United States Patent Office 3,250,768 Patented May 10, 1966

3,250,768

SUBSTITUTED-METHYLENE DERIVATIVES OF RING E KETO YOHIMBE ALKALOIDS

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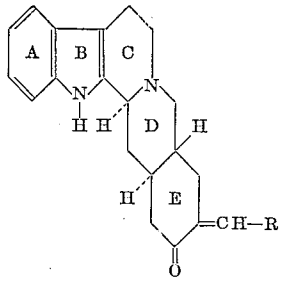
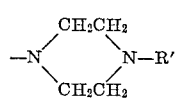
No Drawing. Filed Apr. 28, 1965, Ser. No. 451,627
20 Claims. (Cl. 260—240)

This application is a continuation-in-part of our copending application Serial No. 157,251, filed December 5, 1961, now abandoned.

This invention relates to novel substituted-methylene derivatives of ring E keto yohimbe alkaloids and, more particularly, is concerned with novel substituted-18-methylene derivatives of 17-ketoyohimbane which may be represented by the following general formula:

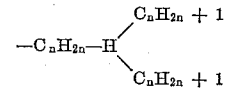


wherein R is lower alkylthio, lower alkylamino, di(lower alkyl)amino, lower cycloalkylamino, anilino, substituted anilino, naphthylamino, pyrrolidino, piperidino, morpholino, pyridylamino, pyridylmethylamino, 4-substituted piperazino, 4-substituted piperidino, lower alkoxy(lower alkyl)amino and di(lower alkyl)amino(lower alkyl)-amino. Suitable lower alkylthio substituents contemplated by the present invention are those having from 1 to 6 carbon atoms such as, for example, methylthio, ethylthio, isopropylthio, tert-butylthio, etc. Suitable lower alkylamino substituents contemplated by the present invention are those having from 1 to 6 carbon atoms such as ethylamino, n-propylamino, n-butylamino, isobutylamino, etc. Suitable di(lower alkyl)amino substituents contemplated by the present invention are those having from 2 to 8 carbon atoms such as, for example, dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino, (N-ethyl-N-hexyl)amino, etc. Suitable lower cycloalkylamino substituents may be cyclopropylamino, cyclopentylamino, cyclohexylamino, and the like. Suitable substituted anilino groups may be, for example, lower alkoxyanilino and lower alkylanilino wherein the lower alkoxy and lower alkyl groups are from 1 to 3 carbon atoms, haloanilino, acetamidoanilino and di(lower alkyl)aminoanilino wherein the di(lower alkyl)amino group is from 2 to 6 carbon atoms. Pyridylamino is exemplified by 2-pyridylamino, 3-pyridylamino and 4-pyridylamino; whereas pyridylmethylamino is exemplified by 2-pyridylmethylamino, 3-pyridylmethylamino and 4-pyridylmethylamino. Suitable 4-substituted piperazino substituents may be represented by the following formula:

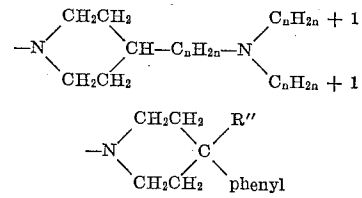


wherein R' is phenyl, lower alkyl of from 1 to 4 carbon

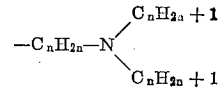
atoms, lower alkoxycarbonyl of from 2 to 4 carbon atoms or a side chain of the formula:



wherein *n* is a whole number from 1 to 4. Suitable 4-substituted piperidino substituents may be represented by the following general formulae:



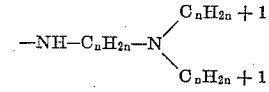
wherein *n* is a whole number from 1 to 4 and R'' is cyano, acetamidomethyl, lower alkoxy of from 1 to 4 carbon atoms, lower alkanoyl of from 2 to 4 carbon atoms, lower alkanoyloxy of from 2 to 4 carbon atoms, lower alkoxycarbonyl of from 2 to 4 carbon atoms or a side chain of the formula:



wherein *n* is a whole number from 1 to 4. Suitable lower alkoxy(lower alkyl)amino substituents contemplated by the present invention may be represented by the following formula:

$$—NH—C_nH_{2n}—OR'''$$

wherein R''' is lower alkyl of from 1 to 3 carbon atoms and *n* is a whole number from 2 to 4. Suitable di(lower alkyl)amino(lower alkyl)amino substituents contemplated by the present invention may be represented by the following general formula:



wherein *n* is a whole number from 1 to 4.

The novel compounds of the present invention are, in general, white to tan crystalline solids, the free bases of which are soluble in organic solvents such as lower alkanols, chloroform, dimethylformamide, dioxane, pyridine and the like; and the salts of which are soluble in polar solvents such as water or lower alkanols.

The organic free bases of this invention form non-toxic acid-addition salts with a variety of organic and inorganic salt-forming agents. Thus, acid-addition salts, formed by admixture of the organic free base with an acid, suitably in a neutral solvent, are formed with such acids as sulfuric, phosphoric, hydrochloric, hydrobromic, sulfamic, citric, lactic, tartaric, acetic, gluconic and the like. For purposes of this invention the free bases are equivalent to their non-toxic acid-addition salts.

The novel compounds of the present invention are valuable hypotensive agents of low toxicity and may be administered orally or parenterally. When so administered they have been found to exhibit hypotensive action in amounts ranging from about 25 to about 350 milligrams per kilogram of body weight. In addition, some of the novel compounds of the present invention are also useful as anorexigenic agents and some have been found to exhibit tranquilizing action.

The novel compounds of the present invention may be prepared from yohimban-17-one which has been described by Witkop, Ann. 554, 83 (1943). The first step in the synthesis of the novel compounds of the present invention

consists of the formylation of yohimban-17-one with a lower alkyl formate such as methyl or ethyl formate, in the presence of a suitable base such as an alkali metal alkoxide, sodium hydride, sodamide, and the like. When yohimban-17-one is so treated, there is obtained 18-hydroxymethyleneyohimban-17-one in good yield.

The above-described 18-hydroxymethyleneyohimban-17-one intermediate may be treated wtih an appropriate lower alkyl mercaptan in the presence of an acid catalyst such as p-toluene-sulfonic acid, sulfuric acid, acetic acid and the like to yield the corresponding lower alkylthiomethylene derivatives of the yohimban-17-one. The preferred method is to treat the hydroxy-methylene intermediate with a lower alkyl mercaptan in the presence of glacial acetic acid and anhydrous magnesium sulfate.

The above described hydroxymethyleneyohimban-17-one intermediate may be treated with an appropriate primary or secondary amine at temperatures of from 50° C. to 100° C. for periods of time ranging from half an hour to 5 hours whereby the corresponding monosubstituted aminomethylene or disubstituted aminomethylene derivatives of yohimban-17-one may be readily obtained.

The novel compounds of the present invention may be used as such but more preferably are used in the form of their non-toxic acid-addition salts which may be readily prepared as described hereinabove.

The invention will be described in greater detail in conjunction with the following specific examples.

Example 1.—Preparation of 18-hydroxymethylene-yohimban-17-one

To a cooled mixture of 10.0 g. of yohimban-17-one, 10.0 g. of sodium methoxide, and 300 ml. of sodium-dried benzene was added 14 ml. of ethyl formate. The mixture was stirred under nitrogen at room temperature for 20 hours and poured onto a mixture of 300 g. of ice and 200 ml. of water. The organic layer was separated and washed with three, 100-ml. portions of 0.1 N sodium hydroxide. The basic washings and aqueous layer were combined and neutralized in the cold with acetic acid. Filtration afforded 9.4 g. of 18-hydroxymethyleneyohimban-17-one hemihydrate as tan crystals, M.P. 140°–147° C. On standing in the cold overnight, the mother liquor gave an additional 1.8 g. of crystals. Recrystallization from methanol afforded colorless needles, sintering to a glass at 145°–148° C., M.P. 207°–210° C. (dec.).

Example 2.—Preparation of 18-hydroxymethylene yohimban-17-one

A mixture of 5.0 g. of yohimban-17-one, 5.0 g. of sodium methoxide, 150 ml. of dry peroxide-free dioxane, and 7.0 ml. of ethyl formate was stirred at room temperature under nitrogen for 21 hours. The mixture was neutralized with acetic acid and concentrated nearly to dryness. The residue was crystallized from aqueous methanol to yield 5.3 g. of 18-hydroxymethyleneyohimban-17-one hemihydrate as tan crystals, sintering to a glass at 145°–154° C., M.P. 207°–210° C. (dec.).

Example 3.—Preparation of 18-n-butylthiomethylene-yohimban-17-one

To a mixture of 0.663 g. of 18-hydroxymethyleneyohimban-17-one, 2.0 g. of magnesium sulfate, and 5.0 ml. of 1-butanethiol was added 10 ml. of acetic acid. The mixture was stirred at room temperature for 20 hours and filtered. The filtrate was partitioned between 50 ml. of chloroform and 100 ml. of 4 N sodium hydroxide. After further chloroform extractions the combined organic layers were dried over magnesium sulfate and concentrated to give 0.660 g. of off-white crystals of 18-n-butylthiomethyleneyohimban - 17 - one. Recrystallization from acetone gave colorless crystals, M.P. 219°–222° C. (dec.).

Other compounds which can be prepared according to the above-described procedure are, for example:

18-methylthiomethyleneyohimban-17-one,
18-ethylthiomethyleneyohimban-17-one,
18-n-hexylthiomethyleneyohimban-17-one.

Example 4.—Preparation of 18-n-butylaminomethylene-yohimban-17-one

A mixture of 8.29 g. of 18-hydroxymethyleneyohimban-17-one, 6.0 ml. of butylamine and 100 ml. of ethanol was refluxed for 2 hours. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. Chilling and filtering gave 7.1 g. of tan crystals, M.P. 237°–240° C. (dec.). The solid was dissolved in acetone-ethanol (95:5) and the solution concentrated on a steam bath. Dilution with water and chilling gave 4.45 g. of 18-n-butylaminomethyleneyohimban-17-one as light tan crystals, M.P. 244°–246° C. (dec.).

Other compounds which can be prepared according to the above-described procedure are, for example:

18-methylaminomethyleneyohimban-17-one,
18-ethylaminomethyleneyohimban-17-one,
18-isopropylaminomethyleneyohimban-17-one,
18-sec-butylaminomethyleneyohimban-17-one.

Example 5.—Preparation of 18-isobutylaminomethylene-yohimban-17-one

A mixture of 2.0 g. of 18-hydroxymethyleneyohimban-17-one, 1.5 ml. of isobutylamine, and 30 ml. of ethanol was refluxed for 5 hours. After standing overnight, the solution was treated with activated charcoal, filtered, and the filtrate concentrated under reduced pressure to a brown glass. The glass was triturated with 100 ml. of ether to give 1.42 g. of 18-isobutylaminomethyleneyohimban-17-one, containing one-fourth mole of water of crystallization, as tan crystals, M.P. 210°–220° C. (dec.). Recrystallization from aqueous ethanol with the aid of activated charcoal afforded hygroscopic pale yellow needles, M.P. 222°–226° C. (dec.).

Other compounds which can be prepared according to the above-described procedure are, for example:

18-(1-ethylbutyl)aminomethyleneyohimban-17-one,
18-(2-methylamyl)aminomethyleneyohimban-17-one,
18-(1,1,2-trimethylpropyl)aminomethyleneyohimban-17-one.

Example 6.—Preparation of 18-tert-butylaminomethyl-eneyohimban-17-one

A mixture of 10.6 of 18-hydroxymethyleneyohimban-17-one, 7.0 ml. of tert-butylamine and 150 ml. of ethanol was refluxed for 5 hours. The solvent was removed under reduced pressure and the residue was dissolved in benzene. The solvent was removed under reduced pressure and the residue was triturated with methanol. The resulting suspension was chilled and filtered and the filtrate was concentrated under reduced pressure. The residue was triturated with ether and filtered to give 7.4 g. of tan crystals. Precipitation from ethyl acetate and recrystallization from aqueous acetone and acetone gave 2.84 g. of 18-tert-butylaminomethyleneyohimban-17-one as tan needles, M.P. 240°–243° C. (dec.).

Example 7.—Preparation of 18-diethylaminomethylene-yohimban-17-one

A mixture of 8.29 g. of 18-hydroxymethyleneyohimban-17-one, 5.0 ml. of diethylamine and 50 ml. of ethanol was refluxed for 1.5 hours. The solvent was removed under pressure. The residue was dissolved in acetone and the solvent removed under pressure. The residue was triturated with acetone and the mixture chilled and filtered to give 6.0 g. of tan crystals, M.P. 222°–226° C. (dec.). Recrystallization from acetone with the aid of activated charcoal gave 2.90 g. of 18-diethylaminomethyleneyohimban-17-one as tan crystals, M.P. 225°–228° C. (dec.).

Other compounds which can be prepared according to the above-described procedure are, for example:

18-dimethylaminomethyleneyohimban-17-one,
18-di-n-propylaminomethyleneyohimban-17-one.

Example 8.—Preparation of 18-di-n-proplaminomethyleneyohimban-17-one

A mixture of 8.29 g. of 18-hydroxyyohimban-17-one, 6.0 ml. of dipropylamine and 100 ml. of ethanol was refluxed for 1.5 hours. The mixture was chilled and filtered to give 7.75 g. of yellow crystals, M.P. 241°–245° C. (dec.). Recrystallization from ethanol gave 6.70 g. of 18-di-n-propylaminomethyleneyohimban-17-one as tan crystals, M.P. 236°–238° C. (dec.).

Other compounds which can be prepared according to the above-described procedure are, for example:

18-(N-methyl-N-amyl)aminomethyleneyohimban-17-one,
18-(N-ethyl-N-hexyl)aminomethyleneyohimban-17-one,
18-(N-ethyl-N-isobutyl)aminomethyleneyohimban-17-one,

Example 9.—Preparation of 18-cyclohexylaminomethyleneyohimban-17-one

A mixture of 8.29 g. of 18-hydroxymethyleneyohimban-17-one, 6.0 ml. of cyclohexylamine and 100 ml. of ethanol was refluxed for 1.5 hours. The mixture was chilled and filtered to give 5.6 g. of tan crystals, M.P. 275°–280° C. (dec.). Recrystallization from ethanol gave 3.95 g. of 18-cyclohexylaminomethyleneyohimban-17-one as tan crystals, M.P. 275°–278° C. (dec.).

Other compounds which can be prepared according to the above-described procedure are, for example:

18-cyclopropylaminomethyleneyohimban-17-one,
18-cyclobutylaminomethyleneyohimban-17-one,
18-cyclopentylaminomethyleneyohimban-17-one,
18-(2-methylcyclopenyl)aminomethyleneyohimban-17-one.

Example 10.—Preparation of 18-anilinomethyleneyohimban-17-one

A mixture of 2.65 g. of 18-hydroxymethyleneyohimban-17-one, 0.90 ml. of aniline, and 40 ml. of ethanol was refluxed for 3 hours. The mixture was cooled and filtered to give 2.55 g. of 18-anilinomethyleneyohimban-17-one, containing one-fourth mole of water of crystallization, as yellow crystals, M.P. 305°–310° C. (dec.). Recrystallization from N,N-dimethylformamide afforded yellow crystals, M.P. 303°–307° C. (dec.).

Other compounds which can be prepared according to the above-described procedure are, for example:

18-(o-methoxyanilino)methyleneyohimban-17-one,
18-(p-ethoxyanilino)methyleneyohimban-17-one,
18-(m-isopropoxyanilino)methyleneyohimban-17-one,
18-(o-methylanilino)methyleneyohimban-17-one,
18-(m-ethylanilino)methyleneyohimban-17-one,
18-(p-isoamylanilino)methyleneyohimban-17-one,
18-(o-chloroanilino)methyleneyohimban-17-one,
18-(m-bromoanilino)methyleneyohimban-17-one,
18-(p-iodoanilino)methyleneyohimban-17-one,
18-(m-acetamidoanilino)methyleneyohimban-17-one,
18-(p-dimethylaminoanilino)methyleneyohimban-17-one,
18-(1-naphthylamino)methyleneyohimban-17-one,
18-(2-naphthylamino)methyleneyohimban-17-one.

Example 11.—Preparation of 18-pyrrolidinomethyleneyohimban-17-one

A mixture of 2.0 g. of 18-hydroxymethyleneyohimban-17-one and 1.5 ml. of distilled pyrrolidine in 30 ml. of absolute ethanol was refluxed for two and one-half hours. Cooling and filtration gave 1.49 g. of 18-pyrrolidinomethyleneyohimban-17-one as yellow crystals, M.P. 306°–309° C. (dec.) (when inserted in an oil bath preheated to 150° C.). Recrystallization from absolute ethanol with the aid of activated charcoal gave yellow crystals, M.P. 308°–309° C. (dec.) (when inserted in an oil bath preheated to 305° C.).

Another compound which can be prepared according to the above-described procedure is 18-piperidinomethyleneyohimban-17-one.

Example 12.—Preparation of 18-morpholinomethyleneyohimban-17-one

A mixture of 6.63 g. of 18-hydroxymethyleneyohimban-17-one, 2.0 ml. of morpholine and 75 ml. of ethanol was refluxed for 2 hours. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate-acetone (95:5) was treated with activated carbon and filtered. The filtrate was chilled and filtered and the precipitate was washed with ethyl acetate to give 4.1 g. of orange amorphous solid. The solid was dissolved in dichloromethane and chromatographed over 3.5 g. of Florsil. Elution with dichloromethane and evaporation of the eluate gave 1.8 g. of 18-morpholinomethyleneyohimban 17-one as a pale orange glass, sintering above 160° C. and slowly melting with decomposition at 175°–185° C.

Example 13.—Preparation of 18-(2-pyridylamino)methyleneyohimban-17-one

A mixture of 6.63 g. of 18-hydroxymethyleneyohimban-17-one, 2.07 g. of 2-aminopyridine and 75 ml. of ethanol was refluxed for 2 hours. Chilling and filtering gave 2.7 g. of yellow-brown crystals, M.P. 250–253° C. (dec.). The filtrate was concentrated under reduced pressure and the residue triturated with ethanol-ethyl acetate (1:1). Chilling and filtering gave 1.7 g. of yellow crystals, M.P. 258°–261° C. (dec.). The two crops were combined, dissolved in ethanol-dichloromethane and the solution treated with activated carbon. The mixture was filtered and the filtrate concentrated to give 1.8 g. of 18-(2-pyridylamino)methyleneyohimban-17-one as yellow crystals, M.P. 262°–264° C. (dec.).

Example 14.—Preparation of 18-(3-pyridylamino)methyleneyohimban-17-one

A mixture of 6.63 g. of 18-hydroxymethyleneyohimban-17-one, 2.07 g. of 3-aminopyridine and 75 ml. of ethanol was refluxed for 2 hours. The mixture was chilled and filtered to give 5.5 g. of yellow crystals, M.P. 308°–311° C. (dec.). Concentration of the filtrate gave an additional 1.3 g. of product, M.P. 300°–304° C. (dec.). The two crops of crystals were combined, dissolved in dichloromethane-acetone, and the solution concentrated. Chilling and filtering gave 3.0 g. of 18-(3-pyridylamino)methyleneyohimban-17-one as yellow crystals, M.P. 311°–314° C. (dec.).

Example 15.—Preparation of 18-(4-pyridylamino)methyleneyohimban-17-one

A mixture of 6.63 g. of 18-hydroxymethyleneyohimban-17-one, 2.07 g. of 4-aminopyridine and 75 ml. of ethanol was refluxed for 2 hours. The dark solution was treated with activated carbon, filtered and the filtrate diluted with cyclohexane. The mixture was chilled and filtered and the filtered concentrated to a glass. The glass was dissolved in acetone and the solution diluted with water. Chilling and filtering gave 1.8 g. of product which was recrystallized from acetone to give 18-(4-pyridylamino)methyleneyohimban-17-one as tan crystals, M.P. 306°–309° C. (dec.).

Example 16.—Preparation of 18-(2-pyridylmethylamino)methyleneyohimban-17-one

A mixture of 6.63 g. of 18-hydroxymethyleneyohimban-17-one, 2.38 g. of 2-aminomethylpyridine and 75 ml. of ethanol was refluxed for 1.5 hours. The solvent was removed under reduced pressure and the residue was dis-

solved in acetone. The solution was diluted with ethyl acetate and the insoluble gum which separated was removed by filtration. The filtrate was concentrated under reduced pressure to give a glass which was dissolved in 50 ml. of hot benzene. Dilution with 10 ml. of cyclohexane gave a gum which on trituration, changed to a tan amorphous solid. The solid (7.0 g.) was dissolved in 100 ml. of ethyl acetate, treated with activated carbon and the mixture was filtered. The filtrate was diluted with 100 ml. of petroleum ether (B.P. 30°–60° C.) to give 5.5 g. of solid, changes to dark mass 125°–135° C. The solid was purified by slurrying in 150 ml. of ethyl acetate, filtering from the insoluble solid and diluting the filtrate with 300 ml. of petroleum ether (B.P. 30°–60° C.). Chilling and filtering gave 3.58 g. of 18-(2-pyridylmethylamino)methyleneyohimban-17-one as a tan amorphous solid, sinters above 100° C. to a red glass which slowly changes to a dark liquid.

Example 17.—Preparation of 18-(3-pyridylmethylamino)-methyleneyohimban-17-one

A mixture of 6.63 g. of 18-hydroxymethyleneyohimban-17-one, 2.38 g. of 3-aminomethylpyridine and 75 ml. of ethanol was refluxed for 2 hours. The solvent was removed under reduced pressure to give a brown glass. The glass was dissolved in acetone and the solution was chilled to give 5.62 g. of tan crystals, M.P. 220°–225° C. (dec.). Recrystallization from acetone gave 2.25 g. of 18-(3-pyridylmethylamino)-methyleneyohimban-17 - one as tan crystals, M.P. 238°–241° C. (dec.).

Example 18.—Preparation of 18-(4-pyridylmethylamino)-methyleneyohimban-17-one

A mixture of 6.63 g. of 18-hydroxymethyleneyohimban-17-one, 2.38 g. of 4-aminomethylpyridine and 75 ml. of ethanol was refluxed for 2 hours. The solvent was removed under reduced pressure and the residual glass dissolved in acetone. Chilling and filtering gave 4.68 g. of tan crystals, M.P. 160°–170° C. (dec.). The crystals were dissolved in a mixture of 300 ml. of acetone and 15 ml. of methanol and the solution was treated with activated carbon, filtered and the filtrate concentrated. Chilling and filtering gave 3.1 g. of tan crystals, M.P. 176°–180° C. (dec.) (with previous sintering). Recrystallization from acetone gave 1.95 g. of 18-(4-pyridylmethylamino)methyleneyohimban-17-one as tan crystals, M.P. 181°–185° C. (dec.) (with previous sintering).

Example 19.—Preparation of 18-(4-ethoxycarbonyl-1-piperazinyl)-methyleneyohimban-17-one

A mixture of 8.29 g. of 18-hydroxymethyleneyohimban-17-one, 6.0 ml. of 1-carbethoxypiperazine and 50 ml. of ethanol was refluxed for 2.5 hours. The solvent was removed under reduced pressure and the residue was triturated with acetone. The mixture was chilled and filtered to give 9.0 g. of yellow crystals, M.P. 217°–220° C. (dec.). Recrystallization from acetone gave 5.50 g. of 18-(4-ethoxycarbonyl-1 - piperazinyl) - methyleneyohimban-17-one as yellow crystals, M.P. 222°–224° C. (dec.).

Other compounds which can be prepared according to the above-described procedure are, for example:

18-(4-methoxycarbonyl-1-piperazinyl)methyleneyohimban-17-one,
18-(4-phenyl-1-piperazinyl)methyleneyohimban-17-one,
18-(4-methyl-1-piperazinyl)methyleneyohimban-17-one,
18-(4-ethyl-1-piperazinyl)methyleneyohimban-17-one,
18-(4-isobutyl-1-piperazinyl)methyleneyohimban-17-one.

Example 20.—Preparation of 18-[4-(3-dimethylaminopropyl)-1-piperazinylmethylene]yohimban-17-one

A mixture of 5.0 g. of 18-hydroxymethyleneyohimban-17-one, 2.57 g. of 1-(3-dimethylaminopropyl)piperazine and 50 ml. of ethanol was refluxed for 3 hours. The solvent was removed under reduced pressure and benzene was added several times and the solvent removed after each addition under reduced pressure. The residue was dissolved in acetone and the solution was treated with activated carbon and filtered. The filtrate was diluted with heptane and filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in ether-dichloromethane (9:1) and filtered through a column of Florisil (30 g.). Elution with 600 ml. of ether-dichloromethane (9:1) and 400 ml. of dichloromethane, and concentration of the eluate, gave the product as an orange glass. Purification was accomplished by chromatography over 50 g. of Florisil with dichloromethane as the solvent. There was obtained 1.2 g. of 18-[4-(3-dimethylaminopropyl)-1 - piperazinylmethylene]yohimban-17-one as a pale orange glass, sintering above 115° C. and slowly melting at 125°–140° C.

Other compounds which can be prepared according to the above-described procedure are, for example:

18-[4-(2-diethylaminoethyl)-1-piperazinylmethylene]-yohimban-17-one,
18-[4-(4-diisopropylaminobutyl)-1-piperazinylmethylene]yohimban-17-one,
18-[4-(4-diethylamino-1-methylbutyl)-1-piperazinylmethylene]yohimban-17-one.

Example 21.—Preparation of 18-[4-(3-dimethylaminopropyl)-piperidinomethylene]yohimban-17-one

A mixture of 6.63 g. of 18-hydroxymethyleneyohimban-17-one, 3.75 g. of 4-(3-dimethylaminopropyl)piperidine and 75 ml. of ethanol was refluxed for 2.5 hours. The solvent was removed under reduced pressure to give a glass and the glass was triturated with acetone to give crystals. Chilling and filtering gave 6.54 g. of product. Recrystallization from acetone gave 4.4 g. of 18-[4-(3-dimethylaminopropyl)piperidinomethylene]yohimban - 17-one as tan crystals, M.P. 193°–196° C. (dec.).

Other compounds which can be prepared according to the above-described procedure are, for example:

18-[4-(2-diethylaminoethyl)piperidinomethylene]-yohimban-17-one,
18-[4-(4-diisopropylaminobutyl)piperidinomethylene]-yohimban-17-one,
18-[4-(4-diethylamino-1-methylbutyl)piperidinomethylene]yohimban-17-one,
18-[4-phenyl-4-(3-dimethylaminopropyl)piperidinomethylene]yohimban-17-one,
18-[4-phenyl-4-(2-diethylaminoethyl)piperidinomethylene]yohimban-17-one.
18-[4-phenyl-4-(4-diisopropylaminobutyl)piperidinomethylene]yohimban-17-one,
18-[4-phenyl-4-(4-diethylamino-1-methylbutyl)-piperidinomethylene]yohimban-17-one.

Example 22.—Preparation of 18-(3-methoxypropylamino)-methyleneyohimban-17-one

A mixture of 6.63 g. of 18-hydroxymethyleneyohimban-17-one, 2.23 g. of 3-methoxypropylamine and 75 ml. of ethanol was refluxed for 2 hours. The solvent was removed under reduced pressure to give a glass which was dissolved in acetone and the solution chilled. Filtration gave 4.80 g. of tan crystals, M.P. 223–225° C. (dec.). Recrystallization from acetone gave 3.25 g. of 18-(3-methoxypropylamino)methyleneyohimban-17-one as light tan crystals, M.P. 228°–230° C. (dec.).

Other compounds which can be prepared according to the above-described procedure are, for example:

18-(2-methoxypropylamino)methyleneyohimban-17-one,
18-(3-isopropoxybutylamino)methyleneyohimban-17-one,
18-(4-methoxybutylamino)methyleneyohimban-17-one.

Example 23.—Preparation of 18-(3-dimethylaminopropylamino)methyleneyohimban-17-one

A mixture of 8.29 g. of 18-hydroxymethyleneyohimban-17-one, 7.0 ml. of 3-dimethylaminopropylamine and 100

ml. of ethanol was refluxed for 1.5 hours. The solvent was removed under reduced pressure and the residue was triturated with ether. Filtration gave 5.90 g. of tan solid. A second crop of 2.0 g. was obtained from the mother liquors. Several recrystallizations from acetone with the aid of activated charcoal give 3.2 g. of 18-(3-dimethylaminopropylamino)methyleneyohimban-17-one as tan crystals, M.P. 201°–203° C. (dec.).

Other compounds which can be prepared according to the above-described procedure are, for example:

18-(2-diethylaminoethylamino)methyleneyohimban-17-one,
18-(4-diisopropylaminobutylamino)methyleneyohimban-17-one,
18-(4-diethylamino-1-methylbutylamino)methyleneyohimban-17-one.

Example 24.—Preparation of 18-(4-acetamidomethyl-4-phenylpiperidino)methyleneyohimban-17-one

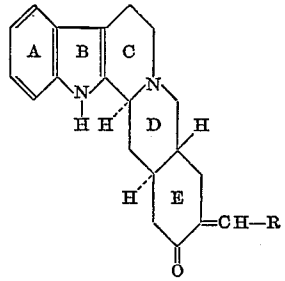
A mixture of 6.63 g. of 18-hydroxymethyleneyohimban-17-one, 5.11 g. of 4-acetamidomethyl-4-phenylpiperidine and 75 ml. of ethanol was refluxed for two hours. The solvent was removed under reduced pressure. The residue was dissolved in acetone, treated with activated charcoal, filtered and the filtrate was concentrated under reduced pressure. The residue was triturated with ethyl acetate and filtered to give 8.9 g. of 18-(4-acetamidomethyl-4-phenylpiperidino)methyleneyohimban-17-one as an amorphous solid, M.P. 155°–165° C. (with previous sintering).

Other compounds which can be prepared according to the above-described procedure are, for example:

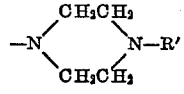
18-(4-cyano-4-phenylpiperidino)methyleneyohimban-17-one,
18-(4-ethoxycarbonyl-4-phenylpiperidino)methyleneyohimban-17-one,
18-(4-acetyl-4-phenylpiperidino)methyleneyohimban-17-one,
18-(4-ethoxy-4-phenylpiperidino)methyleneyohimban-17-one,
18-(4-acetoxy-4-phenylpiperidino)methyleneyohimban-17-one.

What is claimed is:

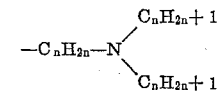
1. A member selected from the group consisting of a compound of the formula:



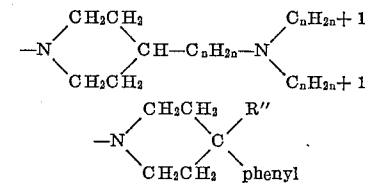
wherein R is selected from the group consisting of lower alkylthio; lower alkylamino; di(lower alkyl)amino; lower cycloalkylamino; anilino; lower alkoxyanilino; lower alkylanilino; haloanilino; acetamidoanilino; di(lower alkyl)aminoanilino; naphthylamino; pyrrolidino; piperidino; morpholino; pyridylamino; pyridylmethylamino; 4-substituted piperazino of the formula:



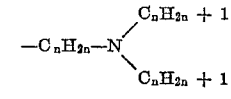
wherein R′ is selected from the group consisting of phenyl, lower alkyl, lower alkoxycarbonyl and a side chain of the formula:



wherein *n* is a whole number from 1 to 4; 4-substituted piperidino of the formulae:



wherein *n* is a whole number from 1 to 4 and R″ is selected from the group consisting of cyano, acetamidomethyl, lower alkoxy, lower alkanoyl, lower alkanoyloxy, lower alkoxycarbonyl and a side chain of the formula:



wherein *n* is a whole number from 1 to 4; lower alkoxy (lower alkyl)amino of the formula:

$$—NH—C_nH_{2n}—OR'''$$

wherein R‴ is lower alkyl and *n* is a whole number from 2 to 4 and di(lower alkyl)amino(lower alkyl)amino.

2. 18-n-butylthiomethyleneyohimban-17-one.
3. 18-n-butylaminomethyleneyohimban-17-one.
4. 18-isobutylaminomethyleneyohimban-17-one.
5. 18-diethylaminomethyleneyohimban-17-one.
6. 18-di-n-propylaminomethyleneyohimban-17-one.
7. 18-cyclohexylaminomethyleneyohimban-17-one.
8. 18-anilinomethyleneyohimban-17-one.
9. 18-pyrrolidinomethyleneyohimban-17-one.
10. 18-morpholinomethyleneyohimban-17-one.
11. 18-(2-pyridylamino)methyleneyohimban-17-one.
12. 18-(4-pyridylamino)methyleneyohimban-17-one.
13. 18-(2-pyridylmethylamino)methyleneyohimban-17-one.
14. 18-(3-pyridylmethylamino)methyleneyohimban-17-one.
15. 18-(4-ethoxycarbonyl-1-piperazinyl)methyleneyohimban-17-one.
16. 18-[4-(3-dimethylaminopropyl)-1-piperazinylmethylene]yohimban-17-one.
17. 18-[4-(3-dimethylaminopropyl)piperidinomethylene]yohimban-17-one.
18. 18-(3-methoxypropylamino)methyleneyohimban-17-one.
19. 18-(3-dimethylaminopropylamino)methyleneyohimban-17-one.
20. 18-(4-acetamidomethyl-4-phenylpiperidino)-methyleneyohimban-17-one.

No references cited.

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