toluene, treated with 18 g of activated manganese dioxide and the mixture was stirred and refluxed for 3.5 hr. using a Dean Stark trap. The reaction mixture was filtered through Celite and the precipitate was washed with 100 ml of tetrahydrofuran and then 100 ml of dichloromethane. The combined filtrates were evaporated and the residue was dissolved in 25 ml of dichloromethane. This solution was chromatographed through a Florisil column with dichloromethane, and then eluted with ether. Elution with ethyl acetate and then a 10% (v/v) solution of methanol in ethyl acetate gave the crude product, which was crystallized from ether and then recrystallized from ethyl acetate to give 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine as white prisms, m.p. 164—168°.

40

45

B) A solution of 1.2 g (0.0041 m) of 3a,4 - dihydro - 6 - (2 - fluorophenyl) - 1 - methyl - 3H - imidazo[1,5 - a][1,4]benzodiazepine in 50 ml of mesitylene and 0.5 g of 10% palladium on charcoal was stirred and refluxed for 28 hr., and then it was filtered and evaporated to dryness. Crystallization from ethyl acetate gave 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine as white prisms, m.p. 162—167°, and a mixed m.p. with authentic product melted at 162—168°.

50

Example 43

55 A solution of 0.3 g (0.00103 m) of 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine in 2 ml of concentrated sulfuric acid was cooled to 0°, and a solution of 0.11 g (0.0011 m) of potassium nitrate in 1.5 ml of concentrated sulfuric acid was added dropwise. After 18 hr. at room temperature an additional 20 mg (0.0002 m) of potassium nitrate was added and the reaction was stirred for 5 hr. and then poured into a beaker containing ice. The mixture was made basic with ammonium hydroxide, and extracted with 50 ml of dichloromethane which was separated, dried over anhydrous sodium sulfate, and

60

evaporated to dryness. The oil was dissolved in 3 ml of dichloromethane and applied to a silica gel thick layer plate which was developed in a mixture of ethyl acetate and ethanol (3:1). The nitrated product was scraped off the plate and stirred with a 1:1 (v/v) mixture of methanol and dichloromethane and filtered. The filtrate was evaporated and the residue was crystallized from methanol. Recrystallization from a mixture of dichloromethane and petroleum ether gave 6-(2-fluoro-5-nitrophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine as white prisms, m.p. 199—203°.

Example 44

41.3 g of 8-chloro-1,4-dimethyl-6-(2-fluorophenyl)-4H-imidazo[1,5-a][1,4]benzodiazepine dihydrochloride was partitioned between methylene chloride and aqueous ammonia. The methylene chloride solution was washed with water, dried over sodium sulfate and evaporated to leave the free base. This material was dissolved in 50 ml of 2-propanol and the solution was treated with a solution of 12 g of maleic acid in 40 ml of 2-propanol. The solution was gradually diluted with 300 ml of ether. The precipitated crystals were collected and dried to leave 8-chloro-1,4-dimethyl-6-(2-fluorophenyl)-4H-imidazo[1,5-a][1,4]benzodiazepine maleate, m.p. 130—132° after recrystallization from ethanol/ether.

Example 45

A solution of 5 g (0.00153 m) of 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine in 75 ml of dry ethylene dichloride was cooled in an ice bath and 5 g (0.0352 m) of boron trifluoride etherate was added. After 10 minutes a solution of 4 g (0.091 m) of ethylene oxide in 5 ml of ethylene dichloride was added with stirring. After 1 hour at room temperature the mixture was made basic with a solution of potassium carbonate in water. The organic layer was separated, dried over anhydrous sodium sulfate, and evaporated. The residue was dissolved in 50 ml of dichloromethane and filtered through 150 g of Florisil. The Florisil was eluted with 750 ml of dichloromethane and then with 750 ml of ether.

The dichloromethane solution was evaporated and partitioned between 100 ml of ether and 100 ml of 0.5N hydrochloric acid. The acid layer was separated, made basic with ammonium hydroxide and extracted with 100 ml of dichloromethane which was dried and evaporated. The oil was dissolved in 15 ml of isopropanol and 0.8 g (0.0069 m) of maleic acid was added. The solution was warmed on the steam bath for 5 minutes, cooled and ether was added. The precipitate was filtered, and recrystallized from a mixture of methanol and ether to give 2-chloro-13a-(2-fluorophenyl)-12,13a-dihydro-6-methyl-9H-11H-imidazo[1,5-a]-oxazolo[3,2-d][1,4]benzodiazepine maleate as white prisms, m.p. 195—200°.

The ether solution from the Florisil was concentrated, filtered and recrystallized from ether to give the base as white prisms, m.p. 178—180°.

Example 46

A stirred solution of 29.9 g (0.1 m) of 1,3-dihydro-5-(2-fluorophenyl)-7-nitro-2H-1,4-benzodiazepin-2-one in 500 ml of dry tetrahydrofuran was treated portionwise under argon 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°.

Example 47

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-

42

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.).

Example 48

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 - benzodiazepin - 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°.

Example 49

A solution of 25 g of 8 - chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine in 50 ml of water and 50 ml of concentrated hydrochloric acid was allowed to stand at room temperature for 3 hours. Following addition of 250 ml of 2-propanol the mixture was evaporated partially under reduced pressure without heating. Additional 200 ml of 2-propanol were added and partial evaporation was resumed. The precipitated crystals were collected and washed well with 2-propanol and ether to yield 5 - aminomethyl - 1 - [4 - chloro 2 - (2 - fluorobenzoyl)phenyl] - 2 - methylimidazole dihydrochloride, m.p. 302—307° (dec.). The analytical sample was recrystallized from methanol/2-propanol without heating.

Example 50

A mixture of 49.9 (0.2 moles) of 2 - amino - 5 - chloro - 2' - fluorobenzophenone, 38.0 g (0.2 moles) of 2,2 - dichloro propanol; 18.0 g (0.11 moles) of hydroxylamine sulfate and 500 ml of ethanol was stirred at room temperature for 2 days.

The mixture was diluted with 200 ml of 10% aqueous sodium carbonate solution with vigorous agitation. A gummy material precipitated from solution and the solution was diluted with 1.0 l of ice-water. The solution was extracted with 3x300 ml of dichloromethane. The extracts were combined, dried over sodium sulfate, filtered and concentrated to dryness in vacuo. The residue was crystallized from dichloromethane and petroleum ether giving 6 - chloro - 2 - (1,1 - dichloroethyl) - 1,2 - dihydro - 4 - (2 - fluorophenyl) - quinazoline 3-oxide as yellow prisms, m.p. 195—8° (dec.).

3.8 ml of nitromethane was added to 50.0 ml of dimethylformamide with stirring and under an atmosphere of nitrogen. The solution was chilled to 0° and 1.3 g (0.012 moles) of potassium tertiary butoxide was added in portions. The temperature was maintained at 0 to 10° by means of an ice water bath. The mixture was stirred at room temperature for 1 hour.

The mixture was chilled at 5° with stirring and 2.2 g (0.006 moles) of the quinazoline prepared above was added at 5° to 9° in portions. After the addition had been completed, the mixture was stirred at room temperature for 17 hours.

The reaction mixture was poured into ice water and dichloromethane neutralizing with glacial acetic acid. The dichloromethane was washed with water; brine and dried over sodium sulfate. After filtration and concentration an amber residue was obtained which was crystallized with ethyl acetate. The crystals were collected and dried giving orange 7 - chloro - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 3 - methyl - 2 - nitromethylene - 2H - 1,4 - benzodiazepine - 4 - oxide as prisms, m.p. 198—200°. Recrystallization from dichloromethane/ethyl acetate gave pure material m.p. 216—218° (dec.).

Example 51

A solution of 0.7 g (0.00203 m) of (2 - fluorophenyl) - [2 - (5 - hydroxymethyl -

2 - methyl - 1 - imidazolyl) - 5 - chlorophenyl] - methanone in 40 ml of dry dichloromethane was cooled in an ice bath and 0.22 ml (0.00227 m) of phosphorus tribromide was added with stirring. After 1 hr. at room temperature the mixture was cooled in an ice bath and 2 ml (0.0328 m) of ethanolamine was added. The solution was stirred for 2 hrs. at room temperature, refluxed for 1 hr. and then poured into 50 ml of water. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated to a small volume. The residue was developed on 4 silica gel thick layer plates in a solution of 5% methanol in ethyl acetate (v/v). The material corresponding to an Rf of 0.5 was removed from the plate and treated with methanol. The solution was filtered and the filtrates were evaporated. The residue was crystallized from ether yielding 2 - chloro - 13a - (2 - fluorophenyl) - 12,13a - dihydro - 6 - methyl - 9H,11H - imidazo[1,5 - a]oxazolo - [3,2 - d][1,4]benzodiazepine. Recrystallization from a mixture of methanol and ether gave pure product as white prisms, mp and mmp with an authentic sample 176—181°.

Example 52

9.5 ml of nitromethane was dissolved in 100 ml of dimethylformamide under nitrogen and with stirring 5.0 g (0.045 moles) of potassium tertiary butoxide was added at 0—10° and the mixture was stirred at room temperature for 1 hour. The mixture was then chilled on ice and 5.1 g (0.015 moles) of 6 - chloro - 2 - dichloromethyl - 1,2 - dihydro - 4 - phenyl - quinazoline 3-oxide was added slowly at a temperature below 9°. The reaction mixture was stirred at room temperature for 17 hours.

The mixture was poured onto ice-water and dichloromethane and made slightly acid with glacial acetic acid. The aqueous phase was re-extracted three times with dichloromethane. The organics were combined; washed consecutively with water and brine, dried over sodium sulfate; filtered and concentrated to dryness in vacuo giving an amber residue. Crystallization from boiling ethanol afforded 7 - chloro - 1,3 - dihydro - 2 - nitromethylene - 5 - phenyl - 2H - 1,4 - benzodiazepine - 4 - oxide as yellow prisms, mp. 245—248° (dec.). Admixture with authentic material gave no depression in melting point.

Example 53

Potassium tert. butoxide (3.37 g, 0.03 m), was added to a stirred suspension of 3.5 g (0.01 m) of 7 - chloro - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2 - nitromethylene - 2H - 1,4 - benzodiazepine 4-oxide in 100 ml of dimethylformamide cooled to -20°. After stirring under nitrogen for 10 min at this temperature 2.13 g (0.015 m) of methyl iodide was added and stirring was continued for 10 min. The reaction mixture was neutralized by addition of glacial acetic acid and was partitioned between water and methylene chloride. The organic phase was separated, dried over sodium sulfate and evaporated. The residue was crystallized from methylene chloride/ethyl acetate to yield 7 - chloro - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 3 - methyl - 2 - nitromethylene - 2H - 1,4 - benzodiazepine 4-oxide as yellow crystals, mp. 215—218°. The analytical sample was recrystallized from the same solvents, mp. 216—218°.

Example 54

A mixture of 7 - chloro - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepine - 2 - carboxamide (64 mg, 0.2 mmole) and lithium aluminum hydride (15 mg, 0.4 mmole) in dry THF (3 ml) was boiled for 15 min. The cooled reaction mixture was quenched by addition of saturated aqueous sodium sulfate solution. Tlc analysis of the resulting solution showed the presence of starting material as the major, more mobile component and the free base 2 - aminomethyl - 7 - chloro - 2,3 - dihydro - 5 - (2 - fluorophenyl) - 1H - 1,4 - benzodiazepine as the minor component. The solution was transferred directly to a 20x20 cm² preparative tlc plate (silica gel) and the plate was developed with ethanol. The lower yellow band was removed and extracted twice with methanol/methylene chloride (2:1). Evaporation of the filtered extract left a clear, colorless oil. This was taken up in ethanol (1 ml), treated with excess maleic acid (50 mg), scratched and stored overnight in the freezer. The yellow crystals were collected, washed with ether and air-dried. The product was identified as 2 - aminomethyl - 7 - chloro - 2,3 - dihydro - 5 - (2 - fluorophenyl) - 1H - 1,4 - benzodiazepine dimaleate by comparison of its infrared spectrum in Nujol (Trade Mark), and of its melting point 185—186.5° with those of an authentic sample (mp. 188°). The mixture melting point was 184—7°.

Example 55

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 mantle 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 - methylamino - 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°.

Nitrosyl chloride was introduced into a solution of 7.8 g (0.03 m) of 2 - methylamino - 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 - nitrosomethylamino) - 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°.

2 - (N - nitrosomethylamino - 5 - phenyl - 3H - thieno[3,2 - e][1,4]diazepine (5.7 g, 0.02 m) was added to a mixture of 15 ml of nitromethane, 4.5 g of potassium t-butoxide and 60 ml of dimethylformamide which had been stirred for 10 minutes at room temperature. Following addition, the reaction mixture was stirred under nitrogen and heated on the steam bath for 10 minutes. After acidification with 4 ml of glacial acetic acid the mixture was partitioned between methylene chloride/toluene and saturated sodium bicarbonate solution. The organic layer was washed with water, dried and evaporated. Crystallization of the residue from methanol with seeding yielded 1,2 - dihydro - 2 - nitromethylene - 5 - phenyl - 3H - thieno[3,2 - e][1,4]diazepine as yellow crystals, m.p. 160—163°. Seeds were obtained by chromatographic purification over 30 fold amount of silica gel using 10% (v/v) of ethyl acetate in methylene chloride. The analytical sample was recrystallized from methanol, m.p. 163—164°.

A solution of 1.42 g (5 mmol) of 1,2 - dihydro - 2 - nitromethylene - 5 - phenyl - 3H - thieno[3,2 - e][1,4]diazepine in 200 ml of ethanol was hydrogenated over Raney nickel (2 teaspoonsful) for 1 hour at atmospheric pressure. The catalyst was removed by filtration and the filtrate was evaporated. The residue was treated with 1.2 g of maleic acid in 10 ml of 2-propanol. The salt was crystallized by addition of ether to yield 2 - amino - methyl - 2,3 - dihydro - 5 - phenyl - 1H - thieno[3,2 - e][1,4]diazepine dimaleate as yellow crystals, m.p. 170—173°. The analytical sample was recrystallized from methanol/2-propanol, m.p. 187—189°.

2 - Aminomethyl - 2,3 - dihydro - 5 - phenyl - 1H - thieno[3,2 - e][1,4]diazepine dimaleate (1 g, 2 mmol), was partitioned between methylene chloride and aqueous ammonia. The methylene chloride layer was dried and evaporated. The residue was heated to reflux for 1 hour with 1 ml of triethyl orthoacetate in 20 ml of xylene. The solvent was evaporated under reduced pressure and the residue was crystallized from 2-propanol/ether to yield 1 - methyl - 3a,4 - dihydro - 6 - phenyl - 3H - imidazo[1,5 - a]thieno[2,3 - f]diazepine, mp. 150—152°. This material was heated to reflux in 30 ml of toluene with 2 g of activated manganese dioxide for 2 hours. The manganese dioxide was filtered off and washed well with methylene chloride. The filtrate was evaporated and the residue was chromatographed over 7 g of silica gel using 3% (v/v) of ethanol in methylene chloride. The fractions containing pure product were combined and evaporated. Crystallization from methylene chloride/ether and recrystallization from ethyl acetate/hexane yielded 1 - methyl - 6 - phenyl - 4H - imidazo[1,5 - a]thieno[2,3 - f]diazepine, m.p. 223—225°.

Example 56

A mixture of 7.7 g (0.278 m) of 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - thieno[2,3 - e][1,4]diazepine - 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 mantle 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°.

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°.

7 - Chloro - 2 - (N - nitrosomethylamino) - 5 - phenyl - 3H - thieno[2,3 - e] [1,4]diazepine (3.2 g, 0.01 m) was added to a mixture of 10 ml of nitromethane, 35 ml of dimethylformamide and 2.26 g (0.02 m) of potassium t-butoxide which had been stirred under nitrogen for 10 minutes at room temperature. After heating for 10 minutes on the steam bath the reaction mixture was acidified by addition of 2 ml of glacial acetic acid and was partitioned between water and toluene. The toluene layer was washed with water, dried and evaporated. The residue crystallized from ethyl acetate/hexane to yield crude 7 - chloro - 2,3 - dihydro - 2 - nitromethylene - 5 - phenyl - 1H - thieno[2,3 - e] [1,4]diazepine. It was purified by chromatography over 40 g of silica gel using 10% (v/v) of ethyl acetate in methylene chloride. The pure product was obtained as yellow crystals with m.p. 154—156°.

A) A solution of 320 mg (1 mmol) of 7 - chloro - 2,3 - dihydro - 2 - nitromethylene - 5 - phenyl - 1H - thieno[2,3 - e] [1,4]diazepine in 20 ml of ethanol was hydrogenated over Raney nickel for 5 hours at atmospheric pressure. The catalyst was removed by filtration and the filtrate was evaporated. The residue was chromatographed over 7 g of silica gel using methylene chloride, methanol and triethylamine in a ratio of 13:6:1. The fractions containing pure product were combined, evaporated and the residue was treated with maleic acid in 2-propanol. Crystallization of the dimaleate salt from 2-propanol/ether and recrystallization from ethyl acetate/ethanol yielded 2 - aminomethyl - 7 - chloro - 2,3 - dihydro - 5 - phenyl - 1H - thieno[2,3 - e] [1,4]diazepine dimaleate as yellow crystals, m.p. 176—177°.

B) A solution of 320 mg (1 mmol) of 7 - chloro - 2,3 - dihydro - 2 - nitromethylene - 5 - phenyl - 1H - thieno [2,3 - e] [1,4]diazepine in 3 ml of tetrahydrofuran was added to a suspension of 0.8 g of lithium aluminum hydride in 20 ml of tetrahydrofuran. After heating to reflux for 5 minutes, the reaction mixture was cooled and hydrolyzed by addition of 5 ml of water. The inorganic material was separated by filtration and the filtrate was evaporated. The residue was chromatographed as described above and the pure product was converted to the maleate to give 2 - aminomethyl - 7 - chloro - 2,3 - dihydro - 5 - phenyl - 1H - thieno[2,3 - e] [1,4]diazepine dimaleate as, m.p. 176—178°.

2 - Aminomethyl - 7 - chloro - 2,3 - dihydro - 5 - phenyl - 1H - thieno[2,3 - e] [1,4]diazepine dimaleate (0.52 g, 1 mmol) was partitioned between methylene chloride and aqueous ammonia. The methylene chloride solution was dried and evaporated. The residue was heated to reflux for 1 hour with 0.5 ml of triethyl orthoacetate in 10 ml of xylene. The crude product obtained after evaporation under reduced pressure was dissolved in 25 ml of toluene and the solution was heated to reflux for 1-1/2 hours after addition of 2.5 g of activated manganese dioxide. The manganese dioxide was then filtered off and the filtrate was evaporated. The residue was chromatographed over 6 g of silica gel using 4% (v/v) of ethanol in methylene chloride. Fractions containing the pure compound were combined and evaporated. Crystallization of the residue from ether/hexane yielded 8 - chloro - 1 - methyl - 6 - phenyl - 4H - imidazo[1,5 - a]thieno[3,2 - f] [1,4]diazepine, m.p. 168—170°.

Example 57

A solution of 50 g (0.161 m) of 7 - chloro - 5 - (2 - chlorophenyl) - 1,3 - dihydro -

2H - thieno[2,3 - e][1,4]diazepin - 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°.

Example 58

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°.

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

Example 59

A mixture of 3.3 g (0.01 m) of 7 - chloro - 1,3 - dihydro - 2 - nitromethylene - 5 - phenyl - 2H - 1,4 - benzodiazepine 4-oxide, 3.3 ml of phosphorus trichloride and 300 ml of methylene chloride was stirred at room temperature for 4 hours. The solution was washed with 10% aqueous sodium carbonate solution, was dried over sodium sulfate and evaporated. The crude product was purified by chromatography over 100 g of silica gel using 10% (v/v) ethyl acetate in methylene chloride. The combined clean fractions were crystallized from methylene chloride/hexane to yield 7 - chloro - 1,3 - dihydro - 2 - nitromethylene - 5 - phenyl - 2H - 1,4 - benzodiazepine as light yellow crystals, m.p. 184—186°.

Example 60

A mixture of 3.6 g (0.01 m) of 7 - bromo - 2 - (N - nitrosomethylamino) - 5 - (2 -

pyridyl) - 3H - 1,4 - benzodiazepine, 30 ml of dimethylformamide, 5 ml of nitromethane and 2 g (0.018 m) of potassium t-butoxide was stirred at room temperature for 15 minutes and then heated up slowly. When the temperature reached 100° the mixture was cooled and neutralized by addition of glacial acetic acid. The product was precipitated by addition of saturated aqueous sodium bicarbonate and was collected, washed with water and dissolved in methylene chloride. The solution was dried over sodium sulfate and evaporated. Crystallization of the residue from methylene chloride/ethanol yielded 7 - bromo - 1,3 - dihydro - 2 - nitromethylene - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepine as a light yellow product, m.p. 232—235° (dec.). For analysis it was recrystallized from tetrahydrofuran/ethanol, m.p. 240—245° (dec.).

Example 61

A solution of 2.8 g (0.00932 m) of DL - 2 - aminomethyl - 7 - chloro - 2,3 - dihydro - 5 - (2 - fluorophenyl) - 1H - 1,4 - benzodiazepine in 40 ml of dichloromethane was treated with 2.5 g (0.0119 m) of trifluoroacetic acid anhydride and after 5 minutes the reaction mixture was washed with 15 ml of a 10% potassium carbonate solution, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was crystallized from dichloromethane and was recrystallized from a mixture of dichloromethane and hexane to give 7 - chloro - 2,3 - dihydro - 5 - (2 - fluorophenyl) - 2 - trifluoroacetaminomethyl - 1H - 1,4 - benzodiazepine as pale yellow prisms, m.p. 140—143°.

Example 62

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 phosphorodimorpholidic 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°.

A solution of 27 g (0.443 m) of nitromethane in 450 ml of dry dimethyl sulfoxide was cooled to 0° under argon and then 5.4 g (0.119 m) of 54% sodium hydride was added with stirring. After 2 hours at room temperature the mixture was cooled to 0° and 39.5 g (0.066 m) of 5 - (2 - fluorophenyl) - 7 - iodo - 2 - bis(morpholino) - phosphinyloxy - 3H - 1,4 - benzodiazepine was added all at once. The reaction was stirred for 18 hours and then poured into 3 l of ice and water, which contained 15 ml of acetic acid. The mixture was filtered, the precipitate was dissolved in 700 ml of dichloromethane which was then washed with 300 ml of water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was crystallized and recrystallized from a mixture of dichloromethane and ether to give 2,3 - dihydro - 5 - (2 - fluorophenyl) - 7 - iodo - 2 - nitromethylene - 1H - 1,4 benzodiazepine as yellow prisms, m.p. 214—216°C.

Example A

A parenteral formulation containing the following ingredients:

	per ml	
8 - Chloro - 1 - methyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate	1.0 mg	
Benzyl Alcohol	0.15 ml	
Tartaric Acid Buffer containing sodium hydroxide		50
Water for Injection q.s.ad	1 ml	

was prepared as follows (for 10 liters).

In a clean glass or glass-lined vessel, 8 l of water for injection were heated to 90°. It was then cooled to 50—60°, and 1.5 l of benzyl alcohol was added and dissolved with stirring. The solution was then allowed to cool to room temperature. The 10.0 g of 8 - chloro - 1 - methyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate were added under an atmosphere of nitrogen and stirred until completely dissolved. The pH was now adjusted to 3.0±1.0, preferably 3.0±0.5 with a combination of tartaric acid buffer and sodium hydroxide solution. Sufficient water for injection was then added to make a total

volume of 10 liters. This solution was then filtered through candle, filled into suitable size ampoules, gassed with nitrogen and sealed.

Example B

A tablet formulation containing the following ingredients:

5		per tablet	5
	8 - Chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate	10.0 mg	
	Lactose	113.5 mg	
	Corn Starch	70.5 mg	
10	Pregelatinized Corn Starch	8.0 mg	10
	Calcium Stearate	3.0 mg	
	Total Weight	205.0 mg	

15 8 - Chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 -
a][1,4]benzodiazepine maleate was mixed with the lactose, corn starch and
pregelatinized corn starch in a suitable size mixer and passed through a
comminuting machine. The mixture was returned to the mixer and moistened with
water to a thick paste. The moist mass was passed through a comminuting
machine and the moist granules were dried on paper lined trays at 45°C. The dried
granules were returned to the mixer, the calcium stearate was added and mixed
well. The granules were compressed at a tablet weight of 200 mg. 20

Example C

A tablet formulation containing the following ingredients:

		per tablet	
25	8 - Chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate	25.00 mg	25
	Lactose	64.50 mg	
	Corn Starch	10.00 mg	
	Magnesium Stearate	0.50 mg	
	Total Weight	100.00 mg	

30 was prepared as follows:
8 - Chloro - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine
maleate was mixed with lactose, corn starch and magnesium stearate in a suitable
mixer. The mixture was further blended by passing through a comminuting
machine. The mixed powders were slugged on a tablet compressing machine and
the slugs were comminuted to a suitable mesh size and mixed well. The tablets
were compressed at a tablet weight of 100 mg. 35

Example D

A capsule formulation containing the following ingredients:

		per capsule	
40	8 - Chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate	25 mg	40
	Lactose	158 mg	
	Corn Starch	37 mg	
	Talc	5 mg	
45	Total Weight	225 mg	45

was prepared as follows:

50 8 - Chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 -
a][1,4]benzodiazepine maleate was mixed with the lactose and corn starch in a
suitable mixer. The mixture was further blended by passing through a
comminuting machine. The blended powder was returned to the mixer, the talc
added and blended thoroughly. The mixture was then filled into hard-shell gelatin
capsules on a capsulating machine.

49

Example E

A capsule formulation containing the following ingredients:

		per capsule	
5	8 - Chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate	50 mg	5
	Lactose	125 mg	
	Corn Starch	30 mg	
	Talc	5 mg	
	Total Weight	210 mg	

10 was prepared as follows: 8 - Chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate was mixed with lactose and corn starch in a suitable mixer. The mixture was further blended by passing through a comminuting machine. The blended powder was returned to the mixer, the talc added and blended thoroughly. The mixture was filled into hard-shell gelatin capsules on a capsulating machine. 15

Example F

A capsule formulation containing the following ingredients:

		per capsule	
20	8 - Chloro - 1,4 - dimethyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate	50 mg	20
	Lactose	125 mg	
	Corn Starch	30 mg	
	Talc	5 mg	
25	Total Weight	210 mg	25

was prepared as follows: 8 - Chloro - 1,4 - dimethyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate was mixed with lactose and corn starch in a suitable mixer. The mixture was further blended by passing through a comminuting machine. The blended powder was returned to the mixer, the talc added and blended thoroughly. The mixture was filled into hard-shell gelatin capsules on a capsulating machine. 30

Example G

A capsule formulation containing the following ingredients:

		per capsule	
35	8 - Chloro - 1,4 - dimethyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate	25 mg	35
	Lactose	158 mg	
40	Corn Starch	37 mg	40
	Talc	5 mg	
	Total Weight	225 mg	

was prepared as follows: 8 - Chloro - 1,4 - dimethyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate was mixed with the lactose and corn starch in a suitable mixer. The mixture was further blended by passing through a comminuting machine. The blended powder was returned to the mixer, the talc added and blended thoroughly. The mixture was then filled into hard-shell gelatin capsules on a capsulating machine. 45

Example H

A tablet formulation containing the following ingredients:

		per tablet	
5	8 - Chloro - 1,4 - dimethyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate	25.00 mg	5
	Lactose	64.50 mg	
	Corn Starch	10.00 mg	
	Magnesium Stearate	0.50 mg	
	Total Weight	100.00 mg	
10	was prepared as follows:		10
15	8 - Chloro - 1,4 - dimethyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a] [1,4]benzodiazepine maleate was mixed with the lactose, corn starch and magnesium stearate in a suitable mixer. The mixture was further blended by passing through a comminuting machine. The mixed powders were slugged on a tablet compressing machine and the slugs were comminuted to a suitable mesh size mixed well. The tablets were compressed at a tablet weight of 100 mg.		15

Example I

A tablet formulation containing the following ingredients:

		per tablet	
20	8 - Chloro - 1,4 - dimethyl - 6 - (2 - fluoromethyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate	10.0 mg	20
	Lactose	113.5 mg	
	Corn Starch	70.5 mg	
	Pregelatinized Corn Starch	8.0 mg	
25	Calcium Stearate	3.0 mg	25
	Total Weight	205.0 mg	
	was prepared as follows:		
30	8 - Chloro - 1,4 - dimethyl - 6 - (2 - fluorophenyl) - 4H imidazo[1,5 - a][1,4]benzodiazepine maleate was mixed with the lactose, corn starch and pregelatinized corn starch in a suitable size mixer and passed through a comminuting machine. The mixture was returned to the mixer and moistened with water to a thick paste. The moist mass was passed through a comminuting machine and moist granules were dried on paper lined trays at 45°C. The dried granules were returned to the mixer, the calcium stearate was added and mixed well. The granules were compressed at a tablet weight of 200 mg.		30
35			35

Example J

A parenteral formulation containing the following ingredients:

		per ml	
40	8 - Chloro - 1,4 - dimethyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate	1.0 mg	40
	Benzyl Alcohol	0.15 ml	
	Tartaric Acid Buffer containing Sodium Hydroxide		
	Water for Injection q.s.ad.	1 ml	
45	was prepared as follows (for 10 liters):		45
50	In a clean glass or glass-lined vessel, 8 l of water for injection were heated to 90°. It was then cooled to 50—60°, and 1.5 l of benzyl alcohol was added and dissolved with stirring. The solution was then allowed to cool to room temperature. The 10.0 g of 8 - chloro - 1,4 - dimethyl - 6 - (2 - fluorophenyl) - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate were added under an atmosphere of nitrogen and stirred until completely dissolved. The pH was now adjusted to 3.0±1.0, preferably 3.0±0.5 with a combination of tartaric acid buffer and sodium hydroxide solution. Sufficient water for injection was then added to make a total volume of 10 liters. This solution was then filtered through a candle, filled into suitable size ampoules, gassed with nitrogen and sealed.		50



* C L M S *

42

1,527,131

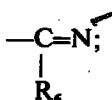
42

WHAT WE CLAIM IS:—

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



5 wherein A is

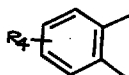


10 R₁ is hydrogen, lower alkyl, phenyl, alkoxy lower alkyl, substituted phenyl, pyridyl or aralkyl; R₂ is hydrogen or lower alkyl; R₃ is hydrogen or lower alkyl; R₅ is hydrogen, alkanoyloxy or hydroxy; R₆ is phenyl, mono-substituted phenyl, di-substituted phenyl, pyridyl or mono-substituted pyridyl, and

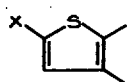


is selected from the group consisting of

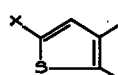
(a)



(b)

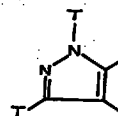


(c)



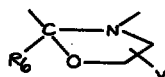
and

(d)

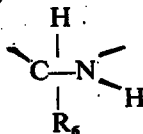


15 wherein R₄ is hydrogen, halogen, nitro, cyano, trifluoromethyl, lower alkyl, substituted amino, amino, hydroxy lower alkyl or lower alkanoyl; X is hydrogen, chlorine, bromine or iodine; and T is hydrogen or lower alkyl; analogs thereof corresponding to formula I but wherein A is selected from the group consisting of

(e)

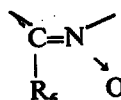


(f)



and

(g)

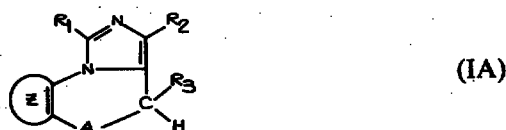


wherein V=hydrogen or lower alkyl,

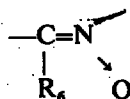


20 is selected from the group consisting of formulae (a), (b) and (c) above, R₁, R₂, R₃ and R₆ are as in Formula I above, and R₅ is hydrogen except that in Formula I with A having structure (f), R₄ is not nitro and R₆ is not nitro substituted; and pharmaceutically acceptable acid addition salts of these compounds and analogs, which process comprises

(a) for the preparation of a compound of formula



wherein A is





R_1 , R_2 , R_3 and R_4 are as in Formula I above and

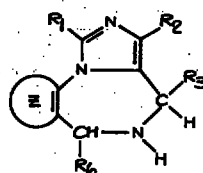


is selected from the group consisting of formulae (a), (b) and (c) above converting a corresponding compound of formula I into the N-oxide thereof, or

(b) converting a compound of formula IA into a corresponding compound of formula I wherein R_5 is alkanoyloxy by methods known in the art, or

(c) converting a compound of formula I wherein R_5 is alkanoyloxy into a corresponding compound of formula I wherein R_5 represents hydroxy by methods known in the art, or

(d) for preparing a compound of formula



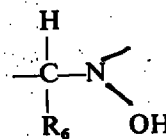
(IA')

wherein R_1 , R_2 , R_3 , R_4 , R_5 and



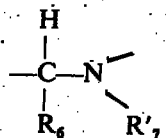
are as in Formula IA but R_4 is not nitro and R_5 is not nitro substituted, reducing a corresponding compound of Formula I, or

(e) dehydrating a compound of formula IA wherein A is



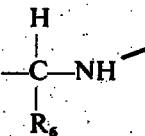
to the corresponding compound of formula I, or

(f) converting a compound of formula IA wherein A is



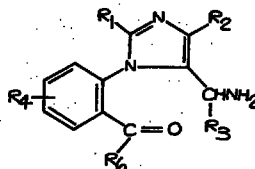
wherein R' is acetyl, mesyl or tosyl, to the corresponding compound of formula I by treatment with a non aqueous base in the presence of an inert solvent, or

(g) converting a compound of formula IA wherein A is



to the corresponding compound of formula I by oxidation of the secondary amine of the 5-position, or

(h) cyclizing a compound of formula





* C L M S *

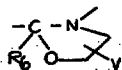
44

1,527,131

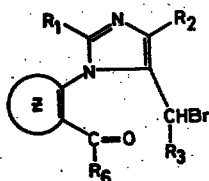
44

wherein R_1 , R_2 , R_3 , R_4 and R_6 are as in formula I, to a corresponding compound of formula I, or

(i) for preparing a compound of formula IA wherein A is



wherein V is hydrogen or lower alkyl, reacting a corresponding compound of formula I with ethylene oxide or propylene oxide in the presence of a Lewis acid catalyst or reacting a corresponding compound of formula



(XXIV)

wherein R_1 , R_2 , R_3 , R_4 and

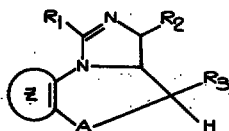


are as in formula I, except that R_4 is not amino or substituted amino, with a compound selected from the group consisting of ethanol-amine, a 1-alkyl substituted ethanol-amine and a 2-alkyl substituted ethanol-amine, or

(j) converting a ketal group present as R_4 substituent in an imidazobenzodiazepine to the corresponding ketone substituent, or

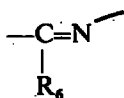
(k) converting a ketone group present as R_4 substituent in an imidazobenzodiazepine to a secondary or tertiary alcohol substituent, or

(l) dehydrogenating a compound of formula



(VII)

wherein A is



R_1 , R_2 , R_3 , R_4 , R_6 and



are as in formula I but R_4 is not nitro and R_6 is not nitro substituted, to a corresponding compound of formula I, or

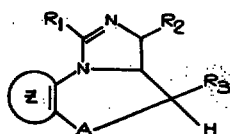
(m) converting a compound of formula I, wherein



represents an aminophenyl group, into the corresponding nitro-, cyano-, chloro- or bromo-substituted compound, or

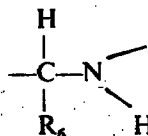
(n) subjecting a compound of formula I wherein R_4 is acylamino to a mild hydrolysis so as to obtain a corresponding compound of formula I wherein R_4 is amino, or

(o) oxidizing a compound of formula



(VII')

wherein A is

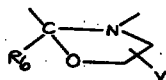


and R_1 , R_2 , R_3 , R_4 , R_5 and

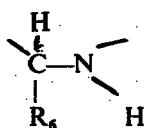


are as in formula VII, to a corresponding compound of formula I, or
 (p) resolving a racemic compound into its optical enantiomers, or
 (q) converting a compound of formula I or an analog thereof corresponding to formula I but wherein A is selected from the group consisting of

(e)

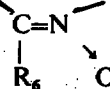


(f)



and

(g)



wherein V=hydrogen or lower alkyl,

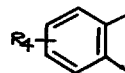


is selected from the group consisting of formula (a), (b) and (c) above, R_1 , R_2 , R_3 and R_5 are as in Formula I above, and R_4 is hydrogen or lower alkyl, except that in formula I with A being structure (f) R_4 is not nitro and R_5 is not nitro-substituted, into a pharmaceutically acceptable acid addition salt.

2. A process as claimed in Claim 1, wherein there are prepared compounds of formula I wherein

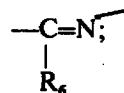


is



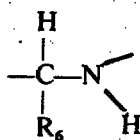
20

A is

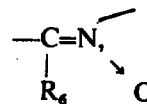


20

R_1 is hydrogen or lower alkyl; R_2 and R_3 are independently hydrogen or lower alkyl; R_5 is hydrogen, alkanoyloxy or hydroxy; R_4 is hydrogen, halogen, nitro, cyano, trifluoromethyl, lower alkyl, amino, substituted amino, hydroxy lower alkyl or lower alkanoyl; and R_6 is phenyl, mono-substituted phenyl, di-substituted phenyl, pyridyl or mono-substituted pyridyl, analogs thereof corresponding to formula I but wherein A is the group



or



and R_5 is hydrogen, or pharmaceutically acceptable acid addition salts thereof

25

25



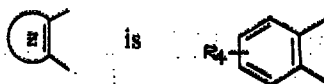
46

1,527,131

46

and wherein at least one of the process embodiments (a), (b), (c), (d), (l), (o) and (p) of Claim 1 is performed.

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



R_4 is hydrogen, nitro or halogen, R_5 is phenyl or halo, nitro or lower alkyl substituted phenyl, R_6 is hydrogen or lower alkyl, and R_7 and R_8 are hydrogen.

4. A process as claimed in Claim 3, wherein R_1 is lower alkyl and R_2 is hydrogen.

5. A process as claimed in any one of Claims 2 to 4, wherein R_4 is 8-halo and R_5 is 2-halophenyl.

6. A process corresponding to that claimed in any one of Claims 3 to 5 but wherein R_1 is lower alkyl.

7. A process as claimed in Claim 6, wherein R_1 is methyl.

8. A process as claimed in Claim 5, wherein 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine or the maleate thereof is prepared.

9. A process as claimed in Claim 7, wherein 8-chloro-6-(2-fluorophenyl)-1,4-dimethyl-4H-imidazo[1,5-a][1,4]benzodiazepine or the maleate thereof is prepared.

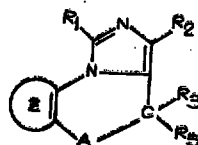
10. A process as claimed in Claim 1, wherein 2-chloro-13a-(2-fluorophenyl)-12,13a-dihydro-6-methyl-9H,11H-imidazo[1,5-a]oxazolo[3,2-d][1,4]benzodiazepine is prepared.

11. A process 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 1-62.

12. A process for the manufacture of preparations having muscle relaxant, sedative and anti-convulsant properties, wherein a compound of formula I as defined in Claim 1 or an analog thereof as defined in Claim 1 or a pharmaceutically acceptable acid addition salt of such compound is mixed, as active substance, with non-toxic, inert, therapeutically compatible solid or liquid carriers, commonly used in such preparations, and/or excipients.

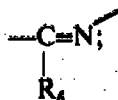
13. Compositions having muscle relaxant, sedative and anti-convulsant properties, containing a compound of formula I as defined in Claim 1 or an analog thereof as defined in Claim 1 or a pharmaceutically acceptable acid addition salt of such compound and a carrier.

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



(I)

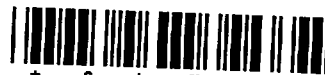
wherein A is



R_1 is hydrogen, lower alkyl, phenyl, alkoxy lower alkyl, substituted phenyl, pyridyl or aralkyl; R_2 is hydrogen or lower alkyl; R_3 is hydrogen or lower alkyl; R_4 is hydrogen, alkanoyloxy or hydroxy; R_5 is phenyl, mono-substituted phenyl, di-substituted phenyl, pyridyl or mono-substituted pyridyl; and



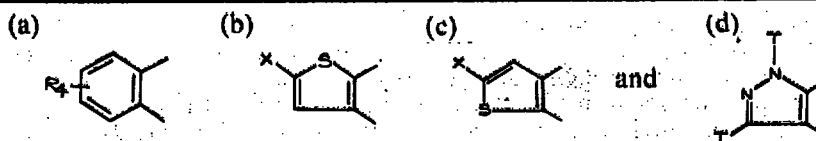
is selected from the group consisting of



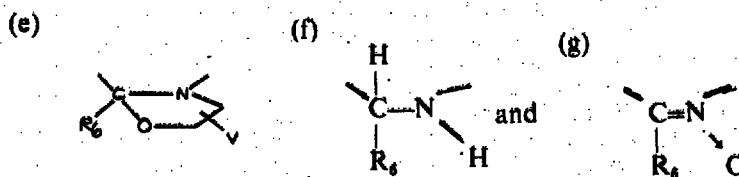
47

1,527,131

47



wherein R_4 is hydrogen, halogen, nitro, cyano, trifluoromethyl, lower alkyl, substituted amino, amino, hydroxy lower alkyl or lower alkanoyl; X is hydrogen, chlorine, bromine or iodine; and T is hydrogen or lower alkyl; analogs thereof corresponding to formula I but wherein A is selected from the group consisting of

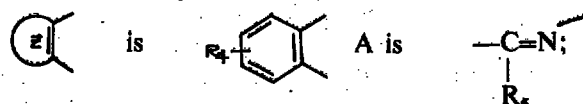


wherein V=hydrogen or lower alkyl,

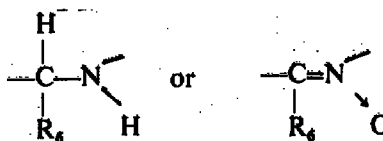


is selected from the group consisting of formulae (a), (b) and (c) above, R_1 , R_2 , R_3 and R_4 are as in Formula I above, R_5 is hydrogen except that in formula I with A being structure (f) R_4 is not nitro and R_5 is not nitro-substituted, and pharmaceutically acceptable acid addition salts of these compounds and analogues, whenever prepared according to the process claimed in Claim 1 or 11 or by an obvious chemical equivalent thereof.

15. Compounds as claimed in Claim 14 which are compounds of formula I wherein

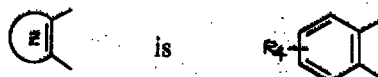


R_1 is hydrogen or lower alkyl; R_2 is hydrogen or lower alkyl; R_3 is hydrogen or lower alkyl; R_4 is hydrogen, alkanoyloxy or hydroxy; R_5 is hydrogen, halogen, nitro, cyano, trifluoromethyl, lower alkyl, amino, substituted amino, hydroxy lower alkyl or lower alkanoyl; and R_6 is phenyl, mono-substituted phenyl, di-substituted phenyl, pyridyl or mono-substituted pyridyl, analogs thereof corresponding to formula I but wherein A is the group



and R_6 is hydrogen, or pharmaceutically acceptable acid addition salts thereof, whenever prepared according to the process claimed in Claim 2 or by an obvious chemical equivalent thereof.

16. Compounds as claimed in Claim 14 which are compounds of formula I wherein R_1 is hydrogen or lower alkyl,



R_4 is hydrogen, nitro or halogen, R_5 is phenyl or halo, nitro or lower alkyl substituted phenyl, R_6 is hydrogen or lower alkyl, and R_7 and R_8 are hydrogen, whenever prepared according to the process claimed in Claim 3 or by an obvious chemical equivalent thereof.

17. Compounds as claimed in Claim 16, wherein R_1 is lower alkyl and R_2 is hydrogen, whenever prepared according to the process claimed in Claim 4 or by an obvious chemical equivalent thereof.



1,527,131

48

18. Compounds as claimed in any one of Claims 15 to 17, wherein R_4 is 8-halo and R_5 is 2-halophenyl, whenever prepared according to the process claimed in Claim 5 or by an obvious chemical equivalent thereof.

19. Compounds according to those claimed in any of Claims 16 to 18 but wherein R_3 is lower alkyl, whenever prepared according to the process claimed in Claim 6 or by an obvious chemical equivalent thereof.

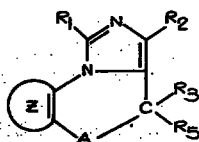
20. Compounds as claimed in Claim 19, wherein R_3 is methyl, whenever prepared according to the process claimed in Claim 7 or by an obvious chemical equivalent thereof.

21. 8 - Chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine or the maleate thereof, whenever prepared according to the process claimed in Claim 8 or by an obvious chemical equivalent thereof.

22. 8 - Chloro - 6 - (2 - fluorophenyl) - 1,4 - dimethyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine or the maleate thereof, whenever prepared according to the process claimed in Claim 9 or by an obvious chemical equivalent thereof.

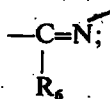
23. 2 - Chloro - 13a - (2 - fluorophenyl) - 12,13a - dihydro - 6 - methyl - 9H,11H - imidazo[1,5 - a]oxazolo[3,2 - d][1,4]benzodiazepine, whenever prepared according to the process claimed in Claim 10 or by an obvious chemical equivalent thereof.

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



(I)

wherein A is

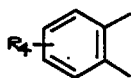


R_1 is hydrogen, lower alkyl, phenyl, alkoxy lower alkyl, substituted phenyl, pyridyl or aralkyl; R_2 is hydrogen or lower alkyl; R_3 is hydrogen or lower alkyl; R_4 is hydrogen, alkanoyloxy or hydroxy; R_5 is phenyl, mono-substituted phenyl, di-substituted phenyl, pyridyl or mono-substituted pyridyl; and

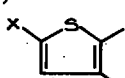


is selected from the group consisting of

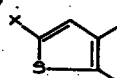
(a)



(b)

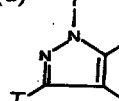


(c)



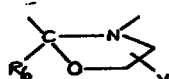
and

(d)

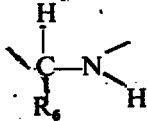


wherein R_4 is hydrogen, halogen, nitro, cyano, trifluoromethyl, lower alkyl, substituted amino, amino, hydroxy lower alkyl or lower alkanoyl; X is hydrogen, chlorine, bromine or iodine; and T is hydrogen or lower alkyl; analogs thereof corresponding to formula I but wherein A is selected from the group consisting of

(e)

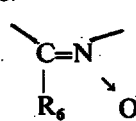


(f)



and

(g)



wherein V=hydrogen or lower alkyl,





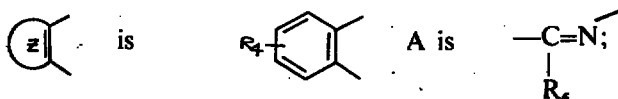
1,527,131

49

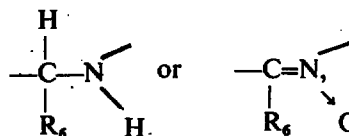
49

is selected from the group consisting of formula (a), (b) and (c) above, R_1 , R_2 , R_3 and R_4 are as in Formula I above, and R_5 is hydrogen except that in formula I with A being structure (f) R_4 is not nitro and R_5 is not nitro-substituted, and pharmaceutically acceptable acid addition salts of these compounds and analogs.

25. Compounds as claimed in Claim 24 which are compounds of formula I wherein

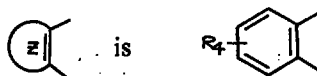


hydrogen or lower alkyl; R_2 is hydrogen or lower alkyl; R_3 is hydrogen or lower alkyl; R_4 is hydrogen, alkanoyloxy or hydroxy; R_5 is hydrogen, halogen, nitro, cyano, trifluoromethyl, lower alkyl, amino, substituted amino, hydroxy lower alkyl or lower alkanoyl; and R_6 is phenyl, mono-substituted phenyl, di-substituted phenyl, pyridyl or mono-substituted pyridyl, analogs thereof corresponding to formula I but wherein A is the group



and R_5 is hydrogen, and pharmaceutically acceptable acid addition salts thereof.

26. Compounds as claimed in Claim 24 which are compounds of formula I wherein R_1 is hydrogen or lower alkyl,



R_4 is hydrogen, nitro or halogen, R_5 is phenyl or halo, nitro or lower alkyl substituted phenyl, R_2 is hydrogen or lower alkyl, and R_3 and R_6 are hydrogen.

27. Compounds as claimed in Claim 26, wherein R_1 is lower alkyl and R_2 is hydrogen.

28. Compounds as claimed in Claim 26 or 27, wherein R_4 is 8-halo and R_5 is 2-halophenyl.

29. Compounds corresponding to those claimed in Claim 27 or 28 but wherein R_3 is lower alkyl.

30. Compounds as claimed in Claim 29, wherein R_3 is methyl.

31. 8 - Chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine.

32. 8 - Chloro - 6 - (2 - fluorophenyl) - 1,4 - dimethyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine or the maleate thereof.

33. 8 - Chloro - 6 - (2 - fluorophenyl) - 1 - methyl - 4H - imidazo[1,5 - a][1,4]benzodiazepine maleate.

34. 2 - Chloro - 13a - (2 - fluorophenyl) - 12,13a - dihydro - 6 - methyl - 9H, 11H - imidazo[1,5 - a]oxazolo[3,2 - d][1,4]benzodiazepine.

For the Applicants,
CARPMAELS & RANSFORD,
Chartered Patent Agents,
43, Bloomsbury Square,
London, WC1A 2RA.