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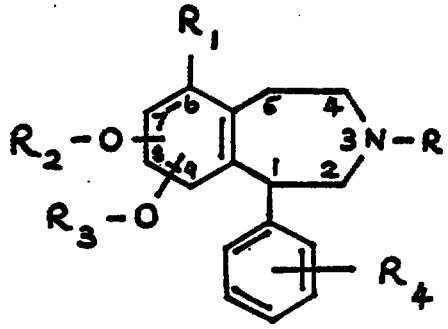
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(71) We, SMITHKLINE CORPORATION, of 1500 Spring Garden Street, Philadelphia, Pennsylvania 19101, United States of America, a corporation organized under the laws of the Commonwealth of Pennsylvania, one of the United States of America, do hereby declare 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 concerns substituted 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepines which can be used as diuretic and/or cardiovascular agents due to their peripheral dopaminergic activity. The invention also provides a process for their preparation and compositions containing them.

According to the present invention there are provided compounds of the formula



I

in which R is hydrogen, benzyl, lower alkanoyl or haloalkanoyl of from 1—5 carbons, for example formyl, acetyl or trifluoroacetyl, lower alkyl of 1—5 carbon atoms, hydroxyethyl, lower alkenyl of 3—5 carbon atoms, propargyl, phenethyl, furoyl, thenoyl, furylmethyl, thienylmethyl, benzoyl or phenacyl, the phenyl, furyl or thienyl groups thereof being optionally substituted for example by methyl, methoxy, hydroxy, acetoxy, halo or trifluoromethyl;

R_1 is halo or trifluoromethyl;

R_2 and R_3, which are the same or different, are each hydrogen, lower alkyl of 1—5 carbon atoms, lower alkanoyl of 2—5 carbon atoms or, when taken together, methylene or ethylene; and

R_4 is H or from 1 to 3 substituents selected from the group of trifluoromethyl, halo, for example F, Cl or Br, methyl, ethyl, methoxy, ethoxy, acetoxy and hydroxy.

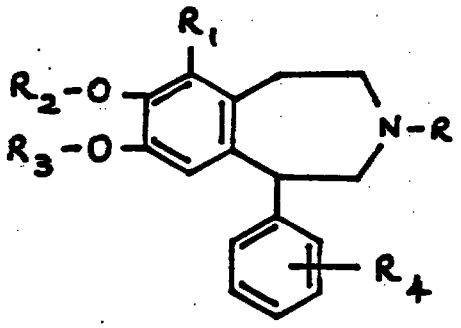
R_2O and R_3O are preferably hydroxy radicals at the 7- and 8-positions for maximal biological activity.

Compounds of the invention have also demonstrated activity in animal tests

which are known to predict anti-Parkinsonism activity by means of activity at the central dopamine receptors. Generally speaking therefore they have potent peripheral or central dopaminergic activity.

A subgeneric group of compounds within the above illustrative generic group are those of Formula I in which R is hydrogen or methyl; and R_2 and R_3 are the same and are hydrogen, methyl or acetyl with R_2O and R_3O being in the 7- and 8-positions respectively; and R_4 is hydrogen, acetoxy or hydroxy, preferably in the para-position.

Individual compounds of note are those of Formula II



II

in which R is hydrogen or methyl; R_1 is Cl or Br; R_2 and R_3 are the same and are hydrogen or acetyl; and R_4 is hydrogen, *p*-hydroxy or *p*-acetoxy.

Particularly active compounds are those of Formula II in which:

(1) R_1 is chloro, and R_2, R_3 and R_4 are all hydrogen;

(2) R_1 is chloro, R_2, R_3 and R_4 are all hydrogen, and R is methyl, which is a very potent central dopaminergic agent indicating, for example, anti-Parkinsonism activity;

(3) R_1 is chloro, R, R_2 and R_3 are all hydrogen, and R_4 is *p*-hydroxy, which shows potent and specific peripheral dopaminergic activity indicating cardiovascular activity; and

(4) R_1 is chloro, R is hydrogen, and R_2, R_3 and R_4 are all acetoxy with R_4 being para.

In another class of compounds of the invention, *R* is allyl.

The compounds in which R_2 and R_3 together form an alkylene chain, such as the methylenedioxy-containing compounds at the 7,8-positions, are of primary interest as intermediates, as are the N-acyl derivatives. Methylenedioxy-3-benzazepines in another series are reported in U.S. Patent Specification No. 3,795,683.

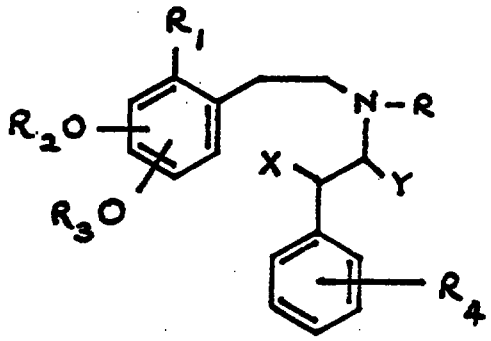
Although reference is made herein to the free bases of formula I it should be appreciated that the present invention includes pharmaceutically acceptable acid addition salts of the free bases, and reference to the free bases includes reference to such salts. Such acid addition salts can be prepared by methods known to the art and be formed with both inorganic or organic acids, for example with maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric or nitric acids. Similarly the invention includes the quarternary salts of the compounds of Formula I and it includes those prepared from organic halides such as methyl iodide, ethyl iodide or benzyl chloride.

Certain 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepines have been described in U.S. Patent Specifications 3,393,192 and 4,011,319; British Patent Specification 1,118,688; and Swiss Patent Specification 555,831, including general methods of preparation. However these patent specifications do not describe benz-trisubstituted compounds, nor 6-substituted compounds of any kind, and no advantage to 6-halo substitution in the structures. The 8,9-disubstituted compounds are relatively less active biologically than are the 7,8-disubstituted compounds which are an important subgeneric group of this invention as described above.

The compounds of Formula I can exist as diastereoisomers which can be resolved into *d,l* optical isomers. Resolution of the optical isomers can be conveniently accomplished by fractional crystallization of their salts with optically

active acids from appropriate solvents. Unless otherwise specified herein or in the claims, it is intended to include all isomers, whether separated or mixtures thereof. Where isomers are separated, the desired pharmacological activity will usually predominate in one of the isomers.

The compounds of Formula I in which R is hydrogen are generally prepared from intermediates of the formula:



III

(in which X is hydroxyl or its functional equivalent; Y is H_2 or =O; R, R_1 and R_4 are as hereinbefore defined; and R_2 and R_3, which are the same or different, are lower alkyl of 1—5 carbons or together represent methylene or ethylene), some of which are described and claimed in British Patent Application 20951/80), (Serial No. 1,595,503), by intramolecular cyclization effected by reaction with a cyclizing agent such as a strong acid, for example sulfuric acid, sulfuric acid in trifluoroacetic acid, polyphosphoric acid, polyphosphoric ester, methanesulfonic acid in methylene chloride, or hydrobromic acid or a Lewis acid such as boron trifluoride, aluminum chloride or stannic chloride which generates the desired carbonium ion from the substituent X. When Y is =O, the product will be reduced to convert the group =O to H_2. As will be appreciated some of the substituents R, R_1, R_2, R_3 and R_4 will react under the conditions of the cyclization reaction. For example carrying out the cyclization in 48% hydrobromic acid when R_2 or R_3 are methyl or R_4 is methoxy splits the ether links to give the corresponding cyclised hydroxy compounds. The starting compounds of formula III and the cyclisation conditions used should therefore be selected with this in mind.

Mixed alkoxy-substituted compounds can be prepared by selecting the phenethylamine starting material. To obtain compounds of Formula I wherein R_2 and R_3 are both hydrogen, cyclization of the corresponding methoxy substituted intermediates can be carried out with 48% hydrobromic acid at reflux temperature for from two to four hours so that demethylation of the methoxy groups also occurs, as described hereinbefore.

The primary phenethylamines which can be used as starting materials to prepare the compounds of Formula III are either known or can be prepared by methods described in U.S. Patent Specification No. 3,211,792, Chem. Abst. 80,95398, U.S. Patent Specification 3,869,474, U.S. Patent Specification 3,804,839 or in the illustrative Examples herein.

The compounds of Formula I R is hydrogen, can in particular be prepared from 1 - phenyl - 2 - oxo - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine intermediates which can be obtained by heating an appropriate phenylalkylamine with an ester of mandelic acid to give the amine of Formula III where Y is =O. The latter can then be cyclized as described above to form the 2-oxobenzazepine intermediates which can be chemically reduced by standard amide reducing agents, for example with borane, diborane, lithium aluminum hydride or sodium bis (2-methoxyethoxy)aluminum hydride, to the desired 1-phenyl-3-benzazepine compounds of Formula I.

The compounds of Formula I in which R_1 is bromo and R_2, R_3, R_4 and R contain only chemically inert groups can surprisingly be prepared in excellent yields by direct bromination at the 6-position of the corresponding 6-unsubstituted compounds. This reaction is carried out most conveniently using about two mole equivalents of bromine in a suitable solvent such as acetic acid at about room or ambient temperature. Yields of the compound of Formula I in which R_1 is bromo, R_2O— and R_3O— are 7,8-dimethoxy, and R and R_1 are both hydrogen of 70—85% have been obtained. The product separates from the bromination mixture as a

complex with one mole of bromine. The complexed bromine is eliminated easily by treatment with methanol/acetone.

The 6-bromo containing compound can optionally serve as an intermediate in a number of ways, for example for preparing the 6-chloro or 6-iodo congeners, as described in the Examples. The 6-bromo compound is also useful for preparing 6-lithium or Grignard intermediates. These can be reacted with a number of conventional reactants to introduce 6-substituents, for example with iodine, halogenating agents, i.e. hexachloroethane chlorine, N-chlorosuccinumide and others to introduce halo substituents. In effect this is a halogen-halogen interchange via a metal substituent.

To prepare the compounds of Formula I where R is hydroxyethyl, lower alkyl or alkenyl, the corresponding benzazepines, wherein R is hydrogen can be alkylated by standard methods with ethylene oxide, a reactive lower alkyl halide, for example the bromide or chloride or a reactive alkenyl halide, for example allyl bromide or chloride. To obtain compounds of Formula I where R_2 and/or R_3 are hydrogen, reaction with the alkylating agent is advantageously carried out on the corresponding methoxy-substituted benzazepines in an inert solvent, for example methanol or acetone, preferably at reflux temperature and in the presence of a basic condensing agent, for example potassium hydroxide or carbonate. Reaction of the resulting product with, for example, boron tribromide, hydrobromic acid, boron trichloride or other ether splitting agents gives hydroxy-substituted benzazepines of Formula I.

The compounds of Formula I where R is methyl are conveniently prepared from the corresponding methoxy-substituted benzazepines wherein R is hydrogen by reaction with formic acid/formaldehyde. Reaction of the resulting product with boron tribromide gives the corresponding hydroxy-substituted benzazepines.

To prepare the compounds of Formula I wherein R_1 or R_2 is alkanoyl, the corresponding 3 - benzyl - di - hydroxy - 3 - benzazepine (obtained by N-alkylation of the hydroxybenzazepine with benzyl bromide in the presence of potassium carbonate) can be reacted with the appropriate alkanoic acid anhydride or chloride, for example acetic anhydride, and the resulting alkanoyloxy-substituted benzazepine then be hydrogenated in the presence of palladium-on-carbon to remove the protective benzyl group. The dialkanoyloxy derivatives, for example the important 7,8-diacetoxy compounds, can also be prepared by direct O-acylation of the 7 - halo - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide in trifluoroacetic acid at ambient temperature with the anhydride or halide. The N- or 3-lower alkanoyl congeners in the dihydroxy series are conveniently prepared by N-acylating the corresponding methylenedioxy derivative followed by splitting the protective methylenedioxy group. Also direct N-alkanoylation of the dihydroxy compounds is possible under controlled conditions and quantities of reactants, as known to the art. As noted in the illustrative Examples any O-acylation may necessitate a mild hydrolysis treatment.

The intermediates of Formula III above are conveniently prepared by heating equimolar amounts of a styrene oxide with a 3,4-dialkoxy-phenethylamine which is either known or can be prepared by methods known to the art, each appropriately substituted, either alone or in an inert organic solvent, for example tetrahydrofuran. Preferably, the heating is effected on a steam bath or at reflux temperature for from 12 to 24 hours. The required styrene oxide is conveniently prepared by reaction of the ylide derivative from sodium hydride and trimethyl-sulfonium iodide with the appropriately-substituted benzaldehyde.

The active dopaminergic compounds of this invention stimulate peripheral dopamine receptors, for example they increase renal blood flow and have as an end result hypotensive activity. This renal vasodilator activity of the benzazepine compounds of Formula I is measured in an anesthetized dog. In this pharmacological procedure, a test compound is administered at progressively increasing (3-fold) infusion rates beginning at 0.1 mcg/kg/min up to 810 mcg/kg/min for 5 minutes each to anesthetized normotensive dogs, and the following parameters are measured: renal artery blood flow, iliac artery blood flow arterial blood pressure and heart rate. Results are reported as a percent change, increase or decrease, at time of peak response (from pre-drug controls), and for a significant effect renal blood flow (increase) and renal vascular resistance (decrease) should be approximately 10% or greater. The effect on renal vascular resistance can be calculated from any change in renal blood flow and arterial blood pressure. To confirm the mechanism of action, representative active renal

vasodilator compounds are checked for blockage by bulbocapnine which is known to be a specific blocker of renal dopamine receptors. Representative advantageous compounds of Formula I, 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine substituted at the 6-position by chloro or bromo, tested by i.v. infusion as described above produced an ED_{15} of 3.5 and 22 (9) mcg/kg respectively with little direct effect on systemic blood pressure in normotensive animals. ED_{15} therefore is the cumulative dose by infusion which produces a 15% decrease in renal vascular resistance

$$(R=\frac{\text{B.P. in mm/Hg}}{\text{B.F. ml/min}}).$$

As a renal vasodilator in the anesthetized dog this 6-chloro compound was 10 times more efficacious than its 6-deschloro congener. Another very active compound, 6 - chloro - 7,8 - dihydroxy - 1 - *p* - hydroxyphenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine gave a 26% decrease in renal resistance and a 29% increase in renal blood flow at a cumulative dose of 30 mcg/kg.

The compounds of this invention unexpectedly also cause a separation of side effects in dogs such as those caused by pressor reactions due to norepinephrine compared with the ED_{15} cardiovascular dose as described above. Here the above 6-chloro and 6-bromo-7,8-dihydroxy compounds have a separation ratio of 1233 and >1388 respectively compared with their deshalo congener (47).

In addition to the renal vasodilator activity via a dopaminergic effect, certain benzazepine compounds of Formula I produce weak diuretic activity. Such diuretic activity is measured in the standard saline-loaded rat procedure. A test compound is administered i.p. at doses of from 10 to 40 mg/kg and the parameters measured are urine volume (hourly for three hours) plus sodium and potassium ion concentrations. Also conventional diuretic tests in the dog may be used. 6 - Chloro - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine tested in the phosphate mannitol dog produced a significant increase in renal plasma flow and natriuresis at a dose as low and 5 and 10 micrograms, μg/kg/min i.v. Similar results were obtained at oral doses of 10 mg/kg (rena-blood flow only). The 6 - chloro - 7,8 - diacetoxy congener has better activity after oral absorption than does its 7,8-dihydroxy parent.

The benzazepine compounds of Formula I also have anti-Parkinsonism activity due to central dopaminergic actiity as demonstrated by employing a modified standard animal pharmacological test procedure reported by Ungerstedt *et al.*, in *Brain Research* 24, 1970, 485—493. This procedure is based on a drug-induced rotation of rats having extensive unilaterial lesions of the substantia nigra. Briefly, the test comprises the quantative recording of rotational behavior in rats in which 6-hydroxydopamine lesions of the nigrostriatal dopamine system have been produced. A unilateral brain lesion in the left substantia nigra causes the dopamine receptor in the left caudate to become hypersensitive following the resulting degeneration of the nigral cell bodies. These lesions destroy the source of the neurotransmitter dopamine in the caudate but leave the caudate cell bodies and their dopamine receptors intact. Activation of these receptors by drugs which produce contralateral rotation, with respect to the lesioned side of the brain, is used as a measure of central dopaminergic activity of the drug.

Compounds which are known to be clinically effective in controlling parkinsonism, such as, for example, L-dopa and apomorphine, are also effective in this rate turning model. These compounds directly activate the dopamine receptors and cause contralateral rotation of the lesioned rat.

Rotational activity is defined as the ability of a compound to produce 500 contralateral rotations during a two-hour period after administration, usually intraperitoneally. The dose corresponding to 500 contralateral rotations per two hours is obtained and assigned as the RD_{500} value.

Once again advantageous compounds of Formula I, 6-chloro or 6 - bromo - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepines when tested as described above in rats produced RD_{500}, i.p. of 0.3 and 0.27 mg/kg respectively. As such they are both about 4 times as active as is the deshalo congener in this test. Further the compounds do not induce emesis or sterotyped behaviour at doses which are effective in the rat turning model.

The same 6-bromo compound showed greater renal plasma flow (RPF) in the rat renal clearance test than did the desbromo congener. At 15 μg/kg/min. the RPF

increased 60% over control with an 85% increase in urine volume. The 6-chloro compound increased the urine volume 80%, RPF 48% and sodium ion excretion. Therefore these compounds demonstrate stronger diuretic properties than does their 6-hydrogen congener.

The present invention therefor provides pharmaceutical compositions having a dopaminergic activity which comprise a compound of the invention and a pharmaceutical carrier. The compositions, preferably in dosage unit form, can be prepared according to accepted procedures. Preferably the compositions will contain the active ingredient in an active but non-toxic amount of from 15 mg to 1000 mg of active ingredient per dosage unit, but the quantity used will depend on the specific biological activity desired and the condition of the patient. Generally speaking, lower doses are needed to stimulate central dopamine receptors than to stimulate peripheral receptors.

The pharmaceutical carrier can be solid or liquid. Examples of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are syrup, peanut oil, olive oil and water. Similarly, the carrier can include a time delay material, for example glyceryl monostearate or glyceryl distearate, alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier for oral administration is used, the compositions can be tableted, placed in a hard gelatin capsule in powder or pellet form; or be in the form of a troche or lozenge. The amount of solid carrier can be varied widely but preferably it will be from 25 mg to 1 g. If a liquid carrier is used, the compositions can be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid, such as in an ampoule or an aqueous or non-aqueous liquid suspension.

The pharmaceutical compositions can be made following the conventional techniques of the pharmaceutical chemist involving mixing, granulating and compressing when necessary, or variously mixing and dissolving the ingredients as appropriate to give the desire composition.

The compositions will in general be administered internally so that sufficient of a compound of the invention is provided to produce the desired dopaminergic activity. Administration can be by any route which effectively transports the active compound to the dopamine receptors which are to be stimulated, for example orally or parenterally, the oral route being preferred. Advantageously, equal doses will be administered several times, for example two or three times a day, with the daily dosage regimen being from 50 mg to 2 g. When the method described above is carried out, hypotensive, diuretic or anti-parkinsonism activity is produced with a minimum of side effects.

The following Examples illustrate the preparation and use of compounds of this invention. The temperatures are in degrees Centigrade.

EXAMPLE 1

A mixture of 100 g (0.55 mol) of 3,4-dimethoxy-phenylethylamine and 66.2 g (0.55 mol) of styrene oxide in 200 ml of tetrahydrofuran was refluxed overnight. The solvent was removed *in vacuo*. About 500 ml of *n*-butyl chloride was added to the residue and the mixture cooled slightly. Filtration furnished N - [2 - (3,4 - dimethoxyphenyl)ethyl] - 2 - phenyl - 2 - hydroxyethylamine, m.p. 92—93°.

The above prepared phenethylamine, 71.5 g (0.238 mol), was dissolved in 400 ml of acetic acid and the solution was cooled. To this solution was added 16.9 g (0.238 mol) of chlorine gas over a 30 to 45 minute period. The reaction mixture was poured into water, made basic with 40% sodium hydroxide solution and about 250 ml of ether added to the stirred solution. The resulting solid was filtered to give N - [2 - (2 - chloro - 4,5 - dimethoxyphenyl)ethyl] - 2 - phenyl - 2 - hydroxyethylamine, m.p. 110—113°.

To 100 ml of concentrated sulfuric acid was added the above phenethylamine (10 g, 30 mmol) with stirring. After about 20 minutes the reaction mixure was poured over ice and extracted with ethyl acetate. The aqueous solution was made basic with sodium hydroxide pellets and 40% sodium hydroxide solution. The oil which forms was extracted with ether, the extract was dried and concentrated to about one-half volume. Ethereal hydrogen chloride was added to furnish 6 - chloro - 8,9 - dimethoxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, m.p. 209—210°.

Heating the dimethoxy compound in an excess of 48% hydrobromic acid at reflux for 2 hours and cooling gives the 8,9-dihydroxy congener as the hydrobromide.

EXAMPLE 2

Isovanillin (200 g, 1.32 mole) was suspended in 1200 cc chloroform. Chlorine (103 g, 1.45 mole) was added by means of 3 500 cc portions of carbon tetrachloride, in which it was dissolved. The suspension was stirred vigorously during the addition and the reaction was kept around 25° by a water bath. The suspension was stirred for 22 minutes after the completion of the addition of chlorine. The precipitate was filtered and crystallized from methanol, then recrystallized from isopropanol/ethyl acetate. Yield 98.7 g (40%, m.p. 204—206°) of 2 - chloro - 3 - hydroxy - 4 - methoxybenzaldehyde.

The aldehyde product (189.3 g, 1.02 mole) was suspended in 1 l. of dry dimethylformamide, 350 g of potassium carbonate was added. 145 cc (124 g, 1.54 mole) of dimethyl sulfate was added dropwise over a 20 minute period. After the addition the reaction was heated on the steam bath for 5 minutes. 70 cc of water were added and the reaction was again heated for 5 minutes on the steam bath. The mixture was then poured into ice water and the precipitate was collected. It was crystallized from acetic acid/water (800 cc—50 cc). A second crop was obtained from the mother liquor. Yield 180 g (90%) of 2 - chloro - 3,4 - dimethoxybenzaldehyde after drying, m.p. 69—70°.

The dimethoxybenzaldehyde (180 g, .9 mole) was dissolved in 500 cc warm acetic acid. 61 g (.8 mole) of ammonium acetate was added, followed by 160 cc of nitromethane. The reaction was heated vigorously on the steam bath for 3 hours. Water was then added to the cloud point, while still heating, and the solution was cooled and scratched. The β-nitrostyrene began to oil out and then crystallized. The solution was cooled. The yellow crystals were collected and dried in a vacuum oven. Yield 175 g (80% m.p. 88—91°) of 2 - chloro - 3,4 - dimethoxy - β - nitrostyrene.

The nitrostyrene (80 g, .33 mole) was dissolved in 800 cc of dry tetrahydrofuran. Lithium aluminum hydride, as a 3.7 M solution (260 cc, .36 mole), was put in a 5 l. 3 neck flask which has been dried and flushed with argon. It was diluted with 500 cc of dry ether. The solution of the nitrostyrene was added in a thin stream. The flask was cooled in an ice bath so that the heat of reaction caused a gentle reflux of the ether. After addition, the reaction was refluxed one hour, then worked up by adding 36 cc of water, 36 cc of 10% sodium hydroxide and 108 cc of water sequentially and carefully, while cooling the reaction in ice.

The precipitate was collected, washed well with ethyl ether and discarded. The ether-tetrahydrofuran mixture was evaporated.

The above reaction was repeated on 83 g of nitrostyrene. The two crude products were combined and distilled at 0.5 mm to collect at 142—155° the product containing fraction which was pure 2 - (2 - chloro - 3,4 - dimethoxyphenyl)ethylamine by t.l.c. (80 g).

The phenethylamine (25.7 g, .12 mole) was heated to 115° in an oil bath styrene oxide (14.4 g, .12 mole) was added and the reaction was heated for 1 hour. After cooling to ~30°, 2:1 petroleum ether/acetone was added to dissolve the oil; N - [(2 - hydroxy - 2 - phenylethyl)] - N - [2 - (2' - chloro - 3',4' - dimethoxyphenyl)ethyl]amine, crystallized out in 37% yield (15 g) m.p. 100—101°.

The hydroxyphenethylamine (15 g, (0.445 mole) was dissolved in 60 cc of trifluoroacetic acid and 4.05 cc of concentrated sulfuric acid was added. The reaction was refluxed 2 hours. After cooling most of the trifluoroacetic acid was stripped off and the residue was poured into water. It was made basic with 10% sodium hydroxide and was extracted with ether twice. The ether was dried, and as it was evaporated, a solid separated which was collected; m.p. 115—121°, 6.0 g of 6 - chloro - 7,8 - dimethoxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine. The remaining ether was treated with ethereal hydrogen chloride and the hydrochloride salt precipitated; yield 3.2 g, total 62% m.p. 234—236°. The dimethoxy derivative was converted to 6 - chloro - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide using boron tribromide in a 77% yield, m.p. 259—260°.

EXAMPLE 3

7,8 - Dimethoxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine (280 g, 0.75 mole) was dissolved in 1700 cc of acetic acid. Bromine (280 g, 1.75 mole) was added in a thin stream. The reaction was stirred for two hours. The precipitate, which formed after 1 hour, was collected and washed with ether. It was dissolved in boiling methanol and acetone was added to destroy the bromine excess. 6 - Bromo - 7,8 - dimethoxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 -

benzazepine hydrobromide was allowed to crystallize from the methanol and a second crop was obtained by adding ether to the mother liquor. Yield 298 g, 77% m.p. 236—238%. This bromination may be applied to any 7,8-dialkoxy or alkanoyloxybenzazepine having a free 6-position.

The hydrobromide was shaken in a mixture of excess 10% sodium hydroxide and methylene chloride. The organic layer was separated, dried and evaporated to give a solid base which was crystallized from toluene-hexane; m.p. 125—128°, yield 238 g (97%).

The base (12 g, 0.033 mole) was dissolved in 200 cc of methylene chloride and was cooled to −15°C. Boron tribromide (15.4 cc, 16 mole) was added cautiously. The reaction was allowed to run at room temperature for two hours. The solvent was stripped off and the flask was cooled to −15°. Dry methanol was added to destroy the boron tribromide complexes. It was then stripped off. The residue was crystallized from water, then boiled in acetonitrile to aid in the drying of the compound. Yield of 6 - bromo - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide; 10.26 g. (75%), m.p. 240—242° after vacuum drying.

Other compounds having a free 6-position and no interfering groups such as unsaturated or aromatic activating centers as known to the art may be similarly brominated.

EXAMPLE 4

6 - Bromo - 7,8 - dimethoxy - 1 - phenyltetrahydrobenzazepine (13 g, .0355 mole) was dissolved in 200 cc of dry acetone. Anhydrous potassium carbonate (10 g, .07 mole) was added, followed by 4.2 cc (.0355 mole) of benzyl bromide. The reaction was refluxed four hours. After cooling, the solid was filtered and the filtrate was stripped off. The resulting oil was dissolved in ether, filtered, and ethereal hydrogen chloride was added. The crystalline precipitate of N-benzyl derivative was filtered and recrystallized from methanol-ether, m.p. 160—165°.

The solid was then dissolved in methylene chloride and was extracted twice with excess 10% sodium hydroxide. The solvent was dried and evaporated. The residue was dissolved in dry benzene and the benzene was distilled to azeotrope any water present. After repeating the procedure, the oil was pumped under vacuum to remove the benzene. Yield of N - benzyl - 6 - bromo - 7,8 - dimethoxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine, 12.5 g, 80%.

The 6-bromobenzyl derivative (12.5 g, .0277 mole) was converted to its 6-lithium salt which is an important intermediate by reaction with n-butyl lithium in ether. The n-butyl lithium (29 cc, 2.2 M, .064 mole) was added via syringe to a 3 neck flask in an argon atmosphere. It was diluted with 3 or 4 volumes of dry ether and cooled to −78° in a dry ice-propanol bath. The benzyl compound was added in 75 cc of dry ether in a thin stream, over a five minute period. The reaction stirred at −78° for five minutes and then 13 g (.0554 mole) of hexachloroethane was added in 75 cc of ether. The precipitate dissolved immediately.

The reaction mixture was poured into water and the ether layer was retained. The water was extracted again with ether and the ether was dried with magnesium sulfate. Addition of ethereal hydrogen chloride gave a precipitate which was crystallized first from ether-methanol, then from ethyl acetate. Yield of 3 - benzyl - 6 - chloro - 7,8 - dimethoxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, 9.4 g (80%), m.p. 201—205°.

This N-benzyl compound (5.33 g, .013 mole) was freed from its hydrochloride by extraction into methylene chloride after making alkaline a solution of the hydrochloride. The methlene chloride was dried, evaporated, and the residue dissolved in benzene. It was stripped down to azeotrope any water remaining and the residue was dissolved in 50 cc of dry benzene.

Cyanogen bromide (1.53 g, .0144 mole) was dissolved in 50 cc of dry benzene and was warmed to 55°. The N-benzyl compound was added dropwise in benzene and the mixture stirred for 3 hours. The volatiles were stripped off, leaving a solid which was triturated with ether. Yield of N-cyano derivative; 4.0 g (89%), m.p. 149—151°.

This material (4.0 g, .0127 mole) was dissolved in a solution of 50 cc of acetic acid, 6 cc of conc. hydrochloric acid and 31 cc of water. It was heated overnight on the stream bath. The solvents were then stripped off and the residue dissolved in hot methanol. Ether was added and 6 - chloro - 7,8 - dimethoxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride crystallized; yield 3.85 g (90%), m.p. 241—245°.

EXAMPLE 5

The product of Example 4 (3.27 g, .0103 mole) was freed from its hydrochloride by making basic its aqueous solution and extracting the mixture with methylene chloride. The solvent was carefully dried and cooled to –15° by a methanol-ice bath. Boron tribromide (4 cc) was added and the reaction was stirred at room temperature for 2 hours. The solvent and excess tribromide were stripped and the flask cooled to –78°. Methanol was added cautiously until all the material was dissolved. The methanol was stripped off and the residue crystallized from hot water. The crystals were boiled in dry acetonitrile for an hour, then collected to give 6 - chloro - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide; (56%), m.p. 256—260°.

EXAMPLE 6

2 - Chloro - 3,4 - dimethoxyphenethylamine (1.0 g) was reacted with 0.70 g of *p*-methoxystyrene oxide as described above to give the hydroxyphenethylamine; m.p. 118.5—121°. This compound (2.16 g) was stirred at room temperature in 15 ml of trifluoroacetic acid with 4 drops of conc. sulfuric acid. Working up as above gave, after purification over a silica gel column with chloroform, 10% methanol/chloroform as eluates, the desired 6 - chloro - 7,8 - dimethoxy - 1 - *p* - methoxyphenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine (0.78 g).

EXAMPLE 7

The product of Example 6 (0.87 g, 2.50 mmoles) in 25 ml of dry methylene chloride was cooled in an ice-methanol bath as 12.5 ml (25.0 mmoles) of boron tribromide in methylene chloride was added dropwise. After stirring for 4 hours, the mixture was cooled in an ice bath while methanol was carefully added to give 0.37 g, after crystallization from methanol/ethylacetate, of 6 - chloro - 7,8 - dihydroxy - 1 - *p* - hydroxyphenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide, m.p. 215°.

The base was regenerated from the hydrobromide salt using sodium carbonate solution in 85% yield. Reacting the base in methanol-tetrahydrofuran with various acids gave the following salts; dl-tartrate, acetate, fumarate, hydrochloride, sulfate, acetate and the most water soluble one, the methylsulfonate, m.p. 272°.

EXAMPLE 8

Dry dimethylformamide (500 cc) was deoxygenated four times by pulling a vacuum and refilling the vacuated flask with argon. 7,8 - Dihydroxy - 1 - phenyl - 3 - trifluoroacetyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine (53.4 g, .152 mole) was added and dissolved as the solution and flask were deoxygenated once more. Methylene bromide (52.5 g, .3 mole), potassium carbonate (50 g, .36 mole) and cupric oxide (1.3 g) were added and the solution was deoxygenated a final time. The reaction was heated at 150° under argon for 2 hours.

It was worked up by pouring into 2 l. of ice water while stirring. The aqueous suspension was extracted 4 times with 300—400 cc ether, and the ether was back extracted 3 times with 1.5 l. water. The ether was dried and evaporated. The residue was dissolved in chloroform and chromatographed on silica gel. Yield of 7,8 - methylenedioxy - 1 - phenyl - 3 - trifluoroacethyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine; 35.3 g (64%), m.p. 94—96° from cyclohexane.

This compound (31.8 g, .0876 mole) was dissolved in 105 cc of acetic acid and bromine (4.86 cc, .089 mole) was added all at once. The reaction stirred at room temperature overnight. The flask was then cooled and the solid was collected. The mother liquors were warmed, diluted with water and then allowed to cool. A second crop was collected. To the mother liquor was added a small amount more or bromine. It stirred for two days at room temperature and the relatively small amount of precipitate was collected. The crude material was recrystallized from acetic acid to give 28 g (72%) of the 6-bromo compound, m.p. 160—165°.

The 6-bromo compound (28 g) was suspended in 250 cc of methanol, 50 cc of 40% sodium hydroxide was added and the reaction mixture was heated to boiling. The mixture was then stirred for one hour. The methanol was stripped off and water and ether were added to the residue. The layers were shaken, separated and the water was washed again with ether. The ether layers were dried and ethereal hydrogen chloride was added. The precipitate was recrystallized from methanol-ethyl acetate to give 6 - bromo - 7,8 - methylenedioxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, 21.3 g (88%), m.p. 240—248.

EXAMPLE 9

A mixture of 4.5 g of 6 - chloro - 7,8 - dimethoxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine, 0.02 ml of *n*-butyl bromide and 0.02 mol of potassium hydroxide is dissolved in 120 ml of dry methanol and refluxed for 48 hours. The reaction mixture is evaporated to dryness, taken up in ethyl acetate and filtered to remove inorganic salts. The filtrate is washed with water, dried and evaporated to give 3 - *n* - butyl - 6 - chloro - 7,8 - dimethoxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine.

The 3 - *n* - butyl benzazepine (0.01 mol) is dissolved in 120 ml of dry methylene chloride and 0.032 mol of boron tribromide is added dropwise at −10°C. The solution is warmed to room temperature and stirred for two hours. The excess boron tribromide is destroyed with methanol added dropwise with ice-cooling. The cold solution is refluxed on the steam bath to remove hydrogen bromide and then evaporated to yield 3 - *n* - butyl - 6 - chloro - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide.

EXAMPLE 10

A mixture of 9.7 g of sodium hydride, 38 g of trimethylsulfonium iodide and 25.2 g (0.185 mol) of *o*-methoxy-benzaldehyde is reacted to give *o*-methoxystyrene oxide.

A mixture of 34 g of 2 - chloro - 3,4 - dimethoxy - phenylethylamine and 28 g of *o*-methoxystyrene oxide is heated with stirring under argon on a steam bath overnight. Chilling and stirring yields the product N - [2 - (2 - chloro - 3,4 - dimethoxyphenyl) - ethyl] - 2 - hydroxy - 2 - (2 - methoxyphenyl) ethylamine.

A solution of 5 g of the above prepared ethylamine in 35 ml of 48% hydrobromic acid is heated at reflux under argon for two hours. The reaction mixture is evaporated and the hydrobromide salt is converted to the free base using bicarbonate and carbonate to pH 8.5 in water. The aqueous solution is extracted with ethyl acetate, the extract is dried and evaporated to give the free base. The latter is dissolved in methanol and treated with ethereal hydrogen chloride to give 6 - chloro - 7,8 - dihydroxy - 1 - (2 - hydroxyphenyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride.

EXAMPLE 11

A 5.20 g sample of 6 - bromo - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine free base is slurried under nitrogen and chilled to about 0°. Sodium bicarbonate (1.68 g, 0.020 mol) is added as a solid and to the stirred mixture is added 5.69 g (0.040 mol) of methyl iodide in 60 ml of acetone, dropwise over a two to three hour period. After addition is completed the mixture is allowed to warm to ambient temperature and stirred for about 40 hours. The reaction mixture is filtered and the filtrate is concentrated to yield additional solid. The combined solids are slurried in water to remove inorganic salts, filtered and the solid dried to give 6 - bromo - 7,8 - dihydroxy - 3,3 - dimethyl - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepinium iodide.

EXAMPLE 12

A 3.9 g sample of 6 - chloro - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine is slurried in 25 ml of acetone and 0.7 g (0.016 mol, 10% excess) of ethylene oxide is added. The mixture is placed in a pressure bottle and stirred at ambient temperature for about 40 hours. The reaction mixture is then heated to 60—80° for 30 minutes, cooled and filtered. Concentration of the filtrate gives a solid which is taken up in ethyl acetate and reprecipitated with ether. The solid thus obtained is dissolved in ethanol and treated with ethereal hydrogen chloride to give 6 - chloro - 7,8 - dihydroxy - 3 - (2 - hydroxy - ethyl) - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride.

EXAMPLE 13

A mixture of 42.0 g of 57% sodium hydroxide dispersed in oil and 700 ml of dimethyl sulfoxide is stirred at 70—75° for one to one and one-half hours. The solution is diluted with 700 ml of dry tetrahydrofuran and cooled to 0°, under nitrogen. A 200 g of (1.0 mol) sample of trimethylsulfonium iodide is added in portions, maintaining the temperature between 0—5°. The mixture is stirred for 15 minutes and then a solution of 70.4 g (0.50 mol) of *o*-chlorobenzaldehyde in 300 ml of dry tetrahydrofuran is added dropwise. The resulting mixture is stirred at room

temperature for four hours, poured into water and extracted with ether. The extract is washed with brine, dried and evaporated *in vacuo* to leave *o*-chlorostyrene oxide.

A solution of 27.5 g of N - benzyl - 2 - chloro - 3,4 - dimethoxyphenylethylamine and 23.3 g (0.15 mol) of m-chlorostyrene oxide in 500 ml of methanol is stirred and refluxed overnight. The methanol is removed *in vacuo* and the residual N - benzyl - N - [2 - (2 - chloro - 3,4 - dimethoxyphenyl) - ethyl] - 2 - hydroxy - 2 - (2 - chlorophenyl)ethylamine is reduced without further purification. This sample (0.01 mol) is dissolved in ether, acidified with ethereal hydrogen chloride and the hydrochloride precipitates. The latter is dissolved in 90 ml of methanol, the solution is added to a mixture of 0.5 g of palladium-on-charcoal in 10 ml of ethyl acetate and the mixture is hydrogenated at room temperature for 90 minutes at 60 psi. The reaction mixture is filtered and the filtrate evaporated *in vacuo* to yield N - [2 - (2 - chloro - 3,4 - dimethoxyphenyl)ethyl] - 2 - hydroxy - 2 - (2 - chlorophenyl)ethylamine hydrochloride.

A solution of 6.0 g (0.0161 mol) of the above prepared compound in 250 ml of 48% hydrobromic acid is stirred and refluxed for three hours. The reaction mixture is evaporated *in vacuo* to give 6 - chloro - 1 - (2 - chlorophenyl) - 7,8 - dihydroxy - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide.

EXAMPLE 14

Following the procedure of Example 13 and employing 42.0 g of 57% of sodium hydride in mineral oil, 200 g (0.1 mol) of trimethylsulfonium iodide and 70.4 g (0.50 mol) of o-bromo-benzaldehyde there is obtained o-bromostyrene oxide.

Similarly 2.71 g of N - benzyl - 2 - chloro - 3,4 - dimethoxy - phenethylamine and 2.33 g (0.015 mol) of o-bromostyrene oxide are reacted in methanol to give N - benzyl - N - [2 - (2 - chloro - 3,4 - dimethoxyphenyl)ethyl - 2 - hydroxy - 2 - (2 - bromophenyl)ethylamine. The latter is converted to its hydrochloride, which is dissolved in 90 ml of methanol and hydrogenated over 1 g of 10% palladium-on-carbon in 10 ml of ethyl acetate at room temperature for six hours. The reaction mixture is filtered and evaporated *in vacuo* to leave N - [2 - (2 - chloro - 3,4 - dimethoxyphenyl)ethyl] - 2 - hydroxy - 2 - (2 - bromophenyl)ethylamine hydrochloride.

A solution of 4.0 g of the above hydrochloride in 250 ml of 48% hydrobromic acid is stirred and refluxed for two hours. The reaction mixture is evaporated *in vacuo* to yield 6 - chloro - 1 - (2 - bromophenyl) - 7,8 - dihydroxy - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide.

Substituting trifluoromethyl, fluoro, methyl, ethyl, ethoxystyrene oxides will give the compounds of this invention whose structures include the corresponding substituted 1-phenyl moieties.

EXAMPLE 15

A solution of 3.7 g of 6 - chloro - 7,8 - dimethoxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine in 15 ml of formic acid and 10 ml of formaldehyde is refluxed for 18 hours. The reaction mixture is evaporated to dryness, 20 ml of 6*N* hydrochloric acid is added and the solution is again evaporated to dryness to give a liquid. The latter is treated with 20 ml of 10% sodium hydroxide solution and the mixture is extracted with ether. The dried extract is evaporated to give 6 - chloro - 7,8 - dimethoxy - 3 - methyl - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine.

The above prepared 3-methyl benzazepine (2.6 g) is dissolved in 120 ml of dry methylene chloride and 6.8 g (0.027 mol) of boron tribromide is added dropwise at −10°. The resulting solution is warmed at room temperature and stirred for two hours. The excess boron tribromide is destroyed with methanol, added dropwise with ice-cooling. The solution is refluxed on the steam bath to remove hydrogen bromide and then evaporated to dryness to furnish 6 - chloro - 7,8 - dihydroxy - 3 - methyl - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide, 247—249°.

EXAMPLE 16

A 4.0 g sample of 3 - benzyl - 6 - chloro - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine (prepared from the 3-unsubstituted benzazepine by reaction with benzyl bromide in the presence of potassium

carbonate) is dissolved in 50 ml of acetic anhydride and the solution is heated on a steam bath for one hour. The reaction mixture is cooled, ice-water is added and the solution is evaporated to dryness. The residue is triturated with ethyl acetate, the solution washed with water, dried and the solvent removed *in vacuo* to leave an oil. The latter is dissolved in ether and ethereal hydrogen chloride is added to precipitate 3 - benzyl - 6 - chloro - 7,8 - diacetoxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride.

The diacetoxy compound prepared above, 3.5 g is dissolved in 100 ml of ethanol and 1 g of 10% palladium-on-carbon is added. The mixture is hydrogenated in a Parr apparatus at 50° under 50 psi of hydrogen for one hour. The reaction mixture is filtered and the filtrate is evaporated to give 6 - chloro - 7,8 - diacetoxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride.

Alternatively 6 - chloro - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide (10 g) is dissolved in trifluoroacetic acid and reacted with a stoichiometric amount of acetyl chloride at room temperature. The next day the reaction mixture is evaporated and the residue recrystallized to give the desired diacetoxy derivative.

Substituting other alkanoyl anhydrides or chlorides gives various 7,8-alkanoyl derivatives.

EXAMPLE 17

Using N-alkylation procedures described but using 6 - chloro - 7,8 - dimethoxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine as a model compound the N-allyl, N-butyl, N-amyl or N-2,2-dimethylallyl derivatives are prepared. Hydrolysis of the methoxy groups as described gives the more active 6-chloro-7,8-dihydroxy compound.

EXAMPLE 18

Substituting a stoichiometric quantity of 2 - fluoro - 3,4 - dimethoxyphenethyl amine in the synthetic procedures of Example 2 gives 6 - fluoro - 7,8 - dimethoxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine. Hydrolysis with boron tribromide as in Example 2 gives 6 - fluoro - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine. Substituting 2 - trifluoromethyl - 3,4 - dimethoxytoluene, in Example 2 gives 6 - trifluoromethyl - 7,8 - dimethoxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine then hydrolysis with boron tribromide gives 6 - trifluoromethyl - 7,8 - dihydroxy - 1 - phenyl - 3,4,5 - tetrahydro - 1H - 3 - benzazepine.

EXAMPLE 19

A mixture of 4.84 g of 50% of sodium hydride in mineral oil and 70 ml of dry dimethylsulfoxide was stirred at 65—70° for 80 minutes. After dilution with 70 ml of dry tetrahydrofuran, the mixture was cooled to 0° while a solution of 19.0 g (0.093 mole) of trimethylsulfonium iodide in 100 ml of dimethylsulfoxide was added. A solution of 12.6 g (0.0928 mole) of *m*-anisaldehyde in 40 ml of tetrahydrofuran was quickly added. After stirring for 15 minutes at 0° and 1-1/2 hour at 25°, the mixture is poured into 1-1/2 l. of ice/water slurry and extracted well with water. The combined organic layers were washed with brine, dried and concentrated to give 13 g of crude epoxide. This is mixed with 13.0 g of 2 - (2 - chloro - 3,4 - dimethoxyphenyl) ethylamine and heated at 110° for 4 hours. The product was chromatographed over silica gel with 3% methanol/chloroform. The product containing cuts were worked up to given 1.9 g of N - [2 - (2 - chloro - 3,4 - dimethoxyphenyl)ethyl] - 2 - hydroxy - 2 - (*m* - methoxyphenyl)ethylamine, m.p. 95.5—96.5°.

The *p*-chlorophenyl congener melted at 99—100°. The *p*-methylphenyl congener melted at 117—118°.

The *m*-methoxy substituted hydroxyphenethylamine intermediate (1.7 g) in 25 ml of 48% hydrogen bromide solution was heated at 135—140° for 3 hours. The solvent was evaporated *in vacuo* and the residue dissolved in methyl alcohol/2-propanol. After charcoal treatment, the solvent was evaporated to leave an amber syrup. This was taken into acetonitrile/2-propanol and a white solid separated by addition of ether. Recrystallization from acetonitrile/ether gave 1.2 g of 6 - chloro - 7,8 - dihydroxy - 1 - (*m* - hydroxyphenyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide m.p. 195—200°.

The *p*-chlorophenyl congener melted at 243—246°. The *p*-methylphenyl congener melted at 250—253°.

EXAMPLE 20

A mixture of 8.0 g of 2 - chloro - 3,4 - dimethoxy - phenethylamine and 5.25 g of *m* - trifluoromethyl - α - methoxy - phenethylbromide is heated at 100—105° for 2-1/2 hours. The product was partitioned between ethyl acetate and 5% sodium bicarbonate solution. The organic layer was removed, washed with brine, dried and concentrated. The residue was passed over 350 g of silica gel with 1 to 2% methanol/chloroform. The resulting product was an oil whose hydrochloride melted at 200—202°. The oily base (2.5 g) was heated with 50 ml of 48% hydrogen bromide and worked up as above to give the desired 6 - chloro - 7,8 - dihydroxy - 1 - (*m* - trifluoromethylphenyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide, m.p. ~250°.

6 - Bromo - 7,8 - dimethoxy - 1 - phenyl - 3 - trifluoroacetyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine (5 g, prepared by reaction of trifluoroacetic anhydride in benzene on the N-hydrogen compound) is reacted with an excess of butyl lithium in ether as in Example 4 to give the 6-lithium salt-3-butyl-lithium adduct. This intermediate is reacted without isolation with iodine. After hydrolysis with water, 6 - iodo - 7,8 - dimethoxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine is obtained. This compound is treated with boron tribromide as in Example 3 to give the 7,8-dihydroxy derivative.

2 - Chloro - 3 - hydroxy - 4 - methoxybenzaldehyde is treated with hydrogen bromide to give 2 - chloro - 3,4 - dihydroxybenzaldehyde which is converted to the methylenedioxy derivative with dibromomethane as described above. The product is condensed with nitromethane and the resulting nitroethylene reduced to give the phenethylamine. This compound is condensed with *p*-methoxystyrene oxide to give the α-hydroxyphenethylamine intermediate which is treated with an excess of trifluoroacetic acid at room temperature for 18 hours to give 6 - chloro - 7,8 - methylenedioxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine. This compound is split using boron trichloride as described above to give 6 - chloro - 7,8 - dihydroxy - 1 - *p* - methoxyphenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine.

EXAMPLE 21

6 - Chloro - 7,8 - dihydroxy - 1 - *p* - hydroxyphenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide (Example 7, 1.0 g) was slurried in 200 ml of trifluoroacetic acid then 1.29 ml of acetyl bromide was added. The mixture was heated at reflux for 2 hours then stirred for 2 hours. After evaporation to dryness the residue was taken up in benzene and concentrated to give a solid which was recrystallized from ethylacetate-hexane to give 6 - chloro - 7,8 - diacetoxy - 1 - (*p* - acetoxyphenyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide; m.p. 214.5—217°, 0.77 g.

EXAMPLE 22

A solution of 0.74 g (0.002 mole) of 6 - chloro - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, 0.55 g (0.0025 mole) of *p*-trifluoromethyl benzoylchloride, 0.17 g (0.002 mole) of sodium bicarbonate and 40 ml of 1:1 acetone-water solution was stirred overnight under nitrogen. The mixture was evaporated to dryness. The residue was extracted with ethylacetate. The extracted material was purified over a silica gel column using methanol-ethyl acetate to give 6 - chloro - 7,8 - dihydroxy - 1 - phenyl - 3 - (*p* - trifluoromethylbenzoyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine, m.p. 243—245° (dec.).

This compound (1.65 g, 0.00357 mole) in 120 ml of tetrahydrofuran was added to 15 ml of 1 M boron hydride-tetrahydrofuran. After heating at reflux for 2 hours methanol was added with 10 ml of 6N hydrochloric acid. The solution was evaporated to give a white solid which was dissolved in 50 ml of 6N hydrochloric acid, heated at reflux for 1 hour and again evaporated. The white solid was purified from methanolethyl acetate-ether to give 6 - chloro - 7,8 - dihydroxy - 1 - phenyl - 3 - (*p* - trifluoromethylbenzyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, m.p. 239—241° (dec.).

Using similar methods 6 - chloro - 7,8 - dihydroxy - 3 - (*p* - methoxybenzoyl) - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine, m.p. 224—225°, and 6 - chloro - 7,8 - dihydroxy - 3 - (*p* - methoxybenzyl) - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, m.p. 190—193°, were prepared.

EXAMPLE 23

Using methods described here in the following compounds were prepared:

6 - chloro - 7,8 - dimethoxy - 1 - phenyl - 3 - α - thenoyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzepine, yellow liquid

6 - chloro - 7,8 - dihydroxy - 1 - phenyl - 3α - thenoyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine, green solid

6 - chloro - 7,8 - dihydroxy - 1 - phenyl - 3 - α - thenyl - 2,3,4,5 - tetrahydro - 1H - benzazepine hydrochloride, m.p. 237—240°

6 - chloro - 7,8 - dimethoxy - 3 - α - furoyl - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine, yellow liquid

6 - dihydro - 7,8 - dihydroxy - 3 - α - furoyl - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine, brown solid

6 - chloro - 7,8 - dihydroxy - 3 - α - furylmethyl - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, m.p. 239—240°

3 - allyl - 6 - chloro - 1 - (*p* - chloro - *m* - hydroxyphenyl) - 7,8 - dihydroxy - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide, m.p. 183—186°

6 - chloro - 1 - (*p* - chloro - *m* - hydroxyphenyl) - 7,8 - dihydroxy - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide, m.p. 270—273°

6 - bromo - 7,8 - dihydroxy - 1 - (*p* - hydroxyphenyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide, m.p. 254° (dec.)

6 - chloro - 1 - (*m,m* - dichloro - *p* - hydroxyphenyl) - 7,8 - dihydroxy - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide, m.p. 290—292°

6 - bromo - 7,8 - diacetoxy - 3 - methyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide, m.p. 224° (dec.)

3 - allyl - 6 - chloro - 1 - (*p* - chloro - *m* - methoxyphenyl) - 7,8 - dimethoxy - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, m.p. 163—165

3 - allyl - 6 - chloro - 1 - (*m* - chlorophenyl) - 7,8 - dimethoxy - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, m.p. 192—194

6 - chloro - 1 - (*m* - chlorophenyl) - 7,8 - dihydroxy - 3 - α - furylmethyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzepine hydrochloride, m.p. 241—243°

6 - chloro - 7,8 - dimethoxy - 3 - α - furylmethyl - 1 - (*m* - methylphenyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, m.p. 235—237°

7,8 - dihydroxy - 1 - (*p* - hydroxyphenyl) - 6 - trifluoromethyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, softens 189° dec. at 223°

6 - chloro - 1 - (*m* - chlorophenyl) - 7,8 - dimethoxy - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, m.p. 160—163°

6 - chloro - 1 - (*m* - chlorophenyl) - 7,8 - dimethoxy - 3 - methyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine fumarate, m.p. 197—199°

6 - chloro - 1 - (*m* - chlorophenyl) - 7,8 - dihydroxy - 3 - methyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide, m.p. 263—265°

3 - allyl - 6 - chloro - 1 - (*m* - chlorophenyl) - 7,8 - dihydroxy - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide, m.p. 258—260°

6 - chloro - 7,8 - dimethoxy - 1 - (*m* - methylphenyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, m.p. 136—140°

6 - chloro - 7,8 - dimethoxy - 3 - methyl - 1 - (*m* - methylphenyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine fumarate, m.p. 185—187°

6 - chloro - 7,8 - dihydroxy - 3 - methyl - 1 - (*m* - methylphenyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide, m.p. 263—265°

3 - allyl - 6 - chloro - 7,8 - dimethoxy - 1 - (*n* - methylphenyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, m.p. 175—180°

3 - allyl - 6 - chloro - 7,8 - dihydroxy - 1 - (*m* - methylphenyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, m.p. 270—273°

6 - chloro - 7,8 - dihydroxy - 3 - α - furylmethyl - 1 - (*m* - methylphenyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, 262—265°

6 - chloro - 7,8 - dihydroxy - 3 - methyl - 1 - (*m* - trifluoromethylphenyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide, m.p. 264—266°

EXAMPLE 24

Ingredients	Mg. per Capsule
6 - Chloro - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine (as an acid addition salt)	125 (free base)
Magnesium stearate	2
Lactose	200

The above ingredients are thoroughly mixed and placed into hard gelatin capsules. Such capsules are administered orally to subjects in need of treatment from 1—5 times daily to induce dopaminergic activity.

EXAMPLE 25

Ingredients	Mg. per Tablet
6 - Chloro - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine (as an acid addition salt)	200 (free base)
Corn starch	30
Polyvinyl pyrrolidone	12
Corn starch	16
Magnesium stearate	3

The first two ingredients are thoroughly mixed and granulated. The granules obtained are dried, mixed with the remaining corn starch and magnesium stearate, and compressed into tablets.

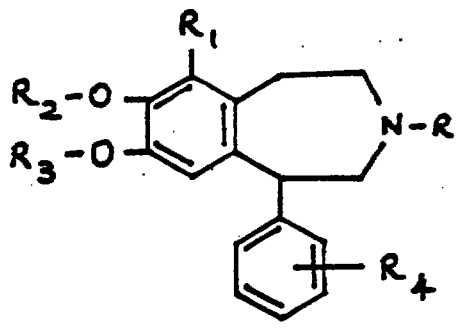
The capsules or tablets thusly prepared are administered orally to an animal or human requiring stimulation of either central or peripheral dopamine receptors within the dose ranges set forth hereinabove. Similarly other compounds of Formula I and the illustrative examples can be formulated in the same manner to give pharmaceutical compositions useful in this invention based on the chemical characteristics and relative biological activity using the test methods outlined.

As stated above 6 - chloro - 7,8 - dihydroxy - 1 - (*p* - hydroxyphenyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine is a very active peripheral dopaminergic agent. Its ED_{15} is 0.3 mcq/kg compared with 3.5 for its deshydroxy congener. It is therefore about 10 times more active than the active ingredient of Examples 24 and 25. It is active in the phosphate mannitol dog renal clearance test at 10 and 20 mg/kg orally but inactive at 10 mg/kg (i.p.) in the rat rotation test.

The 6 - chloro - 7,8 - dihydroxy - 3 - methyl - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrobromide in the rat rotation test had an RD_{500}=0.03 mg/kg (i.p.). RD_{1000}=1.79 mg/kg (p.o.) with diminished effect on the renal blood flow or vascular resistance. Once again is about 10 times as active as a central dopaminergic agent as in the active ingredient of Examples 24 and 25.

WHAT WE CLAIM IS:—

1. A compound of the formula:



in which R is hydrogen, benzyl, hydroxyethyl, lower alkyl of 1 to 5 carbon atoms, lower alkenyl of 3 to 5 carbon atoms, lower alkanoyl or haloalkanoyl of 1 to 5

EXAMPLE 24

Ingredients	Mg. per Capsule
6 - Chloro - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine (as an acid addition salt)	125 (free base)
Magnesium stearate	2
Lactose	200

The above ingredients are thoroughly mixed and placed into hard gelatin capsules. Such capsules are administered orally to subjects in need of treatment from 1—5 times daily to induce dopaminergic activity.

EXAMPLE 25

Ingredients	Mg. per Tablet
6 - Chloro - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine (as an acid addition salt)	200 (free base)
Corn starch	30
Polyvinyl pyrrolidone	12
Corn starch	16
Magnesium stearate	3

The first two ingredients are thoroughly mixed and granulated. The granules obtained are dried, mixed with the remaining corn starch and magnesium stearate, and compressed into tablets.

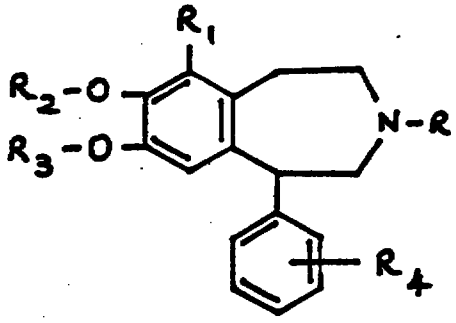
The capsules or tablets thusly prepared are administered orally to an animal or human requiring stimulation of either central or peripheral dopamine receptors within the dose ranges set forth hereinabove. Similarly other compounds of Formula I and the illustrative examples can be formulated in the same manner to give pharmaceutical compositions useful in this invention based on the chemical characteristics and relative biological activity using the test methods outlined.

As stated above 6 - chloro - 7,8 - dihydroxy - 1 - (*p* - hydroxyphenyl) - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine is a very active peripheral dopaminergic agent. Its ED_{15} is 0.3 mcq/kg compared with 3.5 for its deshydroxy congener. It is therefore about 10 times more active than the active ingredient of Examples 24 and 25. It is active in the phosphate mannitol dog renal clearance test at 10 and 20 mg/kg orally but inactive at 10 mg/kg (i.p.) in the rat rotation test.

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WHAT WE CLAIM IS:—

1. A compound of the formula:



in which R is hydrogen, benzyl, hydroxyethyl, lower alkyl of 1 to 5 carbon atoms, lower alkenyl of 3 to 5 carbon atoms, lower alkanoyl or haloalkanoyl of 1 to 5

* C L M S *

carbon atoms, propargyl, phenethyl, furoyl, thenoyl, furylmethyl, thienylmethyl, benzoyl, phenacyl, the phenyl, furyl or thienyl groups thereof being optionally substituted;

R_1 is halo or trifluoromethyl;

R_2 and R_3 which are the same or different, are each hydrogen, lower alkyl of 1—5 carbons, lower alkanoyl of 2—5 carbons, or when taken together, methylene or ethylene; and

R_4 is hydrogen or from 1 to 3 substituents selected from the group of trifluoromethyl, halo, methyl, ethyl, methoxy, ethoxy, hydroxy and acetoxy.

2. A compound according to claim 1, in which R_2 and R_3 are both hydrogen and R_2O— and R_3O— are in the 7- and 8-positions.

3. A compound according to claim 2, in which R is hydrogen or methyl.

4. A compound according to claim 2, in which R is allyl.

5. A compound according to claim 3, in which R_4 is hydrogen, para-hydroxy or para-acetoxy.

6. A compound according to claim 2, in which R_1 is chloro.

7. 6 - Chloro - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine.

8. 6 - Bromo - 7,8 - dihydroxy - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine.

9. 6 - Chloro - 7,8 - dihydroxy - 1 - *p* - hydroxyphenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine.

10. 6 - Chloro - 7,8 - dihydroxy - 3 - methyl - 1 - phenyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine.

11. A compound according to claim 1 wherein R_2 and R_3 are both acetyl.

12. A compound according to claim 1, wherein R is hydrogen, benzyl, hydroxyethyl, lower alkyl of 1—5 carbons, lower alkenyl of 3—5 carbons, lower alkanoyl of 1—5 carbons, and R_4 is hydrogen, trifluoromethyl, halo, methyl, methoxy or hydroxy.

13. A compound according to claim 1, wherein R_4 is hydrogen or para-acetoxy.

14. A compound according to claim 12 wherein R_2 and R_3 are both acetyl.

15. A compound according to any of the preceding claims in the form of a pharmaceutically acceptable acid addition salt thereof.

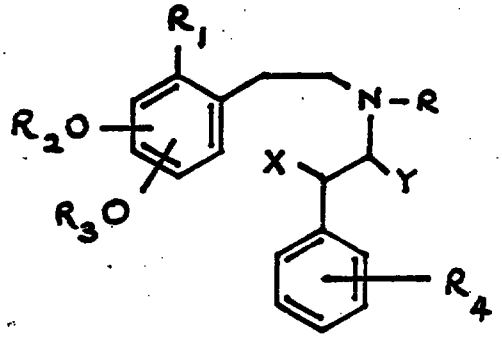
16. A compound according to claim 15, wherein the salt is a hydrobromide, hydrochloride or methanesulfonate salt.

17. A compound according to any of claims 1 to 14 in the form of the free base or the methane sulfonate salt.

18. A compound according to any of the preceding claims as herein specifically described in any of Examples 1 to 23.

19. A process for preparing a compound of formula I as defined in claim 1 which comprises the steps of

(1) cyclizing a compound of the structural formula



III

in which X is hydroxy or its functional equivalent, Y is H_2 or =O, R, R_1 and R_4 are as defined in claim 1, and R_2 and R_3 which are the same or different, are lower alkyl of 1—5 carbons or together represent methylene or ethylene;

(2) reducing the amido group, if present, in the cyclization product from step 1 in which Y is =O;

(3) optionally removing any O- or N-protective groups from the product of steps 1, 2 or 5 using conventional reactions;

* C L M S *

(4) optionally O- or N-acylating or alkylating the product of steps 1, 2, 3 or 5 using conventional reactions; and

(5) optionally forming a pharmaceutically acceptable salt of the product of steps 1, 2, 3 or 4 using conventional reactions.

20. A process according to claim 19, in which R_1 is chloro, R_2 and R_3 are both hydrogen, R_2O and R_3O are in the 7- and 8-positions, R is hydrogen, and R_4 is *p*-hydroxy.

21. A process according to claim 19, in which R_1 is chloro, R_2 and R_3 are both hydrogen, R_2O and R_3O are in the 7- and 8-positions, R is methyl, and R_4 is hydrogen.

22. A process according to any of claims 19 to 21, substantially as hereinbefore illustrated in any one of Examples 1 to 20.

23. A compound according to any of claims 1 to 18, when prepared by a process according to any of claims 19 to 22.

24. A pharmaceutical composition comprising a compound according to any of claims 1 to 18 and 23 and a pharmaceutical carrier.

25. A composition according to claim 24, in dosage unit form.

26. A pharmaceutical composition, substantially as herein described in Example 24 or Example 25.

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