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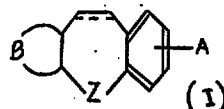
COMPLETE SPECIFICATION

5-Substituted Aza-Dibenzo-Cycloheptenes and the preparation thereof

We, SCHERICO LTD., Winkelriedstrasse 56, Luzern, Switzerland, a body corporate constituted under the laws of 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 aza-dibenzocycloheptenes, to processes for producing such compounds and to pharmaceutical compositions containing such compounds.

One group of products according to the invention are aza-dibenzo-cycloheptene derivatives of the following general formula I



and the pharmaceutically acceptable acid addition salts thereof, whereby in formula I: the dotted line represents an optional double bond; A represents hydrogen, or one or more of the substituents halogen (preferably chlorine or bromine), lower alkyl (preferably methyl or ethyl), trifluoromethyl, alkoxy (preferably methoxy or ethoxy), hydroxy and acyloxy (preferably lower-alkanoyloxy), attached to positions 6, 7, 8 and/or 9 (preferably 7 and/or 8); B represents the grouping of atoms required to form, together with the carbon atoms to which it is attached, a pyridine nucleus; and Z represents either of the groupings $\text{U} > \text{C} < \text{W}$ and $\text{V} < \text{C} <$; in which groupings: U is a univalent

grouping containing an amino group the nitrogen atom of which is separated from C—5 of the tricyclic nucleus by at least two carbon atoms, for example 3- or 4-piperidyl

or $\text{—X—N} < \begin{smallmatrix} \text{R}_1 \\ \text{R}_2 \end{smallmatrix}$; V is a divalent grouping containing an amino group the nitrogen atom of which is separated from C—5 of the tricyclic nucleus by at least two-carbon atoms, for example 3- or 4-piperidylidene or $\text{=Y—N} < \begin{smallmatrix} \text{R}_1 \\ \text{R}_2 \end{smallmatrix}$; and W is H or OH;

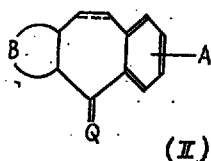
R_1 and R_2 independently being hydrogen, lower alkyl hydroxy-lower alkyl, benzyl or a grouping as required to form, together with the nitrogen atom to which they are attached, a five- or six-membered heterocycle the ring members of which, apart from the

aforesaid nitrogen atom, are all carbon except one which is C, O or N; and X and Y being hydrocarbon residues with from 2 to 9 carbon atoms.

As used throughout this specification (including the claims) the terms "lower alkyl" "lower alkanoyl" and "lower alkoxy" are intended to mean respectively alkyl, alkanoyl and alkoxy groups having not more than 12 carbon atoms in the alkyl portion of the group.

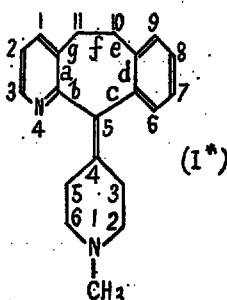
The compounds of above formula I are in essence "final products," although, as it will be later described, some of these "final products" have the additional utility of being intermediates in the preparation of other "final products."

The invention is also directed to another group of compounds, which may be used as intermediates for the preparation of the compounds of formula I, which compounds are also aza-dibenzo-cycloheptene derivatives, and are characterized by the following general formula II,



wherein the meanings of the dotted line and of A and B are as indicated above, and Q represents (H,H) or O.

The nomenclature employed herein is essentially based on that approved by Chemical Abstracts for dibenzo-cycloheptenes. The identification of the positions in the tricyclic system is exemplified by the following formula I* for 4-aza-5-(N-methyl-4-piperidylidene)-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene, one of the preferred final products of the invention:



Embraced by formula I are the respective 1-aza-, 2-aza-, 3-aza-, and 4-aza- analogs all of which fall within the given definition of B. By way of further definition, those compounds according to formula I wherein W is hydroxy, are below sometimes called "hydroxy compounds" or "carbinols," those wherein W represents hydrogen are sometimes called "saturated compounds," and those having the doubly bound substituent V are sometimes called "unsaturated compounds" or "alkylidene compounds."

The substituent U, as defined above, includes a limited number of amino-hydrocarbyl substituents. Within the definition of U are 3-piperidyl and 4-piperidyl, which are meant to include substituted analogs such as N-lower-alkyl- (preferably methyl)-3-piperidyl and N-lower-alkyl- (preferably methyl)-4-piperidyl. Also included

within the definition of U is the grouping $\text{—X—N} \begin{smallmatrix} \text{R}_1 \\ \text{R}_2 \end{smallmatrix}$, with X being defined as a hydrocarbon residue with from 2 to 9 carbon atoms. Representative of such groupings are those wherein X is a straight or branched divalent hydrocarbon radical, e.g. ethylene, propylene, butylene, pentylene and octylene, one free valence of which is attached to the 5-position of the tricyclic nucleus and the other free valence of which is

attached to the $\text{—N} \begin{smallmatrix} \text{R}_1 \\ \text{R}_2 \end{smallmatrix}$ group; and those wherein X is a cyclic divalent hydrocarbon radical such as phenylenepropyl, cyclohexylene and cyclohexylenemethyl, similarly connected with both the tricyclic nucleus and the amino group.

The substituent V is a doubly bound group which is defined just as is U, except that that carbon atom thereof which is directly attached to the 5-position of the tricyclic nucleus, has one hydrogen atom less and is doubly bound to said position.

Typical representatives for V can be gathered from the above enumeration of representatives of U.

The substituent $-\text{N} \begin{smallmatrix} \text{R}_1 \\ \text{R}_2 \end{smallmatrix} <$ includes NH_2 , lower-alkylamino (preferably methyl-

amino), and di-lower-alkylamino (preferably dimethylamino), hydroxyalkylamino (e.g. β -hydroxyethylamino), di-(hydroxyalkyl)-amino [e.g. di-(β -hydroxyethyl)-amino], pyrrolidino, piperidino, morpholino and piperazino [inclusive of substituted analogs such as lower-alkyl-, e.g. 4'-methyl-piperazino, hydroxy-lower-alkyl-, e.g. 4'-(β -hydroxyethyl)-piperazino, lower alkanoyloxy-alkyl-, e.g. 4'-(β -acetoxyethyl)-piperazino, and hydroxy-lower-alkoxy-alkyl-, e.g. 4-(hydroxy-lower alkoxy)-piperazino].

Among the compounds of formula I within the invention and obtainable by a process according to the invention are:— 5-(N-methyl-4-piperidylidene)-7-chloro-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene, 5-(β -dimethyl-aminoethyl)-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene and its 8-chloro-counterpart, 5-[γ -(4-{ β -hydroxyethyl}-piperazino)-propylidene]-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene, and 4-aza-5H-7-chloro-10,11-dihydro-dibenzo-[a,d]-cycloheptene and the corresponding 5-ketone.

The compounds of formula I are basic in character and form addition salts with acids. These salts sometimes increase solubility and lend themselves better to formulation than do the free bases. Accordingly the pharmaceutically acceptable acid addition salts of the above free bases are contemplated as being within the concept of the invention. Such salts include those derived from maleic, salicylic, succinic, methyl-sulfonic, tartaric, citric, hydrochloric, hydrobromic, sulfuric, nitric and phosphoric acid.

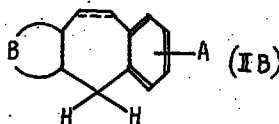
The compounds of formula I, inclusive of the said salts, are characterized by their antihistaminic, antiserotonin and antianaphylactic action and are useful in the treatment of allergic disorders such as urticaria, seasonal rhinitis and pollen sensitivity.

Within the classes of compounds encompassed by formula I (i.e. the "carbinols," the "saturated compounds" and the "alkylidene compounds" of each of the 1-aza, 2-aza, 3-aza and 4-aza series), some appear of greater therapeutic utility than others. Although all of the compounds possess the above described properties, there are certain structure-activity relationships pertaining to potency and utility. For example, the 4-aza compounds appear more potent than the other position isomers as antihistaminic substances; those compounds wherein V is piperidylidene appear more potent as antihistaminic agents than those wherein V is dimethylaminopropylidene, but the latter group appears to be of greater interest in their effect upon the central nervous system; compounds having the 3-aza grouping appear also to exhibit antihypertensive properties; the "hydroxy compounds" and the "saturated compounds" appear to exhibit properties similar to those of the alkylidene analogs, but to a lesser extent; those compounds which are unsaturated at positions 10 and 11 appear somewhat less potent than their saturated analogs.

The compounds of formula I may be administered in pharmaceutical formulations comprising the respective substance in admixture with a pharmaceutical carrier suitable for enteral or parenteral administration. The formulations may be in solid form, as for example tablets and capsules, or in liquid form as for example syrups, elixirs, emulsions, and injectables. In the formulation of pharmaceutical dosage forms there generally is utilized excipients as for example water, gelatin, lactose, starches, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, and petroleum jelly.

The effective dosage of the active ingredient in such formulations depends upon the severity, the stage, and the individual characteristic of each case and will be determined by the attending diagnostician. Generally, a dosage range of from about 0.1 mg. to about 15 mg. per kg. of body weight per day constitutes the overall range, with a range of from about 0.1 mg. to 5 mg. per kg. per day for the preferred form of active ingredient. In its preferred dosage unit forms, therefore, the active ingredient will usually be present in amounts of about 5 to 150 mg.

The compounds of formula I may, in accordance with the invention, be produced by reacting a compound of the general formula IIB



or a reactive derivative thereof (as hereinafter defined), wherein the dotted line, A and B each have the above meaning, with a reactive derivative (as hereinafter defined) of a compound of the formula VH_2 , wherein V has the above meaning, or by reacting a reactive derivative (as hereinafter defined) of a compound of the formula IIB above with a compound of the formula VH_2 , so as to replace the grouping at position 5 of the aza-dibenzo-cycloheptene compound by the grouping Z (Z having the above meaning) or a grouping convertible into the grouping Z by one or more of the steps of hydrolysis, dehydration, reduction and dehydrogenation, and, if necessary, subjecting the product thus produced to one or more of the steps of hydrolysis, dehydration, reduction and dehydrogenation required to convert it to a compound of formula I.

By the term "reactive derivative" of one of the two compounds, i.e. a compound of formula IIB and a compound of formula VH_2 , is meant a derivative in which one or both of the hydrogen atoms attached to the 5-position of the compound of formula IIB or to V, as the case may be, have been substituted by a grouping such that when the derivative is contacted with the other of the two compounds or with a reactive derivative thereof, if necessary in the presence of a catalyst or initiator for the reaction and under appropriate conditions of temperature, of pressure and of other reaction parameters, reaction occurs leading to the formation of a direct carbon-carbon bond (either single or double bond) between position 5 of the compound of formula IIB and V.

The preferred reactive derivative of a compound of formula IIB is an organo-metallic derivative. The organo-metallic derivative may be an organo-Mg-Halogen compound or it may be an organo-zinc, organo-cadmium, or organo-mercury compound, or it may be an organo-alkali-metal compound, e.g. an organo-sodium, -lithium or -potassium compound, the metallic atom or group being attached to the 5-position. When the reactive derivative of a compound of formula IIB is an organo-metallic derivative it is reacted with a reactive derivative of a compound of the formula VH_2 ,

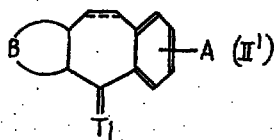
preferably with the keto compound $V=O$. The derivative $V<\begin{smallmatrix} H \\ Halogen \end{smallmatrix}$ may be employed as alternative for reaction with certain organo-metallic derivatives, in particular organo-alkali-metal compounds such as the sodium compound.

Alternatively the reactive derivative of the compound of formula IIB may be the 5-keto derivative thereof, which may be reacted with an organo-metallic derivative of a compound of formula VH_2 as the reactive derivative thereof, preferably with an organo-metallic derivative having the formula $V<\begin{smallmatrix} H \\ Mg-Halogen \end{smallmatrix}$, or an organo-alkali-metal compound.

In a further alternative embodiment of the above-defined process of the invention a compound of formula IIB is reacted directly with a reactive derivative of a compound of formula VH_2 , preferred reactive derivatives having the formula $V=O$ and

$V<\begin{smallmatrix} H \\ Halogen \end{smallmatrix}$

Thus, a compound of the general formula II'



may be reacted with a compound of the general formula $V=T_2$, whereby in the formulae, the dotted line, A, B and V are as defined above, except that any hydrogen atom at the N in the amino group of V is protected, if necessary, by substitution with an easily removable group, e.g. the benzyl group, and of T_1 and T_2 , one is an oxygen

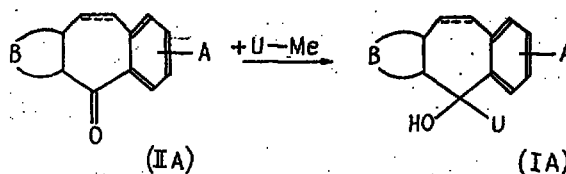
atom and the other is the grouping $<\begin{smallmatrix} Me \\ H \end{smallmatrix}$ (Me representing the metal-containing part of an organo-metallic compound, e.g. -Mg-halogen, Zn/2, Hg/2, Cd/2, an alkali metal atom, e.g. Li, Na or K or T_1 is $<\begin{smallmatrix} H \\ H \end{smallmatrix}$ and T_2 is $<\begin{smallmatrix} H \\ Halogen \end{smallmatrix}$.

The resulting compound may be subjected to one or more of the following steps

as necessary or required to produce a desired compound of formula I; hydrolysis of any organo-metallic complex if first formed; dehydration of a thus obtained hydroxy compound to the respective 5(1')-unsaturated compound or reduction of the hydroxy compound to the respective 10(11)- and 5(1')-saturated compound; hydrogenation of a 5(1')-unsaturated compound to the respective 10(11) and 5(1')-saturated compound; and the compound of general formula I which has been obtained by one or more of the preceding steps, may be subjected, if desired, to one or more of the following finishing steps, in any desired sequence:

- (i) hydrogenation or dehydrogenation in position 10(11);
- (ii) reductive cleavage of one or two benzyl groups, if attached to the nitrogen atom of the amino group which forms part of the moiety Z;
- (iii) transformation into a pharmaceutically acceptable acid addition salt by reaction with the respective acid or with a reactive derivative thereof.

A commonly preferred embodiment of the latter, essentially consists in reacting a 5-keto-aza-dibenzo-cycloheptene derivative (IIA), wherein A and B are as above defined, with an organometallic compound U-Me, wherein U is as defined above, and Me represents the metal-containing part of the organometallic compound (e.g. -Mg-Halogen, Zn/2, or an alkali metal atom such as Li, Na or K) or the corresponding phosphorus-containing moiety of a Wittig-type reagent; and hydrolyzing any complex thereby formed. (In Grignard-type reagents, such as N-methyl-4-piperidyl magnesium halides, the halogen preferably is chlorine or bromine.) This reaction may roughly be summarized by the following sequence:



wherein A, B, U, Me and the dotted line are as defined above. [An exception is the embodiment in which a Wittig-type reagent is used, such embodiment giving direct rise to the corresponding 5(1')-unsaturated compound (IB).] This reaction is limited to the production of those carbinols of formula IA wherein the substituent U contains at least three carbon atoms separating the amino group from the 5-position of the tricyclic nucleus.

In this reaction, any free amino group, such as primary or secondary amino, must be protected prior to formation of the organometallic reactant. It is preferred to effect such protection by means of benzylation. The carbinol (IA) so formed will accordingly contain the benzyl blocking group, which, if desired, may easily be cleaved in known manner, such as by catalytic hydrogenation on Pd/C, to regenerate the corresponding primary or secondary amino group. For example, to produce 5-hydroxy-5-(γ-aminopropyl)-1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene, the organometallic reactant may conveniently be dibenzylamino-propyl magnesium bromide which, when condensed with the appropriate ketone and the reaction product hydrolysed, produces 5-hydroxy-5-(γ-dibenzyl-amino-propyl)-1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene, which in turn is de-benzylated to produce 5-hydroxy-5-(γ-aminopropyl)-1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene. Similarly, to produce 5-hydroxy-5-(γ-methylamino-propyl)-1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene there may be utilized together with the appropriate ketone, benzylmethylamino-propyl-magnesium bromide to produce, after hydrolysis, 5-hydroxy-5-(γ-benzylmethylamino-propyl)-1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene, which is de-benzylated to produce the desired compound.

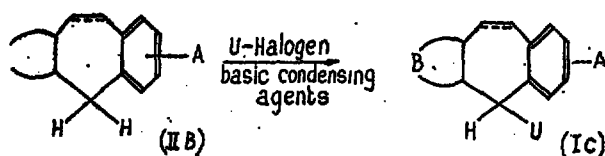
Most conveniently, the intermediate (IIA) is added either in solid (preferably finely pulverized) form or in solution in an inert solvent, to the solution of a Grignard reagent containing the substituent U in an inert solvent such as, for example, ether, benzene or tetrahydrofuran. Representatives of the Grignard reactant are N-methyl-4-piperidyl magnesium chloride and dimethylamino-propyl magnesium chloride, which may be obtained in a known manner from magnesium and the corresponding aminoalkyl-halide. The reaction mixture may be heated, preferably under reflux. Upon completion of the condensation, the condensation product is subjected to hydrolysis, preferably under practically neutral conditions such as by ammonium chloride. The

resulting carbinol (IA) may be isolated from the reaction mixture by extraction with a water-immiscible solvent such as ether or a chlorinated hydrocarbon. It may be transformed into one of its acid addition salts.

The carbinols (IA) may be dehydrated to yield the corresponding exocyclically unsaturated compounds (IB), that is those compounds wherein Z represents C=V. The dehydration may relatively easily be effected by heating the carbinol (IA) with known dehydrating agents such as alcoholic hydrogen chloride, phosphorus oxychloride, phosphoric acids such as poly-phosphoric acid, sulfuric acid, zinc chloride, alkali metal pyrosulfates or other similarly acting agents. The unsaturated products (IB) may be isolated as free bases or in the form of their acid addition salts. The piperidylidene compounds of this class are particularly useful in the treatment of allergies. The unsaturated compounds (IB) may be hydrogenated, e.g. catalytically, to yield the corresponding saturated compounds (IC), i.e. compounds of formula I wherein Z represents

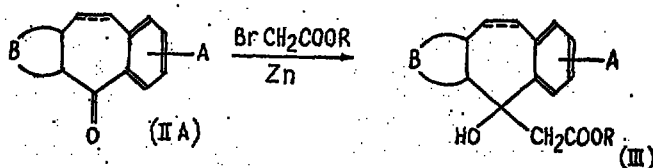
$C < \begin{smallmatrix} U \\ H \end{smallmatrix}$. Preferably, catalytic hydrogenation is effected with palladium and hydrogen. This reductive step is not selective, and if the desired end-product is to contain an additional ethylenic double bond such as the 10,11-double bond, another technique is employed, as will be described hereinbelow.

The saturated compounds (IC) are also preparable by direct "alkylation" of corresponding compounds (IIB) of formula II wherein Q is (H,H), according to the following reaction scheme:



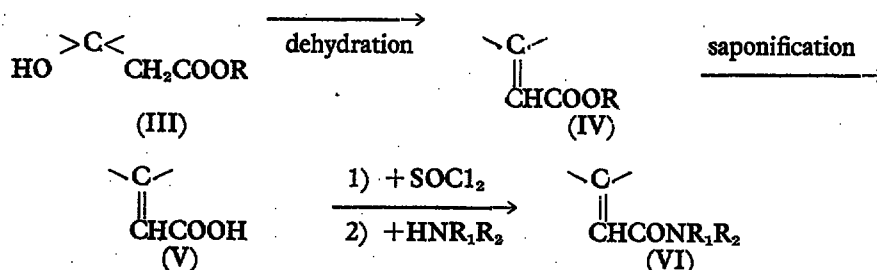
In the foregoing reaction scheme, the symbols A, B, U and the dotted line have the same meanings as described heretofore. This reaction constitutes the condensation of an organic halide (preferably chloride or bromide) bearing the substituent U, with an appropriate aza-dibenzo-cycloheptene (IIB). The reaction is desirably carried out in an inert solvent such as liquid ammonia (preferred), toluene or xylene, preferably at reflux temperature, and in the presence of a condensing agent such as sodium amide or potassium amide. Representative of the halides which may be used in this reaction are γ -dimethylamino-propylchloride and β -dimethylamino-ethylchloride. The reaction product may be isolated by neutralization of the mixture with mineral acid, followed by treatment with aqueous alkali and extraction with a water immiscible solvent. This method is of particular value because it permits the production of "saturated compounds" (IC) having a 10,11-double bond; but it may likewise be applied for the preparation of the 10,11-dihydro-5(1')-saturated compounds.

A route making those unsaturated compounds (IB) readily accessible wherein the substituent V has only two carbon atoms separating the amino moiety from the 5-position of the tricyclic nucleus, but being likewise applicable to the preparation of the corresponding saturated compounds (IC) with so-limited U, is that which first involves the condensation of a 5-keto-aza-dibenzo-cycloheptene (IIA) with a bromo-acetic ester (preferably ethyl bromoacetate) in the presence of zinc, the well known Reformatsky condensation, which gives rise to a carbalkoxymethyl intermediate III, thus:

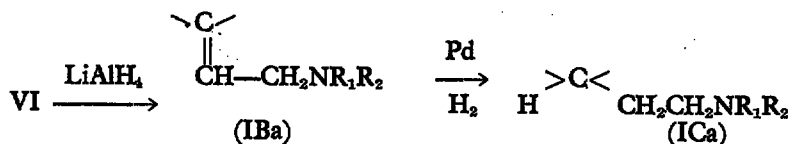


In the foregoing reaction scheme, A, B and the dotted line have the same significance as ascribed heretofore. The reaction is desirably effected in an inert solvent such as refluxing toluene or xylene and the product, III, separated therefrom according to methods well known in the art. The ester, III, is then subjected to dehydration such

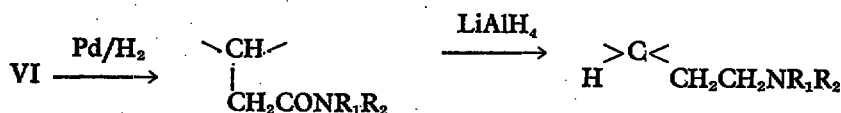
as by heating with thionyl chloride, to afford the exocyclically unsaturated analog, IV, which is saponified by treatment with acid or alkali to yield the carboxylic acid, V. The carboxylic acid, V, is converted into an amide, VI, by first forming the acid chloride by means of thionyl chloride, followed by reaction with an amine HNR_1R_2 , wherein R_1 and R_2 are as above defined, but are preferably both other than hydrogen. This sequence of reactions is depicted in the following scheme, and for convenience only the 5-position of the tricyclic system is shown:



10 Selective reduction of the amide group of VI by means of lithium aluminum hydride, for example, yields the "unsaturated compound" (IBa) which may be hydrogenated to yield the "saturated compound" (ICa), e.g. catalytic hydrogenation on palladium.



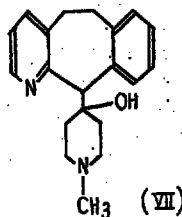
15 Alternatively compound VI may be converted to ICa by reversing the order of the steps, thus



The essential feature of this process thus is the reduction of the keto group depicted in above partial formula VI.

20 Compounds IBa and ICa are representative of those of formula I having two carbon atoms separating the amino group $\text{---NR}_1\text{R}_2$ from the 5-position of the tricyclic nucleus. The last step, that is the catalytic hydrogenation, is not selective and in addition to saturating the exocyclic double bond will also hydrogenate an additional ethylenic double bond such as a 10,11-double bond, if such is present.

25 A still further method for preparing compounds according to general formulae IB and IC is that whereby an intermediate according to general formula IIB, represented by, for example, 4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene, 2-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene, and the 10,11-dehydro analogs of these, is converted to a reactive derivative such as its 5-lithio derivative [e.g. by reaction with butyl lithium in ether at low temperature (-40°C)]. Reaction of such derivative with a compound of the type $\text{O}=\text{V}$, wherein V is as above defined, such as for example with N-methyl-4-piperidone in ether, results in the formation of a condensation product of the type represented by the following formula VII:

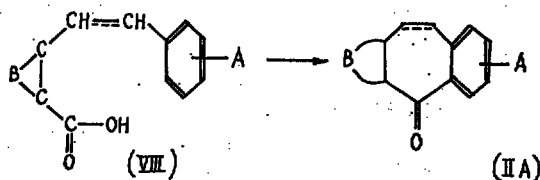


Dehydration of VII, or of the respective analog, preferably by first forming an

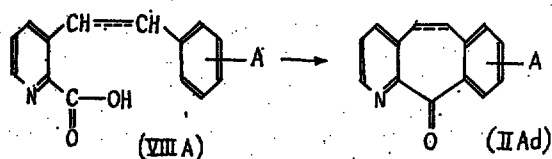
acetate (e.g. by means of acetic anhydride) and pyrolyzing the acetate, will lead to the respective compound according to general formula IB, which may be reduced to the corresponding compound of general formula IC.

The foregoing description relates to processes for the preparation of the compounds of general formula I all utilizing a key intermediate according to general formula II as an immediate or near immediate precursor, and in essence introducing the substituents U, V and W into the existing tricyclic system of the intermediate II, by reaction at the 5-position thereof. Before elaborating about further possible syntheses of the final products of general formula I, it appears therefore desirable to describe methods for the preparation of the intermediate according to general formula II, i.e. of 1-aza-5H-dibenzo-[a,d]-cycloheptene, 2-aza-5H-dibenzo-[a,d]-cycloheptene, 3-aza-5H-dibenzo-[a,d]-cycloheptene, 4-aza-5H-dibenzo-[a,d]-cycloheptene, their 10,11-dihydro analogs, the 5-keto analogs of all the foregoing, and of corresponding compounds containing a further substituent A in the benzenoid ring as described heretofore. Representative of this latter group are, for example, 4-aza-7-chloro-5H-dibenzo-[a,d]-cycloheptene, its 5-keto analog and the 10,11-dihydro derivatives of both; the corresponding 7- and 8-bromo analogs and 7- and 8-methyl analogs.

The intermediates of formula IIA may be prepared by a variety of procedures of which is preferred the intramolecular Friedel-Crafts cyclization of an ortho-styryl- or ortho-phenethyl-pyridine-carboxylic acid (VIII) according to the following reaction scheme:



In the foregoing scheme, A, B and the dotted line have the same significance as ascribed heretofore. The cyclization of the ortho-substituted pyridine-carboxylic acid (VIII), is preferably effected by heating it with polyphosphoric acid in a temperature range of about 100 to 160° C. whereby the cyclization occurs, resulting in the formation of the ketone, IIA. It is thus apparent that the choice of the pyridine-carboxylic acid determines the particular isomer produced. For example, by starting with a compound VIIIA, such as 3-styryl-picolinic acid or 3-phenethyl-picolinic acid, a 4-aza-ketone (IIAd) is produced:



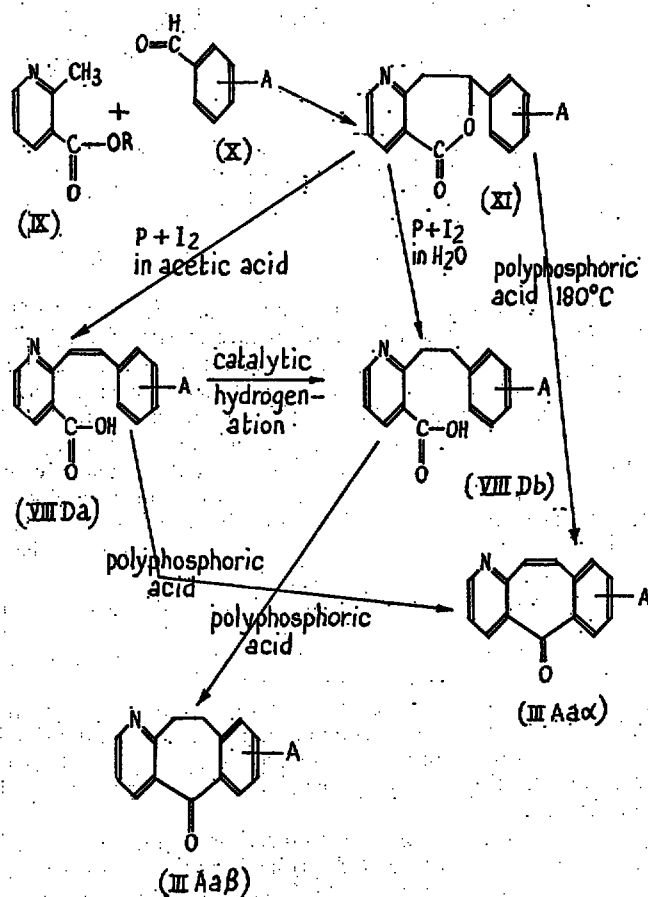
Similarly, by starting with 4-styryl- or 4-phenethyl-nicotinic acids (VIIIB), the corresponding 3-aza-ketones (IIAc) are produced; from 3-styryl- or 3-phenethyl-isonicotinic acids (VIIIC) there are obtained 2-aza ketones (IIAb); and from 2-styryl- or 2-phenethyl-nicotinic acids (VIID), there are obtained 1-aza ketones (IIAa).

The cyclization as depicted above is effected on free pyridine-carboxylic acids (VIII). Alternative and equivalent methods are readily apparent to one skilled in the art. Thus, for the acid may be substituted a functional derivative thereof such as a corresponding ester, amide, nitrile or isomeric lactone; or the carboxylic acid may first be converted to an acid halide, e.g. chloride, by means of a chlorinating agent such as thionyl chloride, phosphorus trichloride or oxalyl chloride, for example, followed by treatment with a Friedel-Crafts catalyst such as aluminum chloride, whereby cyclization occurs resulting in the formation of the respective compound embraced by general formula IIA. The cyclization is carried out generally according to standard techniques for effecting a Friedel-Crafts reaction, namely heating the mixture in an inert solvent such as carbon disulfide, petroleum ether and benzene (benzene, strictly speaking, cannot be called "inert" in a Friedel-Crafts reaction, practically, however, it can be considered as inert in the present case), and isolating the cyclized product therefrom. Other derivatives of the pyridine-carboxylic acids (VIII), such as certain lactones as

exemplified hereinbelow, may likewise be used as starting compounds for the cyclization leading to the intermediates IIA.

The phenethyl-pyridine-carboxylic acid starting compounds of general formula VIII may readily be obtained from the corresponding styryl-pyridine-carboxylic acids by known techniques such as catalytic hydrogenation or by independent synthesis as set forth later herein. In certain instances as will be shown, the cyclic ketones (IIA) having an unsaturation between positions 10 and 11 sometimes are preferably prepared from the 10,11-dihydro analogs by dehydrogenation with selenium dioxide or other methods equivalent in their result, such as by treatment with N-bromosuccinimide or bromination in the presence of sunlight, followed by dehydrohalogenation by means of triethylamine, alcoholic potassium hydroxide or other known dehydrohalogenating agents.

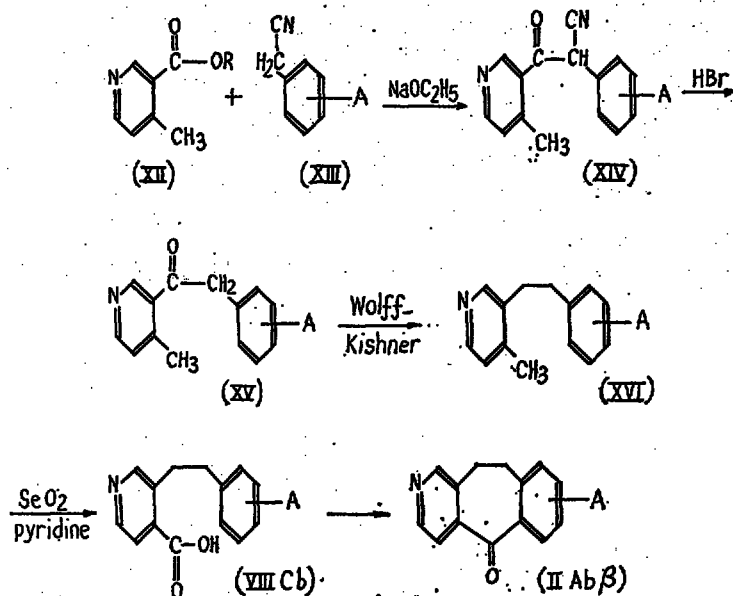
In particular, the 1-aza-ketones (IIAa) are preferably prepared by any sequence of the following reaction scheme:



In the preceding scheme, the reaction between X and 2-methyl-nicotinic acid-ester (IX) such as ethyl 2-methyl-nicotinate is carried out in refluxing acetic anhydride and gives rise to a lactone (XI). The lactone (XI) may be converted directly into the corresponding cyclic ketone (IIAaα) by heating with polyphosphoric acid. It may also be transformed indirectly via a 2-styryl-nicotinic acid (VIII Da) to the cyclic ketone (IIAaα) as shown. Treating the lactone (XI) with phosphorus and iodine in water (or with 57% hydriodic acid and phosphorus), or reducing the 2-styryl-nicotinic acid (VIII Da) yields the corresponding 2-phenethyl-nicotinic acid (VIII Db). This latter, upon heating with polyphosphoric acid is transformed into the 10,11-dihydro analog (IIAaβ) of IIAaα.

In the foregoing reaction, chemical transformation of IX to XI is old in the art for A=H, but is shown herein to establish a basis for preparing those cyclic ketones (IIAaα) and their 10,11-dihydro analogs (IIAaβ) wherein A is other than hydrogen,

The 2-aza-ketones (IIAb) are preferably prepared by the following sequence of reactions:

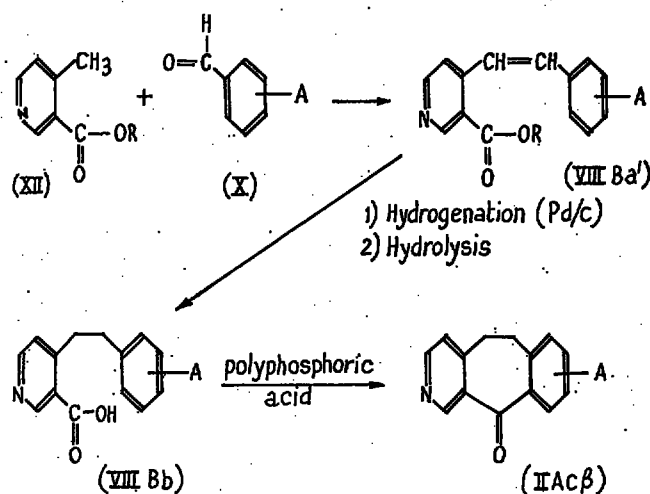


In this reaction sequence, a 4-methyl-nicotinic acid ester (XII) such as ethyl 4-methyl-nicotinate is condensed with a phenylacetonitrile (XIII) giving rise to the respective keto-nitrile (XIV) preferably in the presence of a basic catalyst such as an alkali metal alkoxide, e.g. sodium ethoxide in ethanol; however, other condensation agents may also be used, such as sodium amide or sodium hydroxide in a benzene or toluene solvent. Conversion to the ketone, XV, is effected by heating XIV with a strong mineral acid, preferably concentrated hydrobromic acid. (Alternatively, this step may be affected by heating XIV with concentrated sulfuric acid, whereby it is transformed into the corresponding acid amide which may be hydrolyzed and the product decarboxylated by adding water to the reaction mixture and continuing the heating operation). Reduction of the ketone (XV) is preferably carried out by the well-known Wolff-Kishner reaction which involves heating XV with hydrazine hydrate in a high-boiling polar solvent such as trimethylene-glycol in the presence of an alkali, such as sodium hydroxide or potassium hydroxide. In place of the Wolff-Kishner reduction, there may also be employed copper chromite in dioxane at about 160°C . under about 100 atmospheres pressure of hydrogen. This reduction gives rise to a 3-phenethyl-4-methylpyridine, XVI. This latter compound, upon oxidation with selenium dioxide in pyridine, for example, is transformed into the corresponding 3-phenethyl-isonicotinic acid (VIII Cb) which, upon heating with polyphosphoric acid, undergoes cyclization to form the cyclic ketone, IIAb.

It is apparent that the use of a para-substituted phenylacetonitrile (XIII) will ultimately give rise to a cyclic ketone (IIAb) having said substituent in the 7-position. With a meta-substituted phenylacetonitrile (XIII), a mixture of ketones (IIAb) is obtained, one having the substituent in the 6-position and the other having the substituent in the 8-position. These may be separated either at this final step, or the isomeric intermediates may be separated at any one of the steps of the reaction sequence by standard techniques, such as fractional distillation, fractional crystallization and column chromatography.

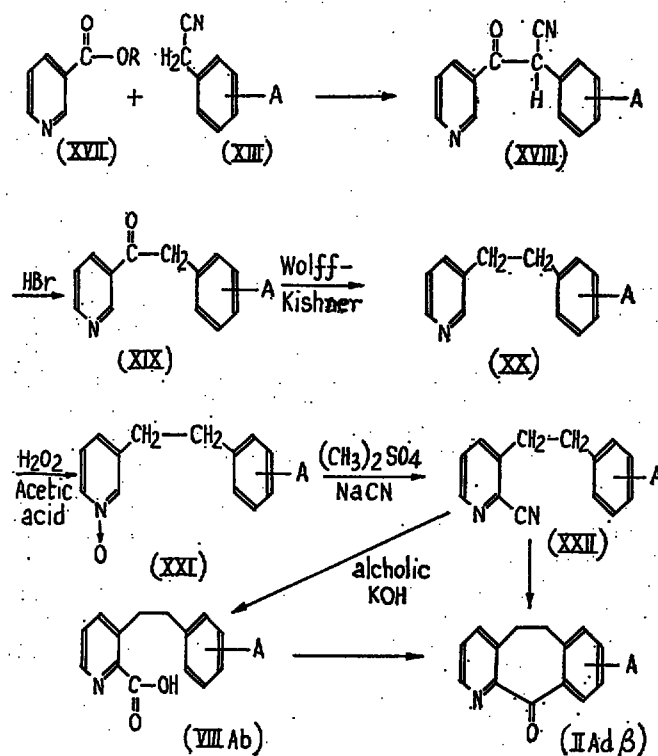
The 10,11-dehydro analog (IIAb α) of IIAb is preferably prepared from the latter by dehydrogenation as effected by selenium dioxide in pyridine, or by treating IIAb with N-bromo-succinimide and then dehydrobrominating the so-formed bromo intermediate.

In order to prepare the 3-aza-ketones (IIAc), the following sequence of reactions is preferred;



In this reaction sequence, a 4-methyl-nicotinic acid ester (XII) such as ethyl 4-methyl nicotinate, the same starting substance as used in the above preferred process for preparing compounds of the 2-aza series, is reacted with X in refluxing acetic anhydride, giving rise to a 4-styryl-nicotinic acid ester (VIII Ba'). Reduction of the ester (VIII Ba'), preferably catalytically such as with palladium and hydrogen, followed by hydrolysis of the ester group, produces a 4-phenethyl-nicotinic acid (VIII Bb), which upon heating with polyphosphoric acid, is cyclized to form the corresponding 3-aza-ketone (IIAcβ). The 10,11-dehydro analogs (IIAα) of IIAcβ are prepared either by dehydrogenation of the ketone (IIAcβ) itself as described heretofore, or by hydrolyzing VIII Ba' to the corresponding free carboxylic acid (VIII Ba) and heating the latter with polyphosphoric acid. If the cyclization is carried out at elevated temperatures in the range of 190° C., there is predominantly obtained IIAα. At lower temperatures, a lactone, the 4-alkyl isomer of XI, is formed as a side-product. This lactone, when heated with polyphosphoric acid according to the procedure described for the 1-aza series, is in turn transformed into the cyclic ketone (IIAα).

To prepare the 4-aza-ketones (IIAd), it is preferred to utilize the following sequence of reactions:



In this sequence, a nicotinic acid ester (XVII), preferably ethyl nicotinate, is converted into a 3-phenethyl-pyridine (XX) by the same sequence of reactions as described for the respective homo compounds in the preparation of the 2-aza series. The condensation of XVII with a phenylacetonitrile (XIII) is preferably carried out in ethanol in the presence of sodium ethoxide or of other condensation agents such as are used in the above-described condensation "XII + XIII → XIV." In place of the Wolff-Kishner reduction, there may also be employed copper chromite in dioxane at about 160° C. under about 100 atmospheres pressure of hydrogen. The phenethyl-pyridine (XX) is transformed into its N-oxide (XXI) by means of a peroxy acid, such as hydrogen peroxide and acetic acid. Reacting of XXI with dimethyl sulfate and then with aqueous sodium cyanide solution gives rise to a 2-cyano-3-phenethyl-pyridine (XXII). The nitrile (XXII) may be cyclized directly to the corresponding 4-aza-ketone (IIAd β) by heating with polyphosphoric acid, or it may first be hydrolyzed to the corresponding carboxylic acid (VIIIAb), and the latter then cyclized. The 10,11-dehydro analogs (IIAd α) of IIAd β may be prepared by direct dehydrogenation of the latter with selenium dioxide in pyridine, for example, or by any of the methods set forth in the Examples which follow later.

The N-oxides XXI are especially valuable in preparing the 4-aza-ketones (IIAd) in that still other transformations may be effected which finally also give rise to such ketones (IIAd). In particular, reacting an N-oxide (XXI) with acetic anhydride gives rise to the corresponding 2-acetoxy-3-phenethyl-pyridine which may be hydrolyzed to its 2-free-hydroxy analog by means of aqueous mineral acid, e.g., hydrochloric acid. The hydroxy group may then be replaced by bromide (by means of phosphorus oxybromide) to yield the respective 2-bromo-3-phenethyl-pyridine. Reaction of this latter intermediate with butyl lithium and then with carbon dioxide results in the formation of the carboxylic acid (VIIIAb) which may then be cyclized to yield IIAd β .

It is apparent to one skilled in the art that there are innumerable variations of the foregoing reactions which produce phenethyl- and styryl-pyridine-carboxylic acids, all of which reactions are deemed chemically equivalent to those depicted. For example, the reaction scheme for preparing a 2-aza-ketone (IIAb), can be adapted to prepare a 4-aza-ketone (IIAd) merely by using a 2-methyl-nicotinic acid ester such as ethyl 2-methyl-nicotinate as starting material. The close analogy between the methods for preparing the 1-aza-ketones (IIAa) and the 3-aza-ketones (IIAc) is also readily apparent.

The preparation of the aza-dibenzo-cycloheptenes (IIB) may be accomplished by any of the known methods for converting a keto group to a methylene group. The Wolff-Kishner reduction technique wherein a ketone (IIA) is treated with hydrazine and an alkali such as potassium hydroxide is the preferred method. On the other hand, the keto group of IIA may first be reduced to hydroxy, and the so obtained carbinol, in turn, further reduced to the corresponding compound IIB. The first step of this sequence can be effected, e.g., by reacting the ketone (IIA) with lithium aluminum hydride, with zinc dust in ammonia, or by catalytic reduction using platinum oxide or Raney Nickel. The so obtained carbinols may then be converted to the methylene compounds (IIB) by chlorinating them with thionyl chloride and then replacing the chlorine atom with hydrogen, e.g. by refluxing the chloro-intermediate in the presence of zinc dust, potassium iodide and acetic acid; or the carbinols may be directly reduced such as with iodine and phosphorus in glacial acetic acid. Other methods of course, would be available. In those instances wherein the aza-dibenzo-cycloheptene-5-one intermediate (IIA) contains halogeno or trifluoromethyl substituents in the benzenoid moiety, it is particularly preferred to apply the Wolff-Kishner reduction technique.

It should be apparent to one skilled in the art that in addition to the above discussed general methods for the preparation of the final products of general formula I, there is also practically an unlimited number of routes for arriving at such compounds (I), said routes involving completion of the tricyclic moiety essentially after the other portions of the molecule have been properly joined. These routes may be characterized by the essential feature that a precursor of the desired compound of formula I, which precursor differs from a compound of formula I only in that the cycloheptene ring is broken at one point only which is adjacent to the 5-position or the 10-position or the 11-position, and that at least one of the carbon atoms adjacent to the break bears a reactive group (as hereinafter defined), provided that, when the break in the cycloheptene ring is between the 11-position and the pyridine ring or between the 10-position and the benzene ring, the carbon atom at the 10-position or the carbon atom at the 11-position may bear a =O substituent to promote the reactivity of the reactive group towards formation of a carbon-carbon bond, is subjected to intra-

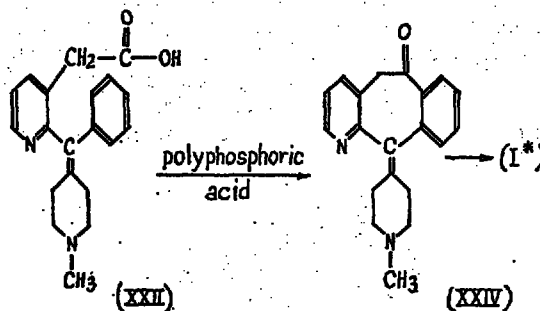
molecular condensation so as to cyclise the compound to form the cycloheptene ring.

The term "reactive group," as used in the preceding paragraph and in claim 43, means a group attached to a carbon atom adjacent to the break in the cycloheptene ring which, either of itself or, only when the reactive group is attached to the 10- or 11-carbon atom which is already attached to the 11- or 10-carbon atom respectively, when promoted by a =O substituent attached to either one of the 10- or 11-carbon atoms, will react, if necessary in the presence of catalyst or initiator for the reaction and under appropriate conditions of temperature and pressure and other reaction parameters, with a hydrogen atom or reactive group attached to the other carbon atom adjacent to the break in the cycloheptene ring so as to cause a direct carbon-carbon bond to be formed between the two carbon atoms adjacent to the break in the cycloheptene ring.

A so-obtained 5-hydroxy compound (IA) may then be dehydrated to the corresponding 5(1')-unsaturated compound (IB) or reduced to the corresponding 5-H-5(1')-saturated compound (IC); a 5(1')-unsaturated compound (IB) obtained by such dehydration or by the above cyclization hydrogenated to the corresponding 10(11)- and 5(1')-saturated compound; and the compound of formula I which has been obtained by one or more of the preceding steps subjected to one or more of the following finishing steps, in any desired sequence:

- (i) hydrogenation or dehydrogenation in position 10(11);
- (ii) reductive cleavage of one or two benzyl groups, if attached to the nitrogen atom of the amino group which forms part of the moiety Z;
- (iii) transformation into a pharmaceutically acceptable acid addition salt by reaction with the respective acid or with a reactive derivative thereof.

One type of such route is that wherein essentially all characteristic groupings of the desired product are built into the molecule with the exception of the two-carbon bridge (positions 10 and 11) joining the two six-membered rings of the tricyclic system, such joining being effected towards the end of the synthesis. For example, to prepare the compound, 4-aza-5-(N-methyl-4-piperidylidene)-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene (I*) by this alternate route, cyclization of α -phenyl- α -(N-methyl-4-piperidylidene)- α -(3-carboxymethyl-2-pyridyl)-methane (XXIII) gives rise to a ketone intermediate (XXIV) which upon reduction such as with hydrazine-hydrate and alkali is converted to I*:



The cyclization may, for instance, be effected by dehydration procedures such as with polyphosphoric acid or by intramolecular Friedel-Craft reactions using catalysts such as aluminum chloride. The foregoing is set forth merely as a prototype, for it is apparent that other known chemical equivalents of the $-\text{CH}_2\text{COOH}$ group may likewise be employed: For instance, nitrile in place of the carboxyl, or an acid chloride of XXIII, lend themselves readily to that type of intramolecular condensations; further, in place of the $-\text{CH}_2\text{COOH}$ group, there may be present groups such as $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{Br}$, $-\text{CH}_2\text{CH}_2\text{O-tosyl}$ and $-\text{CH}_2\text{CH}_2\text{O-mesyl}$, which undergo cyclization reactions with or without catalysts such as aluminium chloride, directly to I*. So for instance, α -phenyl- α -(N-methyl-4-piperidylidene)- α -[3-(β -hydroxy-ethyl)-2-pyridyl]-methane, obtainable by reactions readily apparent, may be directly cyclized to I*.

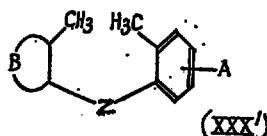
The reactions set forth in the two preceding paragraphs are for illustrative purposes only. As is obvious to the chemist, other compounds of general formula IB may be obtained in analogous manner. In particular, for instance, the position of the nitrogen atom in the pyridine moiety is generally not critical; when it is in a position different from that shown, the corresponding isomer of XXIV and/or I* is produced. Further, the illustration of an N-methyl-4-piperidylidene group is not to be construed as limiting, since any group V (as above defined) may similarly be employed. Analogs sub-

wherein A, B, Q₁, Q₂ and V' are as above defined, is reduced to $\begin{smallmatrix} \text{H} \\ < \\ \text{H} \end{smallmatrix}$, thus giving rise

to a compound according to either of the general formulae IB and IC; that a compound of formula IB obtained by one or both of the preceding steps, if desired, is hydrogenated to the respective compound of formula IC; and that the compound of general formula IB or IC which has been obtained by one or more of the preceding steps is subjected, if desired, to one or more of the following finishing steps, if any desired sequence:

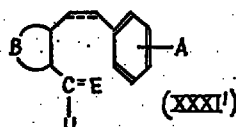
- (a) dehydrogenation in position 10(11);
- (b) reductive cleavage of one or two benzyl groups, if attached to the nitrogen atom of the amino group which forms part of the moiety Z;
- (c) transformation into a pharmaceutically acceptable acid addition salt by reaction with the respective acid or with a reactive derivative thereof.

The foregoing alternative approach to final compounds of formula I involved building of the 10,11-two-carbon-bridge from a substituent on the pyridine moiety. Such chemical construction may also be effected essentially by joining up two substituents—one on the pyridine moiety and the other on the phenyl ring. Such an approach is represented by the reaction of α -(3-methyl-2-pyridyl)- α -(*o*-tolyl)- α -(N-methyl-4-piperidylidene)-methane (XXX) with sodium tert.-butoxide plus either oxygen or amyl nitrite, whereby ring closure to I* occurs. Alternatively, XXX can be dibrominated by N-bromo-succinimide to form a di-bromomethyl intermediate, which upon treatment with metals such as sodium or zinc forms I*. Any number of intramolecular condensations of readily synthesized materials like α -(3-carbalkoxymethyl-2-pyridyl) - α - (2 - aldehydo - phenyl) - α - (N-methyl - 4 - piperidylidene) - methane or α - (3 - aldehydo - 2 - pyridyl) - α - (2 - cyanomethyl) - phenyl - α - (N - methyl-4-piperidylidene)-methane will also give rise to readily apparent cyclized precursors of I*, from which precursors, I* may be obtained by obvious finishing steps such as hydrolysis and decarboxylation of the ester and nitrilo groups, respectively, contained in the exemplified precursors. Also in the present paragraph, I* is but a prototype of all the compounds of general formula I which may be obtained in a manner which is obvious in the light of the above, by substituting the appropriate intermediates for those set forth hereinabove. Essentially thus, a compound of the general formula XXX'



wherein A, B and Z are as defined above, is subjected to oxidative (dehydrogenating) condensation in one or more steps, with or without isolation of intermediates.

A further approach is that whereby essentially all groups are present except for the bonding of the 5-position to the benzenoid ring. For example, reacting of 3-phenethyl-2-cyanopyridine with N-methyl-4-piperidyl magnesium chloride leads either to the intermediary ketone, 3-phenethyl-2-(N-methyl-isonipecotoyl)-pyridine (XXXI), or to the corresponding Ketimide, both of which upon cyclization form I*. This may be dehydrogenated in position 10(11) as described above. Here again, I* and its 10,11-dehydro analog are but prototypes for all the compounds according to general formula I, compounds the preparation of which is obvious to the chemist in the light of the above. The essential feature of this latter approach consists in that a compound of the general formula XXXI'



wherein the dotted line, A, B and U are as above defined and E is O or NH, is subjected to intramolecular condensation, to yield the respective compound of formula IB.

The following Examples are illustrative of the product, process and pharmaceutical composition aspects of the invention. In particular, Examples 1 to 5 illustrate the preparation of the preferred intermediates (II) according to the invention; Examples 6 to

19 illustrate the preparation of the final compounds (I) according to the invention; and Examples 20 to 22 show typical pharmaceutical formulations containing a representative of the compounds according to general formula I.

I. PREPARATION OF PREFERRED INTERMEDIATES.

EXAMPLE 1.

1-Aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one and 1-Aza-5H-dibenzo-[a,d]-cycloheptene-5-one.

A. 2-(β -Hydroxy- β -phenyl)-ethyl-nicotinic lactone hydrochloride:

Stir and reflux a mixture of 65 g. ethyl 2-methyl-nicotinate, 57 g. benzaldehyde and 37 ml. acetic anhydride for 20 hours; then cool and pour the mixture into 2.0N hydrochloric acid. After crystallization, filter the solid and recrystallize it from ethanol, obtaining 13.5 g. of 2-(β -hydroxy- β -phenyl)-ethyl-nicotinic lactone hydrochloride, m.p. = 183—185° C.

B. 2-Styryl-nicotinic acid:

Admix 60 g. of red phosphorus, 20 g. of iodine in 1.5 liters glacial acetic acid, and to the so-obtained mixture add portionwise 176 g. of 2-(β -hydroxy- β -phenyl)-ethyl-nicotinic lactone hydrochloride. Reflux for 20 hours and filter the hot solution through a sintered-glass funnel. Pour the filtrate into water and filter the precipitate after allowing time for formation and coagulation. Dissolve the filtered precipitate in 2 liters of warm dilute (10—15%) aqueous ammonia, filter again, and neutralize the filtrate with acetic acid. Cool and separate the precipitated 2-styryl-nicotinic acid by filtration, followed by recrystallization from ethanol, m.p. = 219—221° C.; yield: 130 g.

C. 2-Phenethyl-nicotinic acid:

(1) In a shaker-type (Parr) hydrogenation apparatus, mix 22 g. of 2-styryl-nicotinic acid, 200 ml. of ethanol and 20 ml. of 25% aqueous sodium hydroxide solution. Hydrogenate the mixture at a hydrogen pressure of about 3.6 atmospheres, using a freshly prepared Raney nickel catalyst. When the theoretical amount of hydrogen has been absorbed (1 mole per mole of acid), i.e. usually after about 30 to 60 minutes, filter, and concentrate the filtrate by heating on a steam bath. Dissolve the residue in water, acidify with acetic acid and filter the crude phenethyl-nicotinic acid. After recrystallization from benzene-hexane, m.p. = 162—163° C.

(2) Alternatively, 2-phenethyl-nicotinic acid may be prepared as follows: Heat 100 g. of the lactone of part A of this Example with 1 liter 57% hydriodic acid, while adding 60 g. red phosphorus over a period of 2 hours. Reflux the mixture for 18 hours and filter while hot. Remove most of the excess hydriodic acid by concentration and neutralize the remaining solution with aqueous ammonia whereupon 2-phenethyl-nicotinic acid precipitates.

D. 1-Aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one:

Admix 50 g. of 2-phenethyl-nicotinic acid and 500 g. of polyphosphoric acid and heat at 160—165° C. for 5—6 hours while stirring. Then cool, pour the mixture into ice water, and neutralize with aqueous ammonia. Extract with ether. Wash the ethereal extract with 10% sodium hydroxide solution. Dry the ether layer and concentrate to a residue, which is crystallized from hexane to yield the desired ketone m.p. = 62—64° C.

E. 1-Aza-5H-dibenzo-[a,d]-cycloheptene-5-one:

(1) Dissolve 20 g. of the ketone of part D of this Example in 150 ml. of acetic acid and add 40 ml. of 30% hydrogen peroxide. Heat in a water bath maintained at 65—70° C. for 24 hours, then pour into ice water. Neutralize with concentrated sodium hydroxide solution and allow to crystallize. Filter, recrystallize from dilute ethanol and air dry, obtaining the N-oxide of the ketone of part D.

(2) To 100 ml. of refluxing acetic anhydride, add 15 g. of the N-oxide prepared according to the preceding paragraph. Reflux the mixture for 10 hours, then pour into water. Allow to stand for several hours (to hydrolyze any excess anhydride), then neutralize with sodium bicarbonate. Extract the mixture with chloroform and evaporate the chloroform extract to dryness. Treat the residue with 100 ml. of 48% hydrobromic acid and 100 ml. of acetic acid and then reflux the mixture for 6 hours. Concentrate in vacuo, dissolve the residue in water and make the solution alkaline with aqueous ammonia. Extract the mixture with ether and concentrate the ethereal extract to a residue, which is crystallized from petroleum ether to yield 1-aza-5H-dibenzo-[a,d]-cycloheptene-5-one, m.p. = 95—96° C.

EXAMPLE 2.

2-Aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one and
2-Aza-5H-dibenzo-[a,d]-cycloheptene-5-one.

A. 3-Phenethyl-isonicotinic acid via α -(4-Methyl-nicotinoyl)-phenylacetoneitrile, benzyl-(4-methyl-3-pyridyl)-ketone and 3-phenethyl-4-methyl-pyridine:

Preferably, 3-phenethyl-isonicotinic acid is obtained as follows:

(1) 3-phenethyl-4-methyl-pyridine is first prepared by a process analogous to that described in part A (1 to 3) of Example 4 hereinbelow, starting from ethyl 4-methyl-nicotinate, via α -(4-methyl-nicotinoyl)-phenylacetoneitrile and benzyl-(4-methyl-3-pyridyl)-ketone.

(2) A mixture of 8.6 g. of the so obtained 3-phenethyl-4-methyl-pyridine, of 50 ml. dry pyridine, and of 12 g. powdered selenium dioxide is then refluxed for 3 hours, thereafter diluted with CHCl_3 and filtered. The filtrate is evaporated, the residue dissolved in dilute aqueous ammonia and the solution extracted with ether. The remaining aqueous layer is then acidified with acetic acid, and the precipitate filtered and recrystallized from isopropyl ether, yielding 3.9 g. of the desired product, m.p. = 99—101° C.

B. Alternative Procedure for the Preparation of 3-Phenethyl-isonicotinic Acid:

Alternatively, 3-phenethyl-isonicotinic acid may be obtained by the following sequence of steps:

(1) A solution of 24.2 g. of 3-styryl-4-nitro-pyridine-N-oxide in 250 ml. of glacial acetic acid is reduced in a Parr-hydrogenator in the presence of 10 g. of a 5% palladium-on-carbon catalyst at 55—60° C. and about 3.6 atmospheres pressure. The reduction usually requires about 6 hours. The mixture is then filtered, the filtrate is concentrated in vacuo on a steam bath, and the residue is dissolved in 150 ml. of 20% hydrochloric acid. The acid solution is concentrated to dryness and the so obtained crude 3-phenethyl-4-amino-pyridinium chloride residue is used directly for the procedure of the following paragraph (2).

(2) (a) The product of the preceding paragraph (1) is dissolved in 100 ml. of 10% hydrochloric acid and the solution cooled to 0—5° C. Then a solution containing 6.9 g. of sodium nitrite in 50 ml. of water is slowly added, maintaining the temperature at 0—5° C. The so-formed diazonium salt solution is stirred for an additional half hour. Meanwhile a solution of 0.3 mole of cuprous cyanide is prepared according to directions given in "Organic Synthesis" Collective Vol. 1, 1st Edn. (1932) p.500, and cooled slowly to 0° C. The above cooled diazonium salt solution is added to it and the mixture is allowed to warm to room temperature stirred for an additional hour. Thereafter, with thorough cooling in an ice-salt bath, the solution is made alkaline by careful addition of 50% aqueous sodium hydroxide solution. The so-formed 3-phenethyl-4-cyano-pyridine is extracted with chloroform, the chloroform extract is washed and the chloroform is evaporated off.

(b) Alternatively, the diazonium salt solution of the preceding sub-paragraph (a) may first be transformed by refluxing with 25% aqueous sulfuric acid to 3-phenethyl-4-hydroxy-pyridine; the latter converted, by heating in a glass-lined autoclave with 3 times its weight of phosphorus oxybromide at 160—165° C. for 6 hours, to its 4-bromo analog, which is isolated by pouring the reaction mixture on ice water, neutralizing with sodium carbonate, extracting with chloroform and evaporating off the solvent from the extract; and the so-obtained 4-bromo compound further transformed by dissolving it in four times its weight of anhydrous pyridine, adding an equivalent amount of cuprous cyanide, cautiously heating to 110—115° C. until the initial exothermic reaction is over, and finally heating under vacuo with a bath temperature of 200—220° C., while distilling the 3-phenethyl-4-cyano-pyridine as it forms.

(c) For another alternative route to obtain 3-phenethyl-4-cyano-pyridine, see end of sub-paragraph (a) in part A(5) of Example 4, hereinbelow.

(3) A solution containing 20.8 g. of 3-phenethyl-4-cyano-pyridine, 40 g. of potassium hydroxide, 60 ml. of water and 150 ml. of ethanol is refluxed with stirring for 24 hours or until the evolution of ammonia ceases. Half of the volume is evaporated off and the remainder is poured into water. The resulting solution is cooled and extracted with ether. The aqueous solution is carefully neutralized with acetic acid to crystallize out the 3-phenethyl-isonicotinic acid, which is then filtered and recrystallized from ethanol.

C. 2-Aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one:

(1) Preferably, 2-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one is prepared by heating 3-phenethyl-isonicotinic acid with polyphosphoric acid in a manner analogous to that described in part D of Example 1.

(2) Alternatively, to 20.8 g. of 3-phenethyl-isonicotinic acid, 50 ml. of purified thionyl-chloride are added. The mixture is warmed on a steam bath for $\frac{1}{2}$ hour. The excess thionylchloride is removed in vacuo, and the residue suspended in 2.0 liters of anhydrous petroleum ether (b.p. 60—90° C.). With vigorous stirring 26 g. of anhydrous aluminum chloride granules are slowly added. The resulting mixture is stirred for 4 hours at room temperature, and the solution poured into a mixture of 2 kilograms of ice and 25 ml. of concentrated hydrochloric acid. The petroleum ether is separated and discarded. The aqueous solution, while cooled to 5—10° C., is made alkaline with 50% aqueous sodium hydroxide solution. The product, 2-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one, is extracted with chloroform and the chloroform removed. The residue, after trituration with ice-cold petroleum ether, is recrystallized from a mixture of benzene-hexane.

D. 2-Aza-5H-dibenzo-[a,d]-cycloheptene-5-one:

(1) Preferably, 2-aza-5H-dibenzo-[a,d]-cycloheptene-5-one is prepared by dehydrogenation of its 10,11-dihydro analog (obtainable as per part C of this Example) in a manner analogous to that described in part C, paragraph (1) of Example 4 hereinbelow.

(2) Alternatively, the said dehydrogenation may be effected as follows: Slowly and with vigorous stirring, a solution of 19.7 g. of 2-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one in 150 ml. of dry carbontetrachloride is added to a suspension of 17.8 g. of N-bromo-succinimide in 500 ml. of carbontetrachloride containing 0.1 g. of benzoyl-peroxide. After the initial exothermic reaction is completed, the mixture is refluxed with stirring for an additional 3 hours, the so-formed succinimide removed by filtration, and the carbontetrachloride solution evaporated to dryness. 300 ml. of triethylamine are added to the residue and the mixture warmed on a steam bath for 18 to 20 hours. The product is filtered and the filtrate concentrated to a residue which is poured into water. The obtained mixture is extracted with chloroform, and the 2-aza-5H-dibenzo-[a,d]-cycloheptene-5-one isolated from the extract and purified by recrystallization from dilute ethanol.

EXAMPLE 3.

3-Aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one and 3-Aza-5H-dibenzo-[a,d]-cycloheptene-5-one.

A. Ethyl 4-styryl-nicotinate:

Stir and reflux a mixture of 165 g. of ethyl 4-methyl-nicotinate, 106 g. of benzaldehyde and 1 liter of acetic anhydride for four hours. Pour onto ice, filter and recrystallize from benzene, obtaining the ester of this step.

B. 4-Phenethyl-nicotinic acid:

(1) Reflux for six hours a mixture of 50 g. of the ester from part A of this Example, 50 g. potassium hydroxide, 50 ml. of water and 200 ml. of ethanol. Concentrate to remove the solvents and dissolve the residue in 200 ml. of water. Neutralize with acetic acid, allow to crystallize, filter, and dry; then hydrogenate 22 g. of the so-obtained 4-styryl-nicotinic acid in a manner analogous to that described in part C of Example 1.

(2) Alternatively, dissolve 20.2 g. of the ester from part A of this Example in 200 ml. of ethanol and hydrogenate under about 3.6 atmospheres hydrogen pressure in the presence of 5 g. of 5% palladium-on-carbon catalyst at room temperature. Saponify the so-obtained ethyl 4-phenethyl-nicotinate in a standard manner.

C. 3-Aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one:

Admix 80 g. of 4-phenethyl-nicotinic acid and 1 kg. of polyphosphoric acid and follow a procedure analogous to that described in part D of Example 1. Recrystallize from benzene-petroleum ether, m.p. = 66—67° C.

D. 3-Aza-5H-dibenzo-[a,d]-cycloheptene-5-one:

(1) Admix 50 g. of 4-styryl-nicotinic acid [the compound appearing in paragraph (1) of part B of this Example, before the hydrogenation step] with 1 kg. of polyphosphoric acid, then follow the procedure of part D of Example 1. Recrystallize from benzene-hexane, m.p. = 157—158° C.

(2) Alternatively, 3-Aza-5H-dibenzo-[a,d]-cycloheptene-5-one may be obtained by dehydrogenating the respective 10,11-dihydro compound (product of part C of this Example) in a manner analogous to that described in paragraph (2) of part D of Example 2.

EXAMPLE 4.

*4-Aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one and
4-Aza-5H-dibenzo-[a,d]-cycloheptene-5-one.*

A. 2-Cyano-3-phenethyl-pyridine via α -Nicotinoyl-phenylacetonitrile, benzyl-(3-pyridyl)-ketone, 3-Phenethyl-pyridine and 3-phenethyl-pyridine-N-oxide: 5

(1) To a refluxing solution of 34 g. of sodium metal in 500 ml. of absolute ethanol, add dropwise a mixture of 260 g. of ethyl nicotinate and 133 g. of phenylacetonitrile. After four hours, pour the mixture onto ice and extract with ether. Neutralize the aqueous phase with acetic acid and allow the product to crystallize. Filter, wash with water and air dry. The so-obtained α -nicotinoyl-phenylacetonitrile (m.p. = 137—141° C.) is used in the next step (2) without further purification. 10

(2) Reflux the nitrile obtained by the procedure of the preceding paragraph (1) for 16 hours with 1.4 liters of concentrated hydrobromic acid. Pour the mixture over ice and allow to crystallize. Filter the hydrobromide salt, suspend it in water and neutralize with sodium carbonate solution. Allow to crystallize, filter and air dry, to obtain 126 g. benzyl-(3-pyridyl)-ketone, m.p. = 53—56° C. 15

(3) Admix 26 g. of the ketone obtained by the procedure of the preceding paragraph (2), 11 g. of sodium hydroxide, 11 ml. of 85% hydrazine hydrate and 175 ml. of diethyleneglycol. Place the mixture in a still and heat at 235—240° C. for 3 to 4 hours, permitting distillation to occur ad libitum. Then cool, and extract the mixture and the distillate with benzene. Wash the combined benzene extracts with water and distill in vacuo collecting that fraction boiling at 120—128° C./1 Torr; yield: 21 g. 20

(4) Heat a mixture of 183 g. of 3-phenethyl-pyridine [product of the preceding paragraph (3)], 120 ml. of 30% hydrogen peroxide, and 300 ml. of glacial acetic acid for 20 to 24 hours at 60—65° C. Then pour into ice water and adjust the pH to 8—9 with aqueous ammonia. Filter and dissolve the precipitate with hexane, obtaining 150—158 g. 3-phenethyl-pyridine-N-oxide, m.p. = 82—89° C. 25

(5) (a) 2-Cyano-3-phenethyl-pyridine is preferably prepared from the N-oxide of the preceding paragraph (4) as follows: While stirring, add 75.6 g. of dimethylsulfate, dropwise, to 118.8 g. of 3-phenethyl-pyridine-N-oxide. Heat the mixture at 85° C. for 3 hours. Cool and dissolve in 180 ml. of water. Add the aqueous solution dropwise to a stirred solution of 88.2 g. of sodium cyanide in 250 ml. of water, all under an atmosphere of nitrogen with the reaction temperature in the range of 0—5° C. Stir for 6 hours at 0° C., then allow the mixture to warm to room temperature by standing overnight. Extract with chloroform, wash extracts with water and distill in vacuo, collecting that fraction boiling at 160—167° C. at 0.8 Torr. (A higher boiling fraction, 190—195°/1.5 Torr, is the 4-cyano isomer, which is of use as an intermediate for the preparation of the 2-aza ketone, cf. part B of Example 2.) 30

(b) Alternatively, add 98 g. of 3-phenethyl-pyridine-N-oxide to 1 liter of acetic anhydride and reflux for 20 hours. Evaporate off the excess solvents and pour the residue into water, neutralize the mixture with base and extract the product into chloroform. Evaporate off the chloroform, add 200 ml. of 20% sodium hydroxide solution to the residue, and reflux the resulting solution for 6 hours. Cool, neutralize with acetic acid and allow to crystallize. The 2-hydroxy-3-phenethyl-pyridine so-obtained is further converted into its 2-bromo and finally into its 2-cyano analog in a manner analogous to the second and third steps of the process described in sub-paragraph (b) of part B(2) of Example 2. 35

B. 4-Aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one: 40

(1) Stir and heat 99 g. of 2-cyano-3-phenethyl-pyridine and 5 kg. of polyphosphoric acid at 180° C. for 20 to 24 hours. Pour onto ice, neutralize with 50% aqueous sodium hydroxide solution, and extract with chloroform. Concentrate to a residue, triturate with hexane and filter, obtaining the desired ketone, m.p. = 68—73° C. 50

(2) Alternatively, cyclization may be effected in two steps as follows:

(a) Heat a mixture containing 25 g. of 2-cyano-3-phenethyl-pyridine, 25 g. of potassium hydroxide (dissolved in 50 ml. of water) and 100 ml. ethanol for 24 hours at reflux temperature. Then process in a manner analogous to that described in part B(3) of Example 2, to obtain 3-phenethyl-picolinic acid. 55

(b) Heat a mixture of 20 g. of 3-phenethyl-picolinic acid and 200 g. of polyphosphoric acid for 6 hours at 105—110° C. and process in a manner analogous to that described in part D of Example 1. 60

C. 4-Aza-5H-dibenzo-[a,d]-cycloheptene-5-one:

(1) Reflux a mixture of 15 g. of the ketone obtained as per part B of this Example, 15 g. of selenium dioxide and 60 ml. of pyridine for 4 hours under nitrogen. Cool, 60

filter and wash the precipitate with ethanol. Combine the filtrate and the ethanol washings and concentrate in vacuo to a residue. Add water to the residue and make the resulting mixture alkaline with aqueous ammonia and extract with chloroform. Wash the chloroform solution with water and concentrate to a residue. Crystallize from isopropyl ether or benzene-hexane; m.p. = 118—119° C.

(2) Alternatively, dehydrogenation may be effected as follows: To a solution of 50 g. of 4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one in 150 ml. of anhydrous cymene add 30 g. of 5% palladium-on-carbon catalyst and reflux for 24 hours. Cool the resulting mixture and filter off the palladium and carbon. Pour the filtrate into 250 ml. of 10% hydrochloric acid. Separate and discard the cymene layer. Neutralize the remaining acid solution with aqueous ammonia and extract the resulting oil with chloroform. Remove the chloroform and recrystallize the product from dilute ethanol.

The foregoing Examples set forth methods for synthesizing ketones of formula IIA which are key intermediates in the preparation of the final compounds of formula I. All these Examples give rise to aza-dibenzo-cycloheptenones unsubstituted in the benzenoid ring. As stated heretofore, to prepare ketones having a substituent at one or more of the 6-, 7-, 8- and 9- positions, one merely employs the appropriately substituted reactant. Examples 1 and 3 employ benzaldehyde as an initial reactant, while Examples 2 and 4 employ phenylacetonitrile. If these reactants are substituted, the substituent will be carried through to the respective aza-dibenzo-cycloheptenone, the position dependent upon the position in the initial reactant. For instance, a para-substituent in the initial reactant gives ultimate rise to a 7-substituted aza-dibenzo-cycloheptenone; an ortho-substituent appears in the 9-position; while a meta-substituent gives rise to a mixture consisting of a 6-substituted and an 8-substituted aza-dibenzo-cycloheptenone. (For separating a mixture of 6- and 8-substituted aza-dibenzo-cycloheptenones, is preferably used column chromatography whereby the mixture is absorbed on alumina and eluted with benzene-hexane mixtures containing varying proportions of solvent; combination of like eluates as determined by infrared, ultraviolet and thin-layer chromatography techniques, provides for separation and isolation of the respective isomers.) The initial reactant, the benzaldehyde or the phenylacetonitrile, may thus bear an *o*-, *m*- or *p*-substituent such as methyl, chloro, bromo, trifluoromethyl and methoxy, and such substituent will appear in the respective position of the resulting aza-dibenzo-cycloheptenone. The substituted initial reactants such as *p*-chloro-phenylacetonitrile or *p*-trifluoromethyl-benzaldehyde are either known compounds or are readily obtainable by methods well known to one ordinarily skilled in the art.

EXAMPLE 5.

4-Aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene.

Reflux a mixture of 40 g. of 4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one, 50 g. of potassium hydroxide, 100 g. of hydrazine hydrate and 350 ml. of trimethyleneglycol for 24 hours. Concentrate in vacuo to 30% of the initial volume and pour the residue into ice-water. Extract with ether, wash the ether solution with water, and concentrate to a residue. Crystallize from aqueous methanol. m.p. 99—100° C.

In similar fashion, by utilizing any of the ketones of Examples 1 to 4 and the substitution products thereof as described in the preceding passage, and reacting said ketones as described in Example 5, the corresponding aza-dibenzo-cycloheptenes may be obtained.

II. PREPARATION OF "CARBINOLS."

EXAMPLE 6.

5-Hydroxy-5-(N-methyl-4-piperidyl)-4-aza- and -1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene.

A. Add 17.4 g. of N-methyl-4-chloro-piperidine to a stirred mixture containing 3.2 g. of magnesium, 20 ml. of anhydrous tetrahydrofuran, 1 ml. of ethyl bromide and a crystal of iodine. Reflux for two hours, cool to 30—35° C., and add a solution of 13 g. of 4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one in 25 ml. of tetrahydrofuran. Stir for five hours, remove the solvent by distillation in vacuo, and add 250 ml. of ether. Then add 100 ml. of 10% ammonium chloride solution and extract the mixture with chloroform. Concentrate the chloroform solution to a residue and recrystallize from diisopropylether, obtaining 20 g. of the carbinol of this Example, m.p. = 173—174° C.

B. By substituting in the foregoing the isomeric 1-, 2- and 3-aza-ketones, the

respective 10,11-dehydro compounds, or benzenoid-ring substituted analogs, the corresponding carbinols are obtained. So for instance, the 1-aza isomer of the compound of Example 6(A) may be obtained (m.p. = 170—173° C.) by substituting 1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one for the respective 4-aza reactant of the preceding part A of this Example.

EXAMPLE 7.

5-Hydroxy-5-(γ-dimethylamino-propyl)-1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene.

To a stirred mixture of 6.8 g. of magnesium, 150 ml. of anhydrous ether and 1 ml. of ethylbromide add 39 g. of γ-dimethylamino-propylchloride. While refluxing, add a solution of 20.9 g. of 1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one in 100 ml. of ether and reflux the reaction mixture for three hours, under continued stirring. Then add 200 ml. of 10% ammonium chloride solution and extract with chloroform. Concentrate to a residue and recrystallize from ether, obtaining the carbinol of this Example; m.p. = 106—109° C.

EXAMPLE 8.

5-Hydroxy-5-(4'-dimethylamino-cyclohexylmethyl)-1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene.

To 2.4 g. magnesium in 50 ml. of tetrahydrofuran add a crystal of iodine and 1 ml. of ethylbromide, followed by the dropwise addition of a solution of 17.5 g. of 4-dimethylamino-cyclohexylmethylchloride in 20 ml. of tetrahydrofuran. Heat the resulting mixture under reflux conditions until the magnesium is used up. Add a solution of 10.5 g. of 1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one in 10 ml. of tetrahydrofuran, and process the resulting mixture as described in Example 6, to yield the product of this Example, which is crystallized from ethanol; m.p. = 182—184° C.

EXAMPLE 9.

5-Hydroxy-5-(p-dimethylamino-phenyl)-1-aza-dibenzo-[a,d]-cycloheptene.

To a refluxing solution of p-dimethylamino-phenyllithium (prepared from 40 g. of p-bromo-dimethylaniline and 1.4 g. of lithium shot) in 500 ml. of ether, add a solution of 1-aza-5H-dibenzo-[a,d]-cycloheptene-5-one and reflux the resulting mixture for two hours. Decompose the reaction mixture by adding 100 ml. of a 10% ammonium chloride solution and extract the desired product with ether. Evaporate off the ether and recrystallize the residue from benzene, to obtain 5-hydroxy-5-(p-dimethylamino-phenyl)-1-aza-dibenzo-[a,d]-cycloheptene.

EXAMPLE 10.

5-Hydroxy-5-(2-picoly)-3-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene.

To a refluxing solution of phenyllithium (prepared from 31.4 g. of bromobenzene and 2.8 g. lithium metal shot) in 1 liter of anhydrous ether, add 14 g. of α-picoline and reflux the resulting mixture for 2 hours. Add a solution of 21 g. of 3-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one in ether and reflux the resulting mixture with stirring for 4 hours. Then add 250 ml. of 10% ammonium chloride solution. Extract the desired product with chloroform, evaporate off the chloroform and recrystallize the residue.

The methods of Examples 6 to 10 are representative of the formation of the carbinols of formula I, with Example 6 being applicable to all such carbinols and especially preferred for the synthesis of those such carbinols wherein U represents N-methyl-4-piperidyl. Tetrahydrofuran has a greater application as a solvent in these Grignard reactions and permits the use of higher concentrations, than other solvents commonly used for such reactions. These reactions are not satisfactorily applicable to the preparation of those carbinols of formula I which have less than three carbon atoms separating the amino group of U from C—5 of the tricyclic nucleus.

It is evident that any Grignard reagent of the general formula U-Mg-Halogen, with the foregoing limitation, may be prepared in the usual manner described herein, and used in a manner analogous to Examples 6 to 8 to obtain the corresponding carbinol. Representative of such reagents, in addition to those set forth above, are those wherein U represents: N-ethyl-4-piperidyl, N-methyl-3-piperidyl, 4-piperidyl, N-benzyl-4-piperidyl, di-(lower-alkylamino)-lower-alkyl such as γ-dimethylamino-propyl, δ-dimethylamino-butyl, γ-(N-methyl-N-ethyl-amino)-propyl, ε-dimethylamino-pentyl and γ-dimethylamino-octyl, 4-dimethylamino-cyclohexyl, γ-(4-dimethylamino-cyclohexyl)-propyl, 4-dimethylamino-cyclohexylmethyl, γ-pyrrolidino-propyl, γ-

piperidino-propyl, γ -morpholino-propyl, γ -(4-methyl-piperazino)-propyl, γ -[4-(β -hydroxyethyl)-piperazino]-propyl, γ -(*p*-dimethylamino-phenyl)-propyl and γ -diethyl-amino-butyl.

It is also evident that any of the ketones of Examples 1 to 4, including the benzenoid-ring substituted analogs thereof, when substituted into Examples 6 to 10 with the Grignard or other organometallic reactants described above will give rise to the corresponding carbinol of formula I.

In order to prepare those carbinols of formula I wherein U contains a primary or secondary amino group, such as γ -methylamino-propyl or γ -amino-propyl, the amino group must be protected, e.g. by benzylation, prior to formation of the Grignard reagent. Thus, utilizing the procedure of Example 7, one would react, for instance, γ -(N-methyl-N-benzyl-amino)-propylmagnesium chloride with the appropriate ketone. Subjecting the carbinol so formed to debenylation by methods well known in the art, such as catalytic hydrogenation, affords the corresponding primary- or secondary-amino derivative. Similarly, for the preparation of carbinols of formula I wherein U represents 4-piperidyl, the Grignard reactant of choice is N-benzyl-4-piperidylmagnesium chloride.

It has been stated herein that the substituent U may be a group such as [4-(β -hydroxyethyl)-piperazino]-lower-alkyl. Compounds of the formula I with such type of substituent U are preferably prepared from a Grignard reagent such as γ -(4-benzyl-piperazino)-propylmagnesium chloride, followed by transformation of the hydrogen atom or the benzyl group at position 4 of the piperazino residue to the appropriately substituted moiety by methods well known in the art.

Following the methods taught by Examples 6 to 10, and utilizing knowledge ascribed to one skilled in the art, carbinols such as the following may likewise be prepared from the reaction of the appropriate ketone and appropriate organometallic (such as Grignard) reagent [in the following listing, for the sake of brevity, the phrase "5-hydroxy-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene" is written as "dihydrocarbinol," while the 10,11-unsaturated analog is written as "carbinol," in which abbreviated nomenclature the compound of, e.g., Example 6 would be written as "4-aza-5-(N-methyl-4-piperidyl)-dihydrocarbinol": 4-Aza-5-(4-piperidyl)-dihydrocarbinol, 4-aza-5-(N-benzyl-4-piperidyl)-dihydrocarbinol, 4-aza-5-(γ -dimethylamino-propyl)-dihydrocarbinol, 4-aza-5-(γ -pyrrolidino-propyl)-dihydrocarbinol, 4-aza-5-(4'-dimethylamino-cyclohexylmethyl)-dihydrocarbinol, 4-aza-5-(γ -methylamino-propyl)-dihydrocarbinol, 4-aza-5-(γ -dimethylamino-butyl)-dihydrocarbinol, 4-aza-5-(γ -diethylamino-propyl)-dihydrocarbinol, 4-aza-5-[γ -(4-methyl-piperazino)-propyl]-dihydrocarbinol, 4-aza-5-[γ -(4- β -hydroxyethyl-piperazino)-propyl]-dihydrocarbinol, 4-aza-5-[γ -(methyl-benzyl-amino)-propyl]-dihydrocarbinol, 4-aza-5-(β -methyl- γ -dimethylamino-propyl)-dihydrocarbinol, 4-aza-5-(β -methyl- γ -methylamino-propyl)-dihydrocarbinol, 4-aza-5-(4-piperidyl)-carbinol, 4-aza-5-(N-benzyl-4-piperidyl)-carbinol, 4-aza-5-(N-methyl-4-piperidyl)-carbinol, 4-aza-5-(γ -dimethylamino-propyl)-carbinol, 4-aza-5-(γ -pyrrolidino-propyl)-carbinol, 4-aza-5-(4'-dimethylamino-cyclohexylmethyl)-carbinol, 4-aza-5-(γ -methylamino-propyl)-carbinol, 4-aza-5-(γ -dimethylamino-butyl)-carbinol, 4-aza-5-(γ -diethylamino-propyl)-carbinol, 4-aza-5-[γ -(4-methyl-piperazino)-propyl]-carbinol, 4-aza-5-[γ -(4- β -hydroxyethyl-piperazino)-propyl]-carbinol, 4-aza-5-[γ -(methyl-benzyl-amino)-propyl]-carbinol, 4-aza-5-(β -methyl- γ -dimethylamino-propyl)-carbinol, 4-aza-5-(β -methyl- γ -methylamino-propyl)-carbinol, and the 1-aza-, 2-aza- and 3-aza- analogs of the foregoing, as well as their 7-chloro, 7-trifluoromethyl, 8-chloro, 8-methyl, 9-methyl, 7-bromo-, 6-methoxy and 7-methyl derivatives.

III. "UNSATURATED COMPOUNDS" BY DEHYDRATION OF "CARBINOLS."

EXAMPLE 11.

5-(N-Methyl-4-piperidylidene)-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene.

Heat 5.4 g. of the carbinol of Example 6 and 270 g. of polyphosphoric acid for 12 hours at 140-170° C. Pour into ice water and make alkaline with sodium hydroxide. Extract with ether. Dry the ether solution and concentrate to a residue. Crystallize from isopropylether; m.p. = 124-126° C.

EXAMPLE 12.

5-(N-Methyl-4-piperidylidene)-1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene and its Dihydrochloride.

A. Dissolve 7 g. of 5-hydroxy-5-(N-methyl-4-piperidyl)-1-aza-10,11-dihydro-5H-

dibenzo-[a,d]-cycloheptene in 50 ml. of acetic acid, cool and saturate the solution with anhydrous hydrogen chloride. Add 6 ml. of acetic anhydride and heat the mixture on a steam bath for 6 hours. Concentrate the heated mixture under reduced pressure on a steam bath to the point in which a viscous oil remains. Add 50 ml. of benzene and repeat the concentration. Triturate the residue with ether and recrystallize the resulting solid from isopropanol, m.p. = 170—175° C.

B. To prepare the free base of the foregoing dihydrochloride salt, dissolve the dihydrochloride in water, neutralize with aqueous ammonia, and extract with ether. Evaporate off the ether and crystallize the residue from petroleum ether, to yield 5-(N-methyl-4-piperidylidene)-1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene; m.p. = 136—138° C.

EXAMPLE 13.

5-(4'-Dimethylamino-cyclohexylmethylidene)-1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene and its Dihydrochloride.

Heat a mixture of 5.8 g. of 5-hydroxy-5-(4'-Dimethylamino-cyclohexylmethyl)-1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene with 40 ml. of acetic acid saturated with hydrogen chloride and 5 ml. of acetic anhydride by the method of part A of Example 12, to yield 5-(4'-dimethylamino-cyclohexylmethylidene)-1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene dihydrochloride, m.p. = 212—214° C., which may further be treated as in part B of Example 12, to yield 5-(4'-dimethylamino-cyclohexylmethylidene)-1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene, m.p. = 95—97° C.

EXAMPLE 14.

5-(γ-Dimethylamino-propylidene)-1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene.

Reflux for 8 hours a mixture of 14 g. of the carbinol of Example 7, 160 ml. of glacial acetic acid and 50 ml. of concentrated hydrochloric acid. Concentrate to a residue in water, make alkaline, e.g. by addition of aqueous ammonia, and extract with chloroform. Concentrate the chloroform solution to a residue and distill, collecting that fraction boiling at 175—180° C./1 Torr.

IV. "UNSATURATED COMPOUNDS" HAVING A TWO-CARBON CHAIN.

EXAMPLE 15.

5-(β-Dimethylamino-ethylidene)-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene

A. To a stirred mixture of 13 g. zinc (20 mesh) (USS) and 33.4 g. of ethyl bromoacetate in 400 ml. of benzene-toluene (1:1), add dropwise a solution of 41.4 g. of 4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5-one. Heat for two hours on a steam bath, add 13 g. zinc and continue heating for four hours. Then cool, add 10% acetic acid and separate the layers. Extract the aqueous phase with benzene and combine the benzene fractions. Concentrate to a residue and distill in vacuo, obtaining 5-hydroxy-5-carbethoxymethyl-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene.

B. Dehydrate the product of Step A by heating at 90—100° C. 20 g. thereof with 100 ml. of acetic anhydride containing 1 to 2% sulfuric acid. After three hours, concentrate in vacuo, dilute with water, neutralize, and extract with ether. Concentrate to a residue and distill in vacuo to obtain 5-carbethoxy-methylidene-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene.

C. Reflux 15 g. of the product of Step B with a mixture of 15 g. potassium hydroxide, 50 ml. water and 150 ml. ethanol for six hours on a steam bath. Concentrate to a residue, add water and extract with ether. Neutralize the aqueous layer with acetic acid and allow the product to crystallize. Filter and recrystallize from aqueous methanol, obtaining 5-carboxymethylidene-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene.

D. Reflux 12 g. of the acid obtained by Step C with 50 ml. of thionylchloride. Concentrate in vacuo, add 50 ml. of benzene and evaporate to a residue. Take up in 150 ml. of benzene, and while stirring add a solution of 9 g. of dimethylamine in benzene. Stir and reflux for four hours and then pour into water. Make alkaline with sodium carbonate and extract with benzene. Concentrate in vacuo to obtain 5-dimethylcarboxamidomethylidene-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene. Purify by recrystallization from methanol.

E. Add an ether solution of 10 g. of the amide from Step D to a suspension of 3 g. of lithium-aluminum-hydride in 250 ml. of ether. Stir for two hours, add water, separate the layers and concentrate the ethereal layer to a residue, obtaining 5-dimethylamino-ethylidene-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene. Purify by distillation in vacuo.

All of the carbinols of formula IA described heretofore, when subjected to any of the dehydration methods of Examples 11 to 14, or obvious equivalents thereof, give rise to the corresponding exocyclically unsaturated products (IB). The procedure of Example 15 is used to prepare compounds of Formula IBa. Representative of the unsaturated compounds (IB) obtainable by these methods and their equivalents, are those listed below [wherein for the sake of brevity, the phrase "10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene" is written as "dihydro-heptene," while the 10,11-unsaturated analog is written as "heptene," e.g. the compound of Example 11 as "4-aza-5-(N-methyl-4-piperidylidene)-dihydro-heptene"]:

3-aza-5-(4-piperidylidene)-dihydroheptene, 3-aza-5-(N-benzyl-4-piperidylidene)-dihydroheptene, 3-aza-5-(N-methyl-4-piperidylidene)-dihydroheptene, 3-aza-5-(γ -dimethylamino-propylidene)-dihydroheptene, 3-aza-5-(γ -pyrrolidino-propylidene)-dihydroheptene, 3-aza-5-(4'-dimethylamino-cyclohexyl-methylidene)-dihydroheptene, 3-aza-5-(γ -methylamino-propylidene)-dihydroheptene, 3-aza-5-(γ -dimethylamino-butylidene)-dihydroheptene, 3-aza-5-(γ -diethylamino-propylidene)-dihydroheptene, 3-aza-5-[γ -(4-methylpiperazino)-propylidene]-dihydroheptene, 3-aza-5-[γ -(4- β -hydroxyethyl-piperazino)-propylidene]-dihydroheptene, 3-aza-5-[γ -(methyl-benzyl-amino)-propylidene]-dihydroheptene, 3-aza-5-(β -methyl- γ -dimethylamino-propylidene)-dihydroheptene, 3-aza-5-(β -methyl- γ -methylamino-propylidene)-dihydroheptene, 3-aza-5-(β -dimethylamino-ethylidene)-dihydroheptene, 3-aza-5-(β -pyrrolidino-ethylidene)-dihydroheptene, 3-aza-5-(β -dibenzylamino-ethylidene)-dihydroheptene, 3-aza-5-(4-piperidylidene)-heptene, 3-aza-5-(N-benzyl-4-piperidylidene)-heptene, 3-aza-5-(N-methyl-4-piperidylidene)-heptene, 3-aza-5-(γ -dimethylamino-propylidene)-heptene, 3-aza-5-(γ -pyrrolidino-propylidene)-heptene, 3-aza-5-(4'-dimethylamino-cyclohexylmethylidene)-heptene, 3-aza-5-(γ -methylamino-propylidene)-heptene, 3-aza-5-(γ -dimethylamino-butylidene)-heptene, 3-aza-5-(γ -diethylamino-propylidene)-heptene, 3-aza-5-[γ -(4-methyl-piperazino)-propylidene]-heptene, 3-aza-5-[γ -(4- β -hydroxyethyl-piperazino)-propylidene]-heptene, 3-aza-5-[γ -(methyl-benzyl-amino)-propylidene]-heptene, 3-aza-5-(β -methyl- γ -dimethylamino-propylidene)-heptene, 3-aza-5-(β -methyl- γ -methylamino-propylidene)-heptene, 3-aza-5-(β -dimethylamino-ethylidene)-heptene, 3-aza-5-(β -pyrrolidino-ethylidene)-heptene, 3-aza-5-(β -dibenzylamino-ethylidene)-heptene, and the 1-aza, 2-aza and 4-aza analogs of the foregoing, as well as their 7-chloro, 7-trifluoromethyl, 8-methyl-, 9-methyl, 8-chloro, 7-bromo-, 6-methoxy- and 7-methyl derivatives.

35 V. PREPARATION OF "SATURATED COMPOUNDS."

EXAMPLE 16.

5-(γ -Dimethylamino-propyl)-1-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene.

Hydrogenate in a Parr shaker a solution of 6.8 g. of the compound of Example 14 in 100 ml. of ethanol in the presence of 0.5 g. of platinum oxide under about 3.6 atmospheres pressure of hydrogen, until an equivalent quantity of hydrogen is absorbed, i.e. usually for about one hour. Filter and concentrate the filtrate to a residue and distill, collecting that fraction boiling at 165—170° C./1 Torr.

"Saturated compounds" of formula IC may also be obtained by direct reduction of the "carbinols" (IA), as per the following:

EXAMPLE 17.

5-(*p*-Dimethylamino-phenyl)-1-aza-dibenzo-[a,d]-cycloheptene.

To a solution of 6 g. of 5-hydroxy-5-(*p*-dimethylamino-phenyl)-1-aza-dibenzo-[a,d]-cycloheptene in 150 ml. of acetic acid, add 6 g. of phosphorus and 3 g. of iodine. Stir and reflux for 4 hours and filter while still hot. Pour the filtrate into water and neutralize the solution with aqueous ammonia to precipitate 5-(*p*-dimethylamino-phenyl)-1-aza-dibenzo-[a,d]-cycloheptene.

The method of Examples 1 is generally applicable to the preparation of those "saturated" compounds of Formula IC which are also saturated at the 10,11-position, since the catalytic hydrogenation will reduce the 10,11-double bond. The method of Example 17, namely P+I₂ reduction, generally will not reduce the 10,11-double bond. The method of Example 18 is also valuable for the preparation of 10,11-unsaturated compounds of formula IC.

EXAMPLE 18.

5-(β-Dimethylamino-ethyl)-4-aza-5H-dibenzo-[a,d]-cycloheptene.

Add 18.2 g. of 4-aza-5H-dibenzo-[a,d]-cycloheptene (obtainable by Example 5) to a solution of sodium amide (from 2.5 g. sodium metal) in 200 ml. of anhydrous ammonia. Stir for two hours and then add slowly 10.7 g. of dimethylamino-ethyl-chloride. After one hour displace the ammonia with ether. Concentrate to a residue and distill in vacuo to obtain the compound of this Example.

This method is applicable to the preparation of all the "saturated compounds" of formula IC, of the 10,11-dihydro as well as of the 10,11-unsaturated analogs. Representatives of compounds which may likewise be prepared by the methods of Examples 16 to 18 or by obvious equivalents thereof are set forth in the following listing with the abbreviated nomenclature employed as before: 1-aza-5-(4-piperidyl)-dihydroheptene, 1-aza-5-(N-benzyl-4-piperidyl)-dihydroheptene, 1-aza-5-(N-methyl-4-piperidyl)-dihydroheptene, 1-aza-5-(γ-pyrrolidino-propyl)-dihydroheptene, 1-aza-5-(4'-dimethylamino-cyclohexylmethyl)-dihydroheptene, 1-aza-5-(γ-methylamino-propyl)-dihydroheptene, 1-aza-5-(γ-dimethylamino-butyl)-dihydroheptene, 1-aza-5-(γ-diethylamino-propyl)-dihydroheptene, 1-aza-5-[γ-(4-methyl-piperazino)-propyl]-dihydroheptene, 1-aza-5-[γ-(4-β-hydroxyethyl-piperazino)-propyl]-dihydroheptene, 1-aza-5-[γ-(methyl-benzyl-amino)-propyl]-dihydroheptene, 1-aza-5-(β-methyl-γ-dimethylamino-propyl)-dihydroheptene, 1-aza-5-(β-methyl-γ-methylamino-propyl)-dihydroheptene, 1-aza-5-(β-dimethylamino-ethyl)-dihydroheptene, 1-aza-5-(β-pyrrolidino-ethyl)-dihydroheptene, 1-aza-5-(β-dibenzyl-amino-ethyl)-dihydroheptene, 1-aza-5-(4-piperidyl)-heptene, 1-aza-5-(N-benzyl-4-piperidyl)-heptene, 1-aza-5-(N-methyl-4-piperidyl)-heptene, 1-aza-5-(γ-dimethylamino-propyl)-heptene, 1-aza-5-(γ-pyrrolidino-propyl)-heptene, 1-aza-5-(4'-dimethylamino-cyclohexylmethyl)-heptene, 1-aza-5-(γ-methylamino-propyl)-heptene, 1-aza-5-(γ-dimethylamino-butyl)-heptene, 1-aza-5-(γ-diethylamino-propyl)-heptene, 1-aza-5-[γ-(4-methyl-piperazino)-propyl]-heptene, 1-aza-5-[γ-(4-β-hydroxyethyl-piperazino)-propyl]-heptene, 1-aza-5-[γ-(methyl-benzyl-amino)-propyl]-heptene, 1-aza-5-(β-methyl-γ-dimethylamino-propyl)-heptene, 1-aza-5-(β-methyl-γ-methylamino-propyl)-heptene, 1-aza-5-(β-dimethylamino-ethyl)-heptene, 1-aza-5-(β-pyrrolidino-ethyl)-heptene, 1-aza-5-(β-dibenzylamino-ethyl)-heptene, and the 2-aza, 3-aza and 4-aza analogs of the foregoing, as well as their 7-chloro, 7-trifluoromethyl, 8-methyl-, 9-methyl-, 7-bromo-, 6-methoxy- and 7-methyl derivatives.

VI. PREPARATION OF PHARMACEUTICAL SALTS.

EXAMPLE 19.

5-(N-Methyl-4-piperidylidene)-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene Dimaleate.

To a solution containing 4.3 g. of 5-(N-methyl-4-piperidylidene)-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene in 55 ml. of ethyl acetate, add a solution of 3.45 g. of maleic acid dissolved in ethyl acetate. Filter the resulting precipitate and recrystallize the desired product from an ethyl acetate-methanol mixture, to yield 5-(N-methyl-4-piperidylidene)-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene dimaleate; m.p. = 152—154° C.

VII. PHARMACEUTICAL FORMULATIONS.

EXAMPLE 20.

A syrup containing 25 mg. active ingredient per teaspoonful may be prepared from the following ingredients, with amounts as indicated.

50	5-(N-Methyl-4-piperidylidene)-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene	5.0 g.	50
	Citric acid	5.0 g.	
	Sodium citrate	1.0 g.	
	Sodium benzoate	1.0 g.	
	Sweet orange peel tincture	50.0 ml.	
55	Sucrose	800.0 g.	55
	Purified Water	q.s. ad 1.0 liter	

To prepare the syrup from the above ingredients, dissolve successively the 5-(N-methyl-4-piperidylidene)-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene, the citric acid, the sodium citrate, the sodium benzoate and the sucrose

in sufficient water to make approximately 900 ml. Add the sweet orange peel tincture and sufficient water to make the product measure one liter. Agitate until uniform. Filter, using an appropriate filter aid if necessary, until the product is clear.

EXAMPLE 21.

An injectable containing 10 mg. active ingredient per ml. may be prepared from the following ingredients, with amounts as indicated:

5-(N-Methyl-4-piperidylidene)-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene	10.0 g.
Sodium chloride, U.S.P.	9.0 g.
Methyl <i>p</i> -hydroxy-benzoate	1.8 g.
Propyl <i>p</i> -hydroxy-benzoate	0.2 g.
Benzyl alcohol, reagent grade	9.0 g.
Water for injection	q.s.ad 1.0 liter

To prepare the injectable from the above ingredients, dissolve the methyl and the propyl *p*-hydroxy-benzoate in the benzyl alcohol with the aid of heat and agitation. Add this solution to a volume of water for injection equal to 90% of the desired final volume and dissolve with agitation. Add and dissolve the sodium chloride. Add and dissolve the 5-(N-methyl-4-piperidylidene)-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene. Add water for injection q.s. to final volume. Filter aseptically through an appropriate sterile filter. Fill aseptically into 10 ml. rubber stoppered vials.

EXAMPLE 22.

Tablets each containing 25 mg. active ingredient may be prepared from the following ingredients, with amounts as indicated:

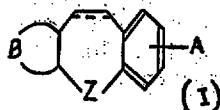
5-(N-Methyl-4-piperidylidene)-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene	250.0 g.
Lactose	1000.0 g.
Corn starch	680.0 g.
Corn starch as 10% paste	50.0 g.
Magnesium stearate	20.0 g.

To prepare tablets from the above ingredients, mix the 5-(N-methyl-4-piperidylidene)-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene, the lactose and 600 g. of the corn starch, and pass through a pulverizing mill if necessary. Granulate the so-obtained mixture with the starch paste, adding additional water if necessary to make a damp granulation. Pass the granulation through an impact mill to produce 8—12 mesh (USS) granules. Spread the granulation on trays and dry in a draft-oven at 35—40° C. Reduce the dried granulation to 16—24 mesh size (USS). Blend the foregoing 1900 grams of "wet" granulation with the remaining 80.0 gm. of corn-starch and with the magnesium stearate until a uniform mixture is obtained. Compress to 200 mg. tablets.

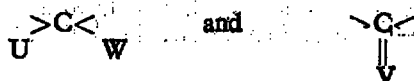
In each of the formulations of Examples 20 to 22 has been mentioned as the active ingredient the compound, 5-(N-methyl-4-piperidylidene)-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene. It is to be understood that this is but a representative of the active compounds of this invention, which may be replaced by one of its pharmaceutically acceptable salts or by another active compound in accordance with general formula I (in its free base or in salt form). The vehicles of the formulations may also be modified in various manners which are obvious from the art.

WHAT WE CLAIM IS:—

1. Aza-dibenzo-[a,d]-cycloheptenes of the general formula



wherein the dotted line represents an optional double bond; A represents hydrogen or one of the substituents halogen, trifluoromethyl, alkoxy, alkyl having up to 12 carbon atoms, hydroxy and acyloxy, attached to one or more of the positions 6, 7, 8 and 9; B represents, together with the carbon atoms to which it is attached, a pyridine ring; and Z represents one of the groupings





EXAMPLE 21.

5-(N-Methyl-4-piperidylidene)-4-aza-10,11-dihydro-

5H-dibenzo-[a,d]-cycloheptene

10.0 g.

Sodium chloride, U.S.P.

9.0 g.

Methyl *p*-hydroxy-benzoate

1.8 g.

Propyl *p*-hydroxy-benzoate

0.2 g.

Benzyl alcohol, reagent grade

9.0 g.

Water for injection

q.s.ad 1.0 liter

To prepare the injectable from the above ingredients, dissolve the methyl and the propyl *p*-hydroxy-benzoate in the benzyl alcohol with the aid of heat and agitation. Add this solution to a volume of water for injection equal to 90% of the desired final volume and dissolve with agitation. Add and dissolve the sodium chloride. Add and dissolve the 5-(N-methyl-4-piperidylidene)-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene. Add water for injection q.s. to final volume. Filter aseptically through an appropriate sterile filter. Fill aseptically into 10-ml. rubber stoppered vials.

EXAMPLE 22.

Tablets each containing 25 mg. active ingredient may be prepared from the following ingredients, with amounts as indicated:

5-(N-Methyl-4-piperidylidene)-4-aza-10,11-dihydro-

5-H-dibenzo-[a,d]-cycloheptene

250.0 g.

Lactose

1000.0 g.

Corn starch

680.0 g.

Corn starch as 10% paste

50.0 g.

Magnesium stearate

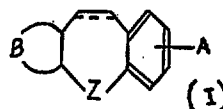
20.0 g.

To prepare tablets from the above ingredients, mix the 5-(N-methyl-4-piperidylidene)-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene, the lactose and 600 g. of the corn starch, and pass through a pulverizing mill if necessary. Granulate the so-obtained mixture with the starch paste, adding additional water if necessary to make a damp granulation. Pass the granulation through an impact mill to produce 8—12 mesh (USS) granules. Spread the granulation on trays and dry in a draft-oven at 35—40° C. Reduce the dried granulation to 16—24 mesh size (USS). Blend the foregoing 1900 grams of "wet" granulation with the remaining 80.0 gm. of corn-starch and with the magnesium stearate until a uniform mixture is obtained. Compress to 200 mg. tablets.

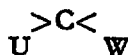
In each of the formulations of Examples 20 to 22 has been mentioned as the active ingredient the compound, 5-(N-methyl-4-piperidylidene)-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene. It is to be understood that this is but a representative of the active compounds of this invention, which may be replaced by one of its pharmaceutically acceptable salts or by another active compound in accordance with general formula I (in its free base or in salt form). The vehicles of the formulations may also be modified in various manners which are obvious from the art.

WHAT WE CLAIM IS:—

1. Aza-dibenzo-[a,d]-cycloheptenes of the general formula



wherein the dotted line represents an optional double bond; A represents hydrogen or one of the substituents halogen, trifluoromethyl, alkoxy, alkyl having up to 12 carbon atoms, hydroxy and acyloxy, attached to one or more of the positions 6, 7, 8 and 9; B represents, together with the carbon atoms to which it is attached, a pyridine ring; and Z represents one of the groupings



and





in which groupings either U and W are both hydrogen or U is a univalent grouping containing an amino group the nitrogen atom of which is separated from C—5 of the tricyclic nucleus by at least two carbon atoms and W is H or OH; and V is oxygen or a divalent grouping containing an amino group the nitrogen atom of which is separated from C—5 of the tricyclic nucleus by at least two carbon atoms.

2. Aza-dibenzo-[a,d]-cycloheptenes claimed in claim 1 in which A represents either hydrogen at positions 6,7,8 and 9 or one of the substituents chlorine, bromine, methyl, ethyl, trifluoromethyl, methoxy, ethoxy and hydroxy at position 7 and/or 8 and hydrogen at the remainder of positions 6,7,8 and 9.

3. Aza-dibenzo-[a,d]-cycloheptenes claimed in claim 1 or 2 in which B represents,



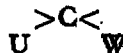
or



4. Aza-dibenzo-[a,d]-cycloheptenes claimed in claim 1 or 2 in which B represents



5. Aza-dibenzo-[a,d]-cycloheptenes claimed in any of the preceding claims in which either Z represents the grouping



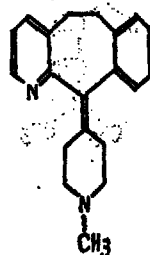
in which W represents H or OH and U represents a univalent grouping containing an amino group the nitrogen atom of which is separated from C—5 of the tricyclic nucleus by at least two carbon atoms; or Z represents the grouping



in which V represents a divalent grouping containing an amino group the nitrogen atom of which is separated from C—5 of the tricyclic nucleus by at least two carbon atoms.

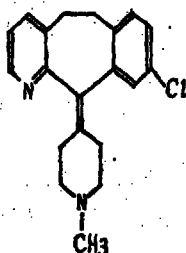
6. Aza-dibenzo-[a,d]-cycloheptenes claimed in claim 5 in which either U represents 3- or 4-piperidyl and W represents H or OH or V represents 3- or 4-piperidylidene.

7. The compound of the formula

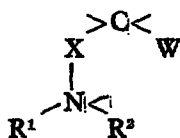




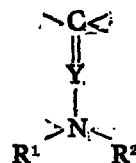
8. The compound of the formula



9. Aza-dibenzo-[a,d]-cycloheptenes claimed in claim 5 in which Z represents either of the groupings

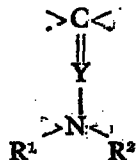
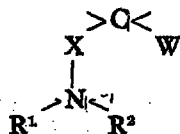


and



W representing H or OH, X and Y representing hydrocarbon residues having from 2 to 9 carbon atoms, and R¹ and R² independently representing hydrogen, alkyl having up to 12 carbon atoms, hydroxyalkyl having up to 12 carbon atoms, or benzyl or together representing, with the nitrogen atom to which they are attached, a five- or six-membered heterocycle of which one of the ring members is the aforesaid nitrogen atom, another is C, O or N and the remainder are all carbon atoms.

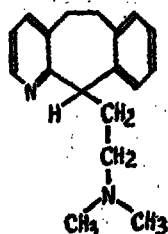
10. Aza-dibenzo-[a,d]-cycloheptene claimed in claim 9 in which Z represents either of the groupings



W representing H or OH, X representing ethyl or propyl, Y representing ethylidene or propylidene and R¹ and R² each representing alkyl having up to 12 carbon atoms.

11. Aza-dibenzo-[a,d]-cycloheptenes claimed in claim 9 in which R¹ and R² together with the N atom to which they are attached represent pyrrolidino, piperidino, morpholino, piperazino or lower-alkyl-, hydroxy-lower-alkyl-, lower-alkanoyloxy-alkyl- or hydroxy-lower-alkoxy-alkyl-substituted derivatives thereof.

12. The compound of the formula

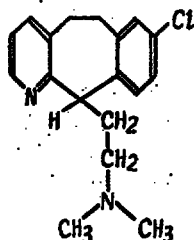




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13. The compound of the formula



14. 5-[gamma-(4-{beta-Hydroxyethyl}-piperazino)-propylidene]-4-aza-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene.

15. Pharmaceutically acceptable acid addition salts of aza-dibenzo-[a,d]-cycloheptene claimed in any of claims 5 to 14.

16. Aza-dibenzo-[a,d]-cycloheptenes claimed in any of claims 1 to 4 in which Z represents $>\text{CH}_2$ or $>\text{C}=\text{O}$.

17. Aza-dibenzo-[a,d]-cycloheptenes claimed in claim 16 in which A represents hydrogen at each of positions 6, 7, 8 and 9.

18. Aza-dibenzo-[a,d]-cycloheptenes claimed in claim 16 in which A represents chlorine at positions 7 or 8 and hydrogen at the others of positions 6, 7, 8 and 9.

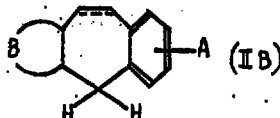
19. 4-Aza-5H-7-chloro-10,11-dihydro-dibenzo-[a,d]-cycloheptene-5-one.

20. 4-Aza-5H-7-chloro-10,11-dihydro-dibenzo-[a,d]-cycloheptene.

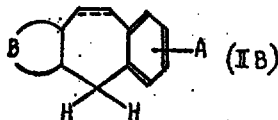
21. A process for the production of a compound of the formula



wherein the dotted line, A and B have the same meaning as in claim 1 and Z has the same meaning as in claim 5, which comprises reacting a compound of the formula:

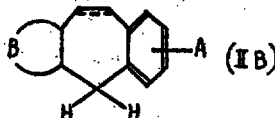


or a reactive derivative thereof (as hereinbefore defined) wherein the dotted line, A and B have the above meaning, with a reactive derivative (as hereinbefore defined) of a compound of the formula VH_2 wherein V has the same meaning as in claim 5 or reacting a reactive derivative (as hereinbefore defined) of a compound of the formula



wherein the dotted line, A and B have the above meaning, with a compound of the formula VH_2 , wherein V has the above meaning, so as to replace the grouping at position C-5 of the aza-dibenzo-cycloheptene compound by the grouping Z or a grouping convertible into the grouping Z by one or more of the steps of hydrolysis, dehydration, reduction and dehydrogenation, and if necessary subjecting the product thus produced to any one or more of the steps of hydrolysis, dehydration, reduction and dehydrogenation required to convert it into the desired final product.

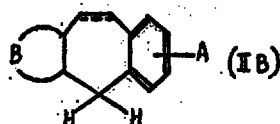
22. A process according to claim 21 wherein a reactive derivative (as hereinbefore defined) of a compound of the formula





is reacted with a reactive derivative (as hereinbefore defined) of a compound of the formula VH_2 .

23. A process according to claim 22 wherein the reactive derivative of a compound of formula



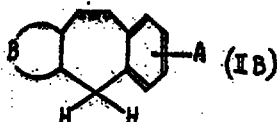
is an organo-metallic compound.

24. A process according to claim 23 wherein the organo-metallic compound is an organo-Mg-Halogen compound.

25. A process according to claim 23 wherein the organo-metallic compound is an organo-alkali metal compound.

26. A process according to claim 25 wherein the organo-metallic compound is an organo-sodium compound.

27. A process according to claim 22 wherein the reactive derivative of a compound of formula



is the 5-keto derivative.

28. A process according to any of claims 23 to 26 wherein the reactive derivative of a compound of formula VH_2 is $V=O$.

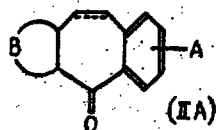
29. A process according to claim 25 or 26 wherein the reactive derivative of a compound of formula VH_2 is $V<\overset{H}{\text{Halogen}}$.

30. A process according to claim 27 wherein the reactive derivative of a compound of formula VH_2 is an organo-metallic compound.

31. A process according to claim 30 wherein the organo-metallic compound has the formula $V<\overset{H}{\text{Mg Halogen}}$.

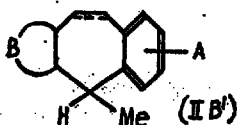
32. A process according to claim 30 wherein the organo-metallic compound is an organo-alkali-metal compound.

33. A process according to any of claims 30 to 32 which comprises reacting a compound of the formula



with a compound of the formula $U-Me$, the dotted line, A and B being as defined in claim 1, U being as defined in claim 5 except that the amino group of U is separated from Me by at least 3 carbon atoms and that any H attached to the N of the amino group of U is protected by an easily removable group, and Me representing the metal containing part of an organo-metallic compound, for example $-MgHalogen$, $Zn/2$ or an alkali metal atom, and hydrolysing any organo-metallic compound thus produced.

34. A process according to claim 28 comprising reacting a compound of the formula



with a compound of the formula $V=O$, the dotted line A and B being as defined in claim 1, V being as defined in claim 5 and Me being as defined in claim 33.



35. A process according to claim 34 wherein B represents one of the groupings

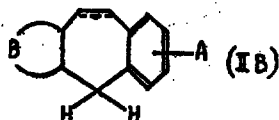


and



and Me represents a lithium atom.

36. A process according to claim 21 wherein a compound of the formula



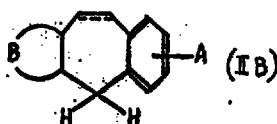
is reacted with a reactive derivative (as hereinbefore defined) of a compound of the formula VH_2 .

37. A process according to claim 36 wherein the reactive derivative of a compound of the formula VH_2 is a compound of the formula $V=O$ or of the formula Halogen.

$V <$

H

38. A process according to claim 37 which comprises reacting a compound of the formula



with a compound of the formula U-Halogen in the presence of a basic condensation agent, the dotted line, A and B being as defined in claim 1 and U being as defined in claim 5.

39. A process according to any of claims 21 to 38 followed by one or more of the following steps:— dehydration of a 5-hydroxy compound to a corresponding 5(1')-unsaturated compound, reduction of a 5-hydroxy compound to a corresponding 10(11)- and 5(1')-saturated compound, and hydrogenation of a 5(1')-unsaturated compound to a corresponding 10(11)- and 5(1')-saturated compound.

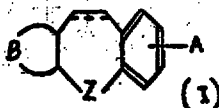
40. A process according to any of claims 21 to 39 followed by one or more of the following steps:

- Hydrogenation or dehydrogenation in position 10(11);
- Reductive cleavage of one or two benzyl groups attached to the nitrogen atom of the amino group which forms part of Z;
- Transformation into an acid addition salt by reaction with an acid or a reactive derivative thereof.

41. A process for the production of a compound claimed in claim 5 from a compound claimed in claim 16 substantially as hereinbefore described and exemplified.

42. A compound claimed in claim 5 when produced from a compound claimed in claim 16.

43. A process for the production of a compound of formula I

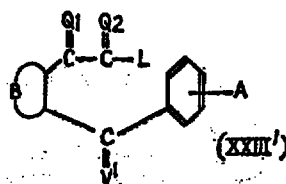


wherein the dotted line, A and B have the same meaning as in claim 1 and Z has the



same meaning as in claim 5, which includes the steps of subjecting to intramolecular condensation a compound which differs from a compound of formula I only in that the cycloheptene ring is broken at one point only which is adjacent to the 5-position or the 10-position or the 11-position, and that at least one of the carbon atoms adjacent to the break bears a reactive group (as hereinbefore defined), provided that, when the break in the cycloheptene ring is between the 11-position and the pyridine ring or between the 10-position and the benzene ring, the carbon atom at the 10-position or the carbon atom at the 11-position may bear a =O substituent to promote the reactivity of the reactive group towards formation of a carbon-carbon bond, so as to cyclise the compound to form the cycloheptene ring, and, when a 10- or 11-carbonyl group is present, reducing the carbonyl group to (H,H).

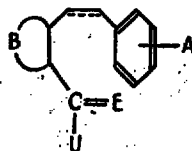
44. A process according to claim 43, in which a compound of the formula



wherein V' is V or $\begin{smallmatrix} U \\ < \\ H \end{smallmatrix}$, A and B are as defined in claim 1 and U and V are as defined

in Claim 5, and wherein either L is a free hydroxy group, halogen, or a hydroxy group esterified by a sulphonic or carboxylic acid, one of Q₁ and Q₂ is (H,H) and the other of Q₁ and Q₂ is (H,H) or O, or L and Q₂ together are nitrilo and Q₁ is (H,H), is subjected to intramolecular condensation, and when Q₁ or Q₂ is O the keto group represented thereby is reduced to (H,H).

45. A process according to claim 43 in which a compound of the formula



wherein the dotted line, A and B have the same meaning as in claim 1, U has the same meaning as in claim 5 and E represents O or NH, is subjected to intramolecular condensation.

46. A process according to any of claims 43 to 45 followed by hydrogenation of a 5(1') unsaturated compound to a corresponding 10(11) and 5(1') saturated compound.

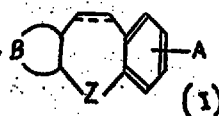
47. A process according to any of claims 43 to 46 followed by one or more of the following steps:

- Hydrogenation or dehydrogenation in position 10(11);
- Reductive cleavage of one or both benzyl groups attached to the N atom of the amino group which forms part of Z;
- Transformation into an acid addition salt by reaction with an acid or reactive derivative thereof.

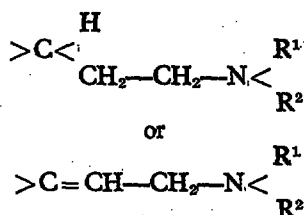
48. A process according to any of claims 43 to 47 substantially as hereinbefore described and exemplified.

49. A compound claimed in claim 5 when produced by a process claimed in any of claims 43 to 48.

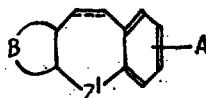
50. A process for the production of a compound of the formula



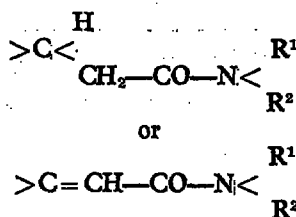
wherein Z represents



the dotted line, A and B have the same meaning as in claim 1 and R¹ and R² have the same meaning as in claim 9, in which a compound of the formula



wherein Z' represents



and the dotted line, A, B, R¹ and R² have the above meanings is reduced at the keto group in Z'.

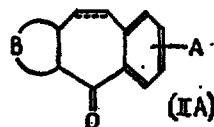
51. A process according to claim 50 followed by one or more of the following steps

- a) Hydrogenation of a 10(11)- or a 5(1')- and 10(11)-unsaturated compound to a corresponding 10(11)- and 5(1')-saturated compound;
- b) Dehydrogenation of a 10(11)-saturated compound;
- c) Reductive cleavage of one or two benzyl groups attached to the N atom of the amino group;
- d) Transformation into an acid addition salt by reaction with an acid, or a reactive derivative thereof.

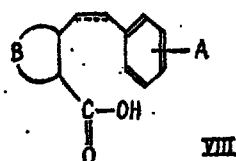
52. A process, according to claim 50 or 51 substantially as hereinbefore described and exemplified.

53. A compound claimed in claim 5 when produced by a process according to any of claims 50 to 52.

54. A process for the production of a compound of the formula



wherein the dotted line, A and B are as defined in claim 1, in which a styryl- or phenethyl-pyridine-carboxylic acid of the formula



wherein the dotted line, A and B have the above meanings, or a functional derivative thereof, is subjected to intramolecular cyclisation.

55. A process according to claim 54 wherein the functional derivative is the acid halide, ester, amide, nitrile or isomeric lactone.



56. A process according to claim 54 or 55 wherein a styryl or phenethyl-pyridine-carboxylic acid, or nitrile or isomeric lactone is treated with a dehydrating agent.

57. A process according to claim 55 wherein a styryl- or phenethyl-pyridine-carboxylic acid halide is treated with a Friedel Crafts catalyst, for example aluminium chloride.

58. A process according to any of claims 54 to 57 followed by one or both of the following steps

a) Hydrogenation or dehydrogenation in position 10(11);

b) Reduction of the 5-keto group to (H₂H).

59. A process according to any of claims 54 to 58 substantially as hereinbefore described and exemplified.

60. A compound claimed in claim 16 when produced by a process claimed in any of claims 54 to 59.

61. A pharmaceutical composition containing a compound claimed in any of claims 5 to 15, 42, 49 and 53 and a pharmaceutical carrier.

MATHYS & SQUIRE,

Chartered Patent Agents,

Staple House, 51/52, Chancery Lane, London, W.C.2,

Agents for the Applicants.

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