United States Patent [19]

Drukker

[11] **3,894,001**

[45] **July 8, 1975**

[54] **11-AMINOALKYL- AND 11-CYCLICAMINOMORPHANTHRIDINES**

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[73] Assignee: **Colgate-Palmolive Company**, New York, N.Y.

[22] Filed: **Nov. 20, 1972**

[21] Appl. No.: **307,933**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 848,355, Aug. 7, 1969, Pat. No. 3,699,099, and a continuation-in-part of Ser. No. 48,506, June 22, 1970, abandoned.

[52] **U.S. Cl.**.....**260/239 D;** 260/247.1 M; 260/247.5 R; 260/326.5 CA; 260/326.81; 260/268 TR; 424/244; 424/248; 424/250; 424/267; 424/274; 260/293.59

[51] **Int. Cl.**..... **C07d 41/08**

[58] **Field of Search**. 260/239 D, 247.1 M, 247.5 R, 260/326.5 CA, 326.81, 268 TR, 293.59

[56] **References Cited**

UNITED STATES PATENTS

3,317,537 5/1967 Drukker..... 260/239 D

Primary Examiner—Henry R. Jiles
Assistant Examiner—Robert T. Bond
Attorney, Agent, or Firm—T. F. Kryshak; M. L. Youngs

[57] ABSTRACT

The compounds are 11-aminoalkylmorphanthridines and 11-cyclicaminomorphanthridines which are useful as central nervous system depressants of the tranquilizing type, muscle relaxants and analgetic agents. Representative of the compounds disclosed are 11-(3-dimethylaminopropyl)morphanthridine and 11-(N-methyl-4-piperidyl)morphanthridine. The method of preparing the compounds is by the oxidation of the corresponding 5,6-dihydromorphanthridine with active manganese dioxide.

10 Claims, No Drawings

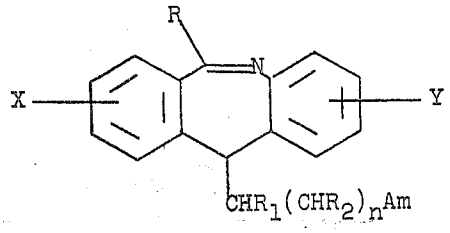
11-AMINOALKYL- AND 11-CYCLICAMINOMORPHANTHRIDINES

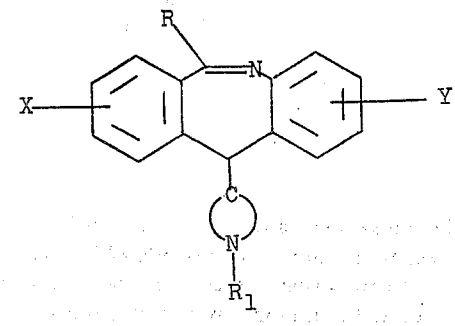
RELATED CASES

This application is a continuation-in-part of my copending applications Ser. Nos. 848,355 now U.S. Pat. No. 3,699,099 and 48,506, now abandoned, filed Aug. 7, 1969, and June 22, 1970, respectively.

DESCRIPTION OF THE INVENTION

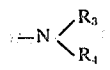
The compounds of the present invention may be represented by the following formulae:





I

in which X and Y are members of the group consisting of hydrogen, halogen such as chloro, bromo and fluoro, an alkyl of 1 to 4 carbon atoms such as methyl and ethyl, an alkoxy of 1 to 3 carbon atoms such as methoxy, ethoxy and propoxy, a thio-lower alkyl such as thiomethyl and thioethyl and trifluoromethyl, R, R_1 and R_2 are hydrogen or a lower alkyl of 1 to 4 carbon atoms, n is 0 to 4 and Am is selected from

a. 

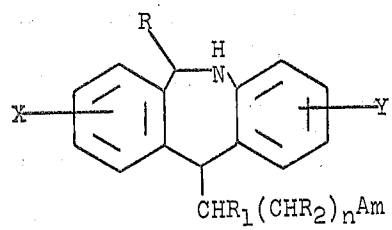
in which R_3 and R_4 are selected from hydrogen, lower alkyl of 1 to 4 carbon atoms such as methyl, ethyl or isopropyl and a phenyl-lower alkyl of 7 to 13 carbon atoms such as benzyl, phenethyl or phenylisopropyl, or

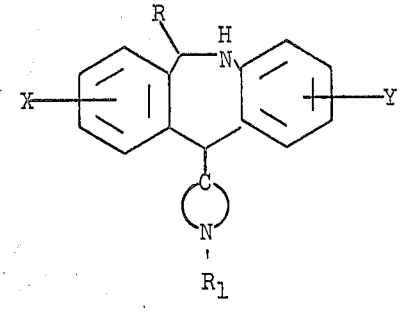
b. a heterocyclicamino group such as morpholino, pyrrolidino, piperidino, N-lower alkyl piperazino in which the lower alkyl is 1 to 4 carbon atoms such as N-methyl piperazino, N-phenyl-lower alkyl piperazino in which the lower alkyl is 1 to 4 carbon atoms such as N-benzyl piperazino and N-(hydroxy-lower alkyl)-piperazino groups in which the lower alkyl is 1 to 4 carbon atoms such as 4-(β-hydroxyethyl piperazino), and

-C◯N-

is a cyclicamino group such as 3-piperidyl, 4-piperidyl, 3-pyrrolidyl, 3-homopiperidyl and 4-homopiperidyl.

The compounds of the present invention may be conveniently prepared from the corresponding 11-aminoalkyl-5,6-dihydromorphanthridines and the 11-cyclicamino-5,6-dihydromorphanthridines which have the following formulae





in which X, Y, R, R_1, R_2, n, Am and

-C◯N-

are as previously defined.

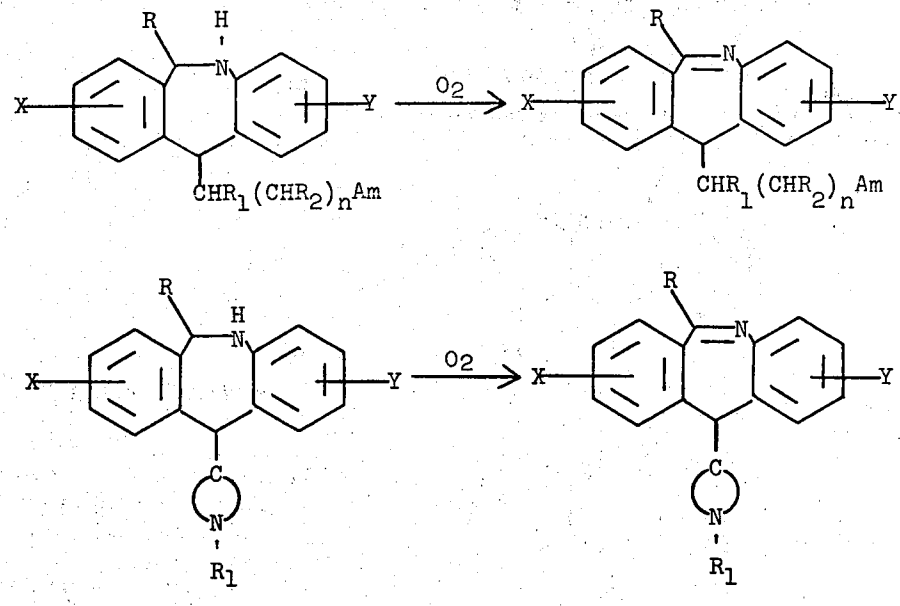
Representative of the compounds which may be employed as starting materials are

11-(3-dimethylaminopropyl)-5,6-dihydromorphanthridine,
2-chloro-11-(3-dimethylaminopropyl)-5,6-dihydromorphanthridine,
8-chloro-11-(3-dimethylaminopropyl)-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-(3-dimethylaminopropyl)-5,6-dihydromorphanthridine,
11-(3-diethylaminopropyl)-5,6-dihydromorphanthridine,
2-chloro-11-(3-diethylaminopropyl)-5,6-dihydromorphanthridine,
8-chloro-11-(3-diethylaminopropyl)-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-(3-diethylaminopropyl)-5,6-dihydromorphanthridine,
11-(3-methylaminopropyl)-5,6-dihydromorphanthridine,
2-chloro-11-(3-methylaminopropyl)-5,6-dihydromorphanthridine,
8-chloro-11-(3-methylaminopropyl)-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-(3-methylaminopropyl)-5,6-dihydromorphanthridine,
11-(N-methyl-N-benzylaminopropyl)-5,6-dihydromorphanthridine,
2-chloro-11-(N-methyl-N-benzylaminopropyl)-5,6-dihydromorphanthridine,
8-chloro-11-(N-methyl-N-benzylaminopropyl)-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-(N-methyl-N-benzylaminopropyl)-5,6-dihydromorphanthridine,
11-(N-methyl-piperazinopropyl)-5,6-dihydromorphanthridine,
2-chloro-11-(N-methyl-piperazinopropyl)-5,6-dihydromorphanthridine,
8-chloro-11-(N-methyl-piperazinopropyl)-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-(N-methyl-piperazinopropyl)-5,6-dihydromorphanthridine,
11-[3-(4-hydroxyethylpiperazinopropyl)]-5,6-dihydromorphanthridine,

2-chloro-11-[3-(4-hydroxyethylpiperazinopropyl)]-5,6-dihydromorphanthridine,
8-chloro-11-[3-(4-hydroxyethylpiperazinopropyl)]-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-[3-(4-hydroxyethylpiperazinopropyl)]-5,6-dihydromorphanthridine,
11-(N-methyl-4-piperidyl)-5,6-dihydromorphanthridine,
2-chloro-11-(N-methyl-4-piperidyl)-5,6-dihydromorphanthridine,
8-chloro-11-(N-methyl-4-piperidyl)-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-(N-methyl-4-piperidyl)-5,6-dihydromorphanthridine,
11-(N-benzyl-4-piperidyl)-5,6-dihydromorphanthridine,
2-chloro-11-(N-benzyl-4-piperidyl)-5,6-dihydromorphanthridine,
8-chloro-11-(N-benzyl-4-piperidyl)-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-(N-benzyl-4-piperidyl)-5,6-dihydromorphanthridine,
11-(N-methyl-3-piperidyl)-5,6-dihydromorphanthridine,
2-chloro-11-(N-methyl-3-piperidyl)-5,6-dihydromorphanthridine,
8-chloro-11-(N-methyl-3-piperidyl)-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-(N-methyl-3-piperidyl)-5,6-dihydromorphanthridine,
11-(N-ethyl-3-pyrrolidyl)-5,6-dihydromorphanthridine,
11-(N-benzyl-3-pyrrolidyl)-5,6-dihydromorphanthridine,
11-(N-methyl-3-homopiperidyl)-5,6-dihydromorphanthridine.

The above described starting materials are disclosed in my U.S. Pat. No. 3,267,094 issued Aug. 16, 1966. They may be prepared by the methods disclosed in that patent as well as other more recently developed methods.

In the preferred practice of the present invention the compounds are prepared by treating the appropriate 5,6-dihydromorphanthridine starting material with active manganese dioxide under reflux conditions in a suitable solvent such as benzene. When the reaction is complete the manganese dioxide is filtered off, rinsed with benzene and the filter concentrated to yield the desired material which may be purified by conventional means. The described process may be illustrated as follows:



in which all symbols are as previously defined.

Representative of the compounds which may be prepared by the described process are the following:

11-(3-dimethylaminopropyl)-morphanthridine,
2-chloro-11-(3-dimethylaminopropyl)-morphanthridine,
8-chloro-11-(3-dimethylaminopropyl)-morphanthridine,
2-trifluoromethyl-11-(3-dimethylaminopropyl)-morphanthridine,
11-(3-diethylaminopropyl)-morphanthridine,
2-chloro-11-(3-diethylaminopropyl)-morphanthridine,
8-chloro-11-(3-diethylaminopropyl)-morphanthridine,
2-trifluoromethyl-11-(3-diethylaminopropyl)-morphanthridine,
11-(3-methylaminopropyl)-morphanthridine,
2-chloro-11-(3-methylaminopropyl)-morphanthridine,
8-chloro-11-(3-methylaminopropyl)-morphanthridine,
2-trifluoromethyl-11-(3-methylaminopropyl)-morphanthridine,
11-(N-methyl-N-benzylaminopropyl)-morphanthridine,
2-chloro-11-(N-methyl-N-benzylaminopropyl)-morphanthridine,
8-chloro-11-(N-methyl-N-benzylaminopropyl)-morphanthridine,
2-trifluoromethyl-11-(N-methyl-N-benzylaminopropyl)-morphanthridine,
11-(N-methyl-piperazinopropyl)-morphanthridine,
2-chloro-11-(N-methyl-piperazinopropyl)-morphanthridine,
8-chloro-11-(N-methyl-piperazinopropyl)-morphanthridine,
2-trifluoromethyl-11-(N-methyl-piperazinopropyl)-morphanthridine,

11-[3-(4-hydroxyethylpiperazinopropyl)]-morphanthridine,
2-chloro-11-[3-(4-hydroxyethylpiperazinopropyl)]-morphanthridine,
8-chloro-11-[3-(4-hydroxyethylpiperzinopropyl)]-morphanthridine,
2-trifluoromethyl-11-[3-(4-hydroxyethylpiperazinopropyl)]-morphanthridine,
11-(N-methyl-4-piperidyl)-morphanthridine,
2-chloro-11-(N-methyl-4-piperidyl)-morphanthridine,
8-chloro-11-(N-methyl-4-piperidyl)-morphanthridine,
2-trifluoromethyl-11-(N-methyl-4-piperidyl)-morphanthridine,
11-(N-benzyl-4-piperidyl)-morphanthridine,
2-chloro-11-(N-benzyl-4-piperidyl)-morphanthridine,
8-chloro-11-(N-benzyl-4-piperidyl)-morphanthridine,
2-trifluoromethyl-11-(N-benzyl-4-piperidyl)-morphanthridine,
11-(N-methyl-3-piperidyl)-morphanthridine,
2-chloro-11-(N-methyl-3-piperidyl)-morphanthridine,
8-chloro-11-(N-methyl-3-piperidyl)-morphanthridine,
2-trifluoromethyl-11-(N-methyl-3-piperidyl)-morphanthridine,
11-(N-ethyl-3-pyrrolidyl)-morphanthridine,
11-(N-benzyl-3-pyrrolidyl)-morphanthridine, and
11-(N-methyl-3-homopiperidyl)-morphanthridine.

The compounds of the present invention have been found to possess utility as pharmaceutical and veterinary agents, especially as central nervous system depressants. For example, in mouse behavioral studies the compound 11-(3-dimethylaminopropyl) morphanthridine was found in a dose of 10 mg/kg intraperitoneally to cause central nervous system depression. The studies also indicated that the compound had an LD_{50} in excess of 100 mg/kg intraperitoneally.

The forementioned compound was also tested for tranquilizing activity in mice which had been isolated to induce an antisocial aggressive behavior. In the tests the compound was administered to the mice in doses of 5 and 20 mg/kg intraperitoneally and found to have an ED_{50} of about 20 mg/kg. The compound was also tested for analgetic activity in mice and was found to be effective against the effects of electrical stimulation in doses of 40 mg/kg intraperitoneally.

When employed as pharmaceutical agents the compounds are preferably used in the form of acid addition salts. Such acid addition salts may be conveniently prepared by conventional means such as by contacting the compounds with a suitable acid in a mutual solvent and then removing the solvent to obtain the desired salt. Examples of acids which may be used are hydrochloric acid, succinic acid, tartaric acid, benzoic acid or fumaric acid.

Quarternary ammonium salts of the compounds may be formed by conventional techniques employing a suitable alkylating agent such as methyl chloride, methyl iodide or ethyl bromide.

Pharmaceutical dosage forms containing the active ingredients are generally prepared by combining the active ingredient or ingredients with a major amount of one or more suitable pharmaceutical diluents and then forming the resulting mixture into unit dosage forms suitable for oral or parenteral administration.

The unit dosage forms will generally contain from 5 to 250 mg. of the active ingredients. One or more of such units may be administered daily depending upon the patient's physical size and the severity of the condition being treated. However, generally the daily dosage will not exceed 150 mg. of the active ingredient per kilogram of the patient's body weight.

Representative of a suitable pharmaceutical composition which may be prepared are the following:

TABLETS

11-(3-Dimethylaminopropyl) morphanthridine	25 g.
Methyl cellulose, 400 cps.	4 g.
Lactose	9 g.
Magnesium stearate	0.4 g.
Starch	1.6 g.

The powders, other than magnesium stearate, are granulated with water, passed through a No. 16 mesh screen and dried at 50° C. Magnesium stearate is mixed in and 40 mg. tablets are pressed.

The practice of the invention is further illustrated by the following examples:

EXAMPLE 1

11-(3-Dimethylaminopropyl)morphanthridine

Active manganese dioxide (25 grams) is refluxed with 250 ml. of benzene using a water separator. After 2 hours, 5.3 grams (0.019 mole) of 11-(3-dimethylaminopropyl)-5,6-dihydromorphanthridine in 100 ml. of benzene is added and the suspension stirred and refluxed for 18 hours. The MnO_2 is filtered off, rinsed with benzene, and the filtrate concentrated to yield the crude base. Chromatography over silica gel using benzene-methanol (19:1) as eluent followed by benzene-diethylamine (40:1) affords 11-(3-dimethylaminopropyl)morphanthridine.

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06.

Found: C, 82.24; H, 8.31; N, 10.22.

EXAMPLE 2

The process of Example 1 is repeated employing in place of 11-(3-dimethylaminopropyl)-5,6-dihydromorphanthridine one of the following:

2-chloro-11-(3-dimethylaminopropyl)-5,6-dihydromorphanthridine,
8-chloro-11-(3-dimethylaminopropyl)-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-(3-dimethylaminopropyl)-5,6-dihydromorphanthridine,
11-(3-diethylaminopropyl)-5,6-dihydromorphanthridine,
2-chloro-11-(3-diethylaminopropyl)-5,6-dihydromorphanthridine,
8-chloro-11-(3-diethylaminopropyl)-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-(3-diethylaminopropyl)-5,6-dihydromorphanthridine,
11-(3-methylaminopropyl)-5,6-dihydromorphanthridine,
2-chloro-11-(3-methylaminopropyl)-5,6-dihydromorphanthridine,
8-chloro-11-(3-methylaminopropyl)-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-(3-methylaminopropyl)-5,6-dihydromorphanthridine,
11-(N-methyl-N-benzylaminopropyl)-5,6-dihydromorphanthridine,

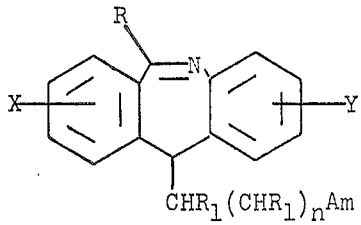
2-chloro-11-(N-methyl-N-benzylaminopropyl)-5,6-dihydromorphanthridine,
8-chloro-11-(N-methyl-N-benzylaminopropyl)-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-(N-methyl-N-benzylaminopropyl)-5,6-dihydromorphanthridine,
11-(N-methyl-piperazinopropyl)-5,6-dihydromorphanthridine,
2-chloro-11-(N-methyl-piperazinopropyl)-5,6-dihydromorphanthridine,
8-chloro-11-(N-methyl-piperazinopropyl)-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-(N-methyl-piperazinopropyl)-5,6-dihydromorphanthridine,
11-[3-(4-hydroxyethylpiperazinopropyl)]-5,6-dihydromorphanthridine
2-chloro-11-[3-(4-hydroxyethylpiperazinopropyl)]-5,6-dihydromorphanthridine,
8-chloro-11-[3-(4-hydroxyethylpiperazinopropyl)]-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-[3-(4-hydroxyethylpiperazinopropyl)]-5,6-dihydromorphanthridine, respectively,
to obtain
2-chloro-11-(3-dimethylaminopropyl)-morphanthridine,
8-chloro-11-(3-dimethylaminopropyl)-morphanthridine,
2-trifluoromethyl-11-(3-dimethylaminopropyl)-morphanthridine,
11-(3-diethylaminopropyl)-morphanthridine,
2-chloro-11-(3-diethylaminopropyl)-morphanthridine,
8-chloro-11-(3-diethylaminopropyl)-morphanthridine,
2-trifluoromethyl-11-(3-diethylaminopropyl)-morphanthridine,
11-(3-methylaminopropyl)-morphanthridine,
2-chloro-11-(3-methylaminopropyl)-morphanthridine,
8-chloro-11-(3-methylaminopropyl)-morphanthridine,
2-trifluoromethyl-11-(3-methylaminopropyl)-morphanthridine,
11-(N-methyl-N-benzylaminopropyl)-morphanthridine,
2-chloro-11-(N-methyl-N-benzylaminopropyl)-morphanthridine,
8-chloro-11-(N-methyl-N-benzylaminopropyl)-morphanthridine,
2-trifluoromethyl-11-(N-methyl-N-benzylaminopropyl)-morphanthridine,
11-(N-methyl-piperazinopropyl)-morphanthridine,
2-chloro-11-(N-methyl-piperazinopropyl)-morphanthridine,
8-chloro-11-(N-methyl-piperazinopropyl)-morphanthridine,
2-trifluoromethyl-11-(N-methyl-piperazinopropyl)-morphanthridine,
11-[3-(4-hydroxyethylpiperazinopropyl)]-morphanthridine,
2-chloro-11-[3-(4-hydroxyethylpiperazinopropyl)]-morphanthridine,
8-chloro-11-[3-(4-hydroxyethylpiperazinopropyl)]-morphanthridine, and
2-trifluoromethyl-11-[3-(4-hydroxyethylpiperazinopropyl)]-morphanthridine, respectively.

EXAMPLE 3

The process of Example 1 is repeated employing in place of 11-(3-dimethylaminopropyl)-5,6-dihydromorphanthridine one of the following:
11-(N-methyl-4-piperidyl)-5,6-dihydromorphanthridine,
2-chloro-11-(N-methyl-4-piperidyl)-5,6-dihydromorphanthridine,
8-chloro-11-(N-methyl-4-piperidyl)-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-(N-methyl-4-piperidyl)-5,6-dihydromorphanthridine,
11-(N-benzyl-4-piperidyl)-5,6-dihydromorphanthridine,
2-chloro-11-(N-benzyl-4-piperidyl)-5,6-dihydromorphanthridine,
8-chloro-11-(N-benzyl-4-piperidyl)-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-(N-benzyl-4-piperidyl)-5,6-dihydromorphanthridine,
11-(N-methyl-3-piperidyl)-5,6-dihydromorphanthridine,
2-chloro-11-(N-methyl-3-piperidyl)-5,6-dihydromorphanthridine,
8-chloro-11-(N-methyl-3-piperidyl)-5,6-dihydromorphanthridine,
2-trifluoromethyl-11-(N-methyl-3-piperidyl)-5,6-dihydromorphanthridine,
11-(N-ethyl-3-pyrrolidyl)-5,6-dihydromorphanthridine,
11-(N-benzyl-3-pyrrolidyl)-5,6-dihydromorphanthridine, and
11-(N-methyl-3-homopiperidyl)-5,6-dihydromorphanthridine, respectively,
to obtain
11-(N-methyl-4-piperidyl)-morphanthridine,
2-chloro-11-(N-methyl-4-piperidyl)-morphanthridine,
8-chloro-11-(N-methyl-4-piperidyl)-morphanthridine,
2-trifluoromethyl-11-(N-methyl-4-piperidyl)-morphanthridine,
11-(N-benzyl-4-piperidyl)-morphanthridine,
2-chloro-11-(N-benzyl-4-piperidyl)-morphanthridine,
8-chloro-11-(N-benzyl-4-piperidyl)-morphanthridine,
2-trifluoromethyl-11-(N-benzyl-4-piperidyl)-morphanthridine,
11-(N-methyl-3-piperidyl)-morphanthridine,
2-chloro-11-(N-methyl-3-piperidyl)-morphanthridine,
8-chloro-11-(N-methyl-3-piperidyl)-morphanthridine,
2-trifluoromethyl-11-(N-methyl-3-piperidyl)-morphanthridine,
11-(N-ethyl-3-pyrrolidyl)-morphanthridine,
11-(N-benzyl-3-pyrrolidyl)-morphanthridine, and
11-(N-methyl-3-homopiperidyl)-morphanthridine,
respectively.

I claim:

1. A compound selected from compounds of the formulae:



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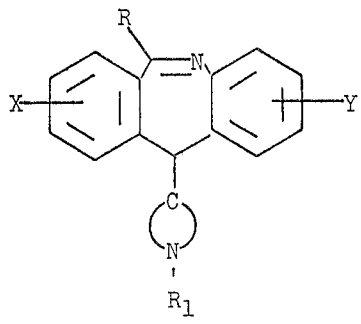
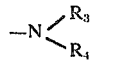


II

in which X and Y are hydrogen, halo, alkoxy of 1 to 3 carbons, alkyl of 1 to 4 carbons, thio-lower alkyl or trifluoromethyl, n is 0 to 4, R, R_1 and R_2 are hydrogen or alkyl of 1 to 4 carbon atoms, Am is

a. 

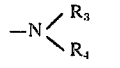
in which R_3 and R_4 are hydrogen, alkyl of 1 to 4 carbons or phenyl-lower alkyl of 7 to 13 carbons, or

b. a heterocyclic amino group selected from morpholino, pyrrolidino, piperidino, N-lower alkyl piperazino, N-phenyl-lower alkyl piperazino and N-(hydroxy-lower alkyl) -piperazino, and

is a cyclicamino group selected from 3-piperidyl, 4-piperidyl, 3-pyrrolidyl, 3-homopiperidyl and 4-homopiperidyl and pharmaceutically acceptable acid addition salts thereof.

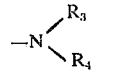
2. A compound of Formula I of claim 1 in which X and Y are hydrogen or chloro.

3. A compound of Formula I of claim 1 in which X and Y are hydrogen or chloro, R, R_1 and R_2 are hydrogen, *n* is 0, Am is



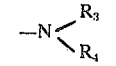
and R_3 and R_4 are hydrogen, alkyl of 1 to 4 carbons or benzyl.

4. A compound of Formula I of claim 1 in which X is hydrogen, Y is chloro, R, R_1 and R_2 are hydrogen, *n* is 0, Am is



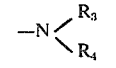
and R_3 and R_4 are hydrogen, alkyl of 1 to 4 carbons or benzyl.

5. A compound of Formula I of claim 1 in which X, Y, R, R_1 and R_2 are hydrogen, *n* is 0, Am is



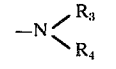
and R_3 and R_4 are hydrogen, alyl of 1 to 4 carbons or benzyl.

6. A compound of Formula I of claim 1 in which X, Y, R, R_1 and R_2 are hydrogen, *n* is 0, Am is



and R_3 and R_4 are methyl.

7. A compound of Formula I of claim 1 in which X is hydrogen, Y is chloro, R, R_1 and R_2 are hydrogen, *n* is 0, Am is



and R_3 and R_4 are methyl.

8. A compound of Formula II of claim 1 in lwhich X and Y are hydrogen.

9. A compound of Formula II of claim 1 in which X is hydrogen and Y is chloro.

10. A compound of Formula II of claim 1 in which X and Y are hydrogen or chloro,

is 3 or 4-piperidyl and R_1 is an alkyl of 1 to 4 carbons.

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