

PATENT SPECIFICATION

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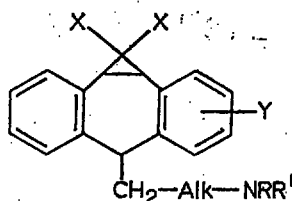
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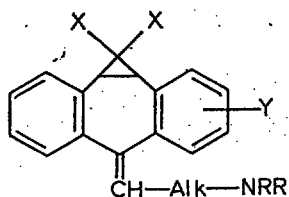
(54) 6-(AMINOALKYL- AND
 AMINOALKYLIDENE)-1,1a,6,10b-TETRAHYDRODIBENZO-
 [a,e]CYCLOPROPA[c]CYCLOHEPTENES

(71) We G. D. SEALE & Co., a corporation organised and existing under the laws of the State of Delaware, United States of America, of P.O. Box 5110, Chicago, Illinois 60680, U.S.A. do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to aminoalkyl and aminoalkylidene derivatives of 1,1a,6,10b - tetrahydro[a,e] cyclopropa[c] cycloheptene and to processes for their preparation. More particularly, the compounds according to the invention have the following general formulae



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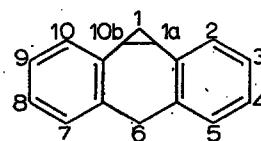


20 wherein the radicals X which may be the
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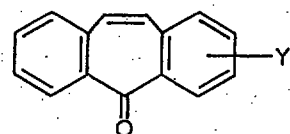
same or different, are hydrogen or halogen; Y is hydrogen or halogen; Alk is a lower alkylene radical; and —NRR' is (lower alkyl) - amino, di(lower alkyl) - amino, piperidino, carbamoylpiperidino, 4 - methyl - 1 - piperazinyl, or 4 - (2 - hydroxyethyl) - 1 - piperazinyl.

The halogen atoms referred to above include fluorine, chlorine, bromine, and iodine. The lower alkylene radicals referred to above include ethylene, propylene, and trimethylene. The lower alkyl radicals referred to above contain up to 6 carbon atoms and can be exemplified by radicals such as methyl, ethyl, propyl, and butyl.

The structure and numbering of the ring system involved is as follows.



The compounds of the present invention are prepared by the reaction of dichlorocarbene with a dibenzocycloheptenone of the formula



wherein Y is as defined above. The dichloro-carbene is preferably obtained by the reaction of sodium methoxide with ethyl trichloroacetate. The indicated reaction gives a 1,1 - dichloro - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - one. Reduction of this ketone can be carried out either selectively to reduce only the carbonyl group or it can be carried out non-selectively to reduce the ketone to the alcohol and reduce off the chlorine substituents at the same time. In the first instance, a hydride reducing agent such as sodium borohydride can be used while in the latter instance, the reducing agent is lithium and *t*-butyl alcohol. Where selective reduction is used, the resulting dichloro alcohol can be further reacted with lithium and *t*-butyl alcohol to reduce off the 2 halogen atoms. Actually, this two step procedure is the preferred method for obtaining the tetracyclic alcohol without the chlorine atoms substituted at the 1-position. The tetracyclic alcohol can then be oxidized with an agent such as chromium trioxide to give the corresponding tetracyclic ketone.

The tetracyclic ketones obtained above can then be reacted with an appropriate aminoalkyl Grignard reagent to give the corresponding amino alcohol. Dehydration of the alcohol with an agent such as hydroidic acid then gives the unsaturated compounds of the present invention.

Alternatively, the tetracyclic ketones described earlier can be reacted with cyclopropylmagnesium bromide to give the corresponding 6 - cyclopropyl alcohol. Rearrangement of the cyclopropyl alcohol with hydrochloric acid then gives the appropriate 6 - (3 - chloropropylidene) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene. This chloropropylidene compound can then be reacted with a variety of amines to give the corresponding aminopropylidene compound.

The saturated compounds of the present invention are prepared by reduction of the appropriate aminoalkylidene compound. Thus, for example, reduction of 1,1 - dichloro - 6 - (3 - dimethylaminopropylidene) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene with lithium and *t*-butyl alcohol gives 6 - (3 - dimethylaminopropyl) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene.

Time, temperature and pressure are not critical factors in these known reactions.

The organic bases of this invention form pharmaceutically acceptable salts with a variety of inorganic and strong organic acids. Such salts are formed with acids such as sulfuric, phosphoric, hydrochloric, hydrobromic, hydroidic, sulfamic, citric, lactic, maleic, malic, succinic, tartaric, cinnamic, acetic, benzoic, gluconic, ascorbic, and oxalic acids.

The compounds of the present invention

are useful because of their pharmacological properties. In particular, the present compounds are anti-depressants and diuretics. In addition the present compounds also possess antibiotic activity against a variety of organisms. Thus, they inhibit the growth of bacteria such as *Diplococcus pneumoniae*, protozoa such as *Tetrahymena gelleii*, and algae such as *Chlorella vulgaris*.

The present compounds also inhibit germination of seeds of *Trifolium*.

The invention is illustrated by the following examples. Quantities are indicated in parts by weight unless otherwise specified, and temperatures are indicated in degrees centigrade (°C.) The relationship between parts by weight and parts by volume is the same as that existing between grams and milliliters.

EXAMPLE 1

To a stirred solution of 60 parts of 5H - dibenzo[a,d]cyclohepten - 5 - one in 880 parts of benzene and 200 parts by volume of hexane at 0-5°C. is added 60 parts of sodium methoxide followed by the portionwise addition of 200 parts of ethyl trichloroacetate over a period of 1 hour. The resulting suspension is stirred at 0-5°C. for 5 hours and then allowed to come to room temperature over a period of 18 hours. 200 Parts of water is added and the benzene is separated, washed with water and dried over magnesium sulfate. Evaporation of the benzene solvent leaves a residual oil which is dissolved in 240 parts of hot ethanol, treated with charcoal, and filtered. Crystals form almost immediately in the filtrate and these are separated by filtration, washed with ethanol, and dried to give 1,1 - dichloro - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - one melting at about 129-131°C.

EXAMPLE 2

To a stirred suspension of 10.0 parts of 1,1 - dichloro - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - one in 240 parts of methanol is added 3.0 parts of sodium borohydride. The mixture is stirred for 15 minutes at 25°C. and then refluxed for 2 hours before it is poured into 1000 parts of water containing 30 parts of concentrated hydrochloric acid. The solid precipitate which forms is separated by filtration, washed with water, and air dried to give 1,1 - dichloro - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - ol melting at about 164-168°C.

EXAMPLE 3

A solution of 30 parts of 1,1 - dichloro - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - ol in 270 parts of tetrahydrofuran is prepared and stirred, 2.5

parts of lithium amide is added, and the resulting suspension is stirred for 30 minutes. 12 Parts of lithium wire and 9 parts of *t*-butyl alcohol are added concomitantly over a period of about 1.5 hours. The reaction mixture is cooled from time to time to keep the mixture below reflux temperature. Once the addition is complete, the mixture is stirred for 1 hour and excess lithium is decomposed by the cautious addition of water. The mixture is then further diluted with water and extracted with ether. The combined ether extracts are washed with water and dried over magnesium sulfate. Evaporation of the ether solvent leaves a residual solid which is recrystallized from ethanol to give 1,1a,6,10b - tetrahydrodibenzo[a,e]-cyclopropa[c]cyclohepten - 6 - ol melting at about 142—152°C.

EXAMPLE 4

To a stirred solution of 8.8 parts of 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - ol in 16 parts of acetone is added dropwise 14 parts by volume of Jones reagent (a solution of chromic acid and sulfuric acid in water). The resulting mixture is stirred for an additional 15 minutes and poured into water. It is then extracted with ether and the ether extracts are washed well with water and dried over magnesium sulfate. The solvent is evaporated to leave a crystalline residue. This is recrystallized from ethanol to give 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - one melting at about 79—82°C.

EXAMPLE 5

To a stirred solution of 64.5 parts of 2-chloro - 5H - dibenzo[a,d]cyclohepten - 6 - one in 2650 parts of benzene at 5°C. is added 60 parts of sodium methoxide followed by the portionwise addition of 200 parts of ethyl trichloroacetate over a period of 1 hour. The reaction is stirred at 0—5°C. for 5 hours and then allowed to come to room temperature. 1000 Parts of water is added and the benzene layer is separated and washed with water. The solvent is evaporated to leave a residual mixture of crystals and oil. Ethanol is added to this residue and the insoluble material is separated by filtration. The ethanol solution is then cooled and the precipitate which forms is separated by filtration and recrystallized from ethanol to give 1,1,3 - trichloro - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - one melting at about 103—110°C.

EXAMPLE 6

To 2.43 parts of magnesium in a dry flask is added 23 parts of tetrahydrofuran which has been distilled from lithium aluminum hydride and then, with stirring, a solution of 13.3 parts of cyclopropyl bromide in 23

parts of tetrahydrofuran is added portionwise. The reaction starts spontaneously and the addition is carried out at a rate to maintain reflux. When the addition is complete, the solution is refluxed for 2 hours and cooled slightly. A solution of 18.9 parts of 1,1-dichloro - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - one in 180 parts of tetrahydrofuran is then added portionwise. The mixture is refluxed for 15 minutes and poured into excess water containing 20 parts of ammonium chloride. The resulting mixture is extracted with ether and the combined ether extracts are washed with water and dried over magnesium sulfate. Evaporation of the ether solvent leaves a yellow oil which is chromatographed on silica. Elution of the column with 30% hexane benzene and evaporation of the solvent from the eluate leaves a solid which is recrystallized from ethanol to give 6 - cyclopropyl - 1,1 - dichloro - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - ol melting at about 140—143°C.

A solution of 14.3 parts of 6 - cyclopropyl - 1,1 - dichloro - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - ol in 210 parts of acetic acid containing 30 parts of concentrated hydrochloric acid is stirred at room temperature for 1 hour and then refluxed for 1.5 hours. The solvent is evaporated, toluene is added to the residue, and the toluene is removed under reduced pressure to leave a light yellow oil. This is triturated with a minimum amount of ethanol and the precipitate which forms is separated by filtration to give 6 - (3 - chloropropylidene) - 1,1 - dichloro - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene melting at about 97.5—98.5°C.

EXAMPLE 7

Cyclopropylmagnesium bromide is prepared from 8 parts of cyclopropyl bromide and 1.4 parts of magnesium in 45 parts of tetrahydrofuran according to the procedure described in Example 6. To the resulting mixture is added a solution of 6.3 parts of 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - one in 90 parts of tetrahydrofuran at a temperature just below reflux. When the addition is complete, the mixture is refluxed for 1 hour and then poured into excess water containing 7 parts of ammonium chloride. This mixture is extracted with ether and the ether extracts are combined and dried over magnesium sulfate. Evaporation of the ether solvent leaves a yellow oil which is chromatographed on a silica gel column. The column is eluted with benzene and evaporation of the benzene solvent from the eluate leaves a colorless oil which is 6 - cyclopropyl - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - ol. A solution of 0.5 parts of 6 - cyclopropyl -

1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa-
[c]cyclohepten - 6 - ol in 5 parts of acetic
acid containing 0.5 part of concentrated
hydrochloric acid is stirred at room tem-
5 perature for 1 hour and then refluxed for 1
hour. When the mixture is cooled, a crystal-
line precipitate forms. This is separated by
filtration and recrystallized from ethanol to
give 6 - (3 - chloropropylidene) - 1,1a,6,10b -
10 tetrahydrodibenzo [a,e] cyclopropa [c] cyclo-
heptene melting at about 148—149°C.

EXAMPLE 8

A solution of 2.7 parts of 6 - (3 - chloro-
propylidene) - 1,1a,6,10b - tetrahydro-
15 dibenzo[a,e]cyclopropa[c]cycloheptene and 50
parts by volume of dimethylamine (liquid,
cooled) in 27 parts of benzene is heated at
100°C. in a pressure reactor for 19 hours.
The solvent is evaporated, and water is added
20 to the residue which is then made alkaline
with ammonium hydroxide. The resulting
mixture is extracted with ether and the com-
bined ether extracts are dried over potassium
carbonate and the solvent is evaporated to
25 leave a residual amber oil which is 6 - (3 -
dimethylaminopropylidene) - 1,1a,6,10b -
tetrahydrodibenzo [a,e] cyclopropa [c] cyclo-
heptene. A solution of this oil in a minimum
amount of ethanol is mixed with a saturated
30 ethanol solution of oxalic acid. The pre-
cipitate which forms is separated by filtra-
tion to give 6 - (3 - dimethylamino-
propylidene) - 1,1a,6,10b - tetrahydro-
dibenzo[a,e]cyclopropa[c]cycloheptene oxalate
35 melting at about 195—197°C.

EXAMPLE 9

The procedure described in Example 8 is
repeated using 1.5 parts of 6 - (3 - chloro-
propylidene) - 1,1a,6,10b - tetrahydro-
40 dibenzo [a,e] cyclopropa [c] cycloheptene, 50
parts by volume of methylamine (liquid,
cooled), and 27 parts of benzene. The pro-
cedure first gives 6 - (3 - methylamino-
propylidene) - 1,1a,6,10b - tetrahydro-
45 dibenzo [a,e] cyclopropa [c] cycloheptene and
this is converted to the oxalate salt which
melts at about 203—205°C.

In a similar manner, 6 - (3 - chloro-
propylidene) - 1,1a,6,10b - tetrahydro-
50 dibenzo[a,e]cyclopropa[c]cycloheptene is re-
acted with ethylamine and diethylamine to
give, respectively, 6 - (3 - ethylamino-
propylidene) - 1,1a,6,10b - tetrahydro-
dibenzo[a,e]cyclopropa[c]cycloheptene and
55 6 - (3 - diethylaminopropylidene) - 1,1a,6-
10b - tetrahydrodibenzo[a,e]cyclopropa[c]-
cycloheptene.

EXAMPLE 10

A solution of 3.1 parts of 6 - (3 - chloro-
propylidene) - 1,1 - dichloro - 1,1a,6, 10b -
60 tetrahydrodibenzo [a,e] cyclopropa [c] cyclo-
heptene and 50 parts by volume of methyl-

amine (liquid, cooled) in 45 parts of benzene
is heated for 18 hours at 95°C. in a pres-
sure reactor. The resulting solution is then
cooled and washed with water, and the
resulting benzene solution is dried over
potassium carbonate. Evaporation of the sol-
vent leaves a residual oil which is 1,1 -
dichloro - 6 - (3 - methylaminopropylidene) -
1,1a,6,10b - tetrahydrodibenzo[a,e]cyclo-
propa[c]cycloheptene. The oil is dissolved in
ethanol and mixed with a saturated ethanol
solution of oxalic acid. The precipitate which
forms is separated by filtration and recrystallized from ethanol to give 1,1 - di-
chloro - 6 - (3 - methylaminopropylidene) -
1,1a,6,10b - tetrahydrodibenzo[a,e]cyclo-
propa[c]cycloheptene oxalate melting at about
209—215°C.

EXAMPLE 11

A solution of 3.0 parts of 6 - (3 - chloro-
propylidene) - 1,1 - dichloro - 1,1a,6,10b -
tetrahydrodibenzo [a,e] cyclopropa [c] cyclo-
heptene and 20 parts by volume of piperidine
is refluxed for 18 hours. The resulting mix-
ture is cooled and poured into water. The
aqueous mixture is extracted with ether and
the combined ether extracts are dried over
potassium carbonate. Evaporation of the sol-
vent leaves an amber oil which is dissolved
in ethanol and mixed with a saturated ethanol
solution of oxalic acid. The precipitate which
forms is separated by filtration and recrystallized from ethanol to give 1,1 -
dichloro 6 - (3 - piperidinopropylidene) - 1,1-
1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa-
[c]cycloheptene melting at about 193—195°C.

EXAMPLE 12

A mixture of 3.5 parts of 6 - (3 - chloro-
propylidene) - 1,1 - dichloro - 1,1a,6,10b -
tetrahydrodibenzo [a,e] cyclopropa [c] cyclo-
heptene and 3 parts of isonipecotamide is
heated at 140°C. under nitrogen for 18 hours.
A solid forms on cooling. This is washed with
water and then dissolved in ethanol. The
ethanol solution is filtered to remove some
insoluble material and the solvent is
evaporated to leave a residual amber oil
which crystallizes on standing. This solid is
redissolved in ethanol and treated with an
excess of hydrogen chloride in 2-propanol
to give 6 - [3 - (4 - carbamoylpiperidino)-
propylidene] - 1,1 - dichloro - 1,1a,6,10b -
tetrahydrodibenzo [a,e] cyclopropa [c] cyclo-
heptene hydrochloride melting at about 242
—247°C. after recrystallization from
ethanol.

EXAMPLE 13

A solution of 3.5 parts of 6 - (3 - chloro-
propylidene) - 1,1 - dichloro - 1,1a,6,10b -
tetrahydrodibenzo [a,e] cyclopropa [c] cyclo-
heptene in 20 parts by volume of 1 - methyl-
piperazine is heated at 90—100°C. for 18

filtration. The remaining ethanol solution is then mixed with an ethanol solution of oxalic acid. The precipitate which forms is separated by filtration and recrystallized from ethanol to give 6 - (3 - dimethylamino-propylidene) - 1,1,3 - trichloro - 1,1a,6,10b - tetrahydrodibenzo [a,e] cyclopropa [c] cycloheptene oxalate melting at about 162—167°C.

EXAMPLE 19

To 2.4 parts of magnesium in a dry flask is added a crystal of iodine and 27 parts of tetrahydrofuran. This mixture is stirred as 1 part of ethyl bromide and then 15 parts of freshly distilled 3 - dimethylamino - 2 - methylpropyl chloride in 27 parts of tetrahydrofuran is added portionwise. After the addition is complete, the mixture is refluxed for 10 minutes and then cooled slightly before 10.0 parts of 1,1 - dichloro - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]-cyclohepten - 6 - one in 67 parts of tetrahydrofuran is added portionwise. The mixture is then stirred for 2 hours at reflux before it is cooled and poured into water containing 20 parts of ammonium chloride. The resultant mixture is extracted with ether and the combined ether extracts are washed with water and dried over potassium carbonate. Evaporation of the solvent leaves a yellow oil which is dissolved in ethanol and then mixed with a saturated solution of oxalic acid in ethanol. The precipitate which forms is separated by filtration and recrystallized from ethanol to give 1,1 - dichloro - 6 - (3 - dimethylamino - 2 - methylpropyl) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - ol oxalate melting at about 171—173°C.

EXAMPLE 20

A solution of 3.0 parts of 1,1 - dichloro - 6 - (3 - dimethylamino - 2 - methylpropyl) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c] - cyclohepten - 6 - ol in 15 parts of acetic acid containing 12 parts by volume of 47% hydroiodic acid and 3.5 parts of concentrated hydrochloric acid is refluxed for 2 hours. The resulting mixture is poured into water and made alkaline with potassium carbonate. The precipitate which forms is separated by filtration and triturated with hot ethanol to give 1,1 - dichloro - 6 - (3 - dimethylamino - 2 - methylpropylidene) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene as the hydroiodic melting at about 245—252°C.

EXAMPLE 21

To a stirred solution of 7.3 parts of 1,1 - dichloro - 6 - (3 - dimethylamino-propylidene) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene in 55 parts of tetrahydrofuran is added 0.46 parts of lithium amide and the resulting suspension

is stirred for 1 hour. Addition of 3 parts of *t*-butyl alcohol followed by 4.0 parts of lithium wire over a period of 1 hour gives an exothermic reaction. The mixture is then stirred for an additional hour and decomposed by the careful addition of water. It is then further diluted with water, the organic layer is separated, and the aqueous layer is extracted with ether. The organic layers are then combined and dried over potassium carbonate. Evaporation of the solvent gives a dark oil. The oil is mixed with ethanol and the insoluble material is separated and discarded. The remaining oil is chromatographed on an alumina column. The column is eluted with benzene containing increasing quantities of ethyl acetate. The solvent is evaporated from the portion eluted with 5% ethyl acetate in benzene to leave a residual oil which is 6 - (3 - dimethylaminopropyl) - 1,1a,6,10b - tetrahydrodibenzo [a,e] cyclopropa [c] cycloheptene. This oil is dissolved in ethanol and mixed with an ethanol solution of oxalic acid. The resulting ethanol solution is further diluted with ether, whereupon a precipitate forms. This is separated by filtration and recrystallized from ethanol to give 6 - (3 - dimethylaminopropyl) - 1,1a,6,10b - tetrahydrodibenzo [a,e] cyclopropa [c] cycloheptene oxalate melting at about 175—178°C.

EXAMPLE 22

To a stirred solution of 5.3 parts of 1,1 - dichloro 6 - (3 - methylaminopropylidene) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene in 45 parts of tetrahydrofuran is added 0.3 part of lithium amide and the suspension is stirred for 1 hour. Then, 2 parts of *t*-butyl alcohol is added followed by 2 parts of lithium wire, cut in small pieces, over a period of 40 minutes. The mixture is then stirred for an additional hour before it is decomposed by the careful addition of water. The resulting mixture is extracted with ether and the combined ether extracts are washed with water and dried over potassium carbonate. Evaporation of the solvent leaves a brown oil. This is mixed with ethanol and the insoluble portion is discarded. Evaporation of the solvent from the solution leaves a brown oil which is chromatographed on neutral alumina. The column is eluted with solutions containing increasing quantities of ethyl acetate in benzene and then with solutions containing increasing quantities of methanol in ethyl acetate. The eluate obtained from elution with 10% methanol in ethyl acetate is separated and the solvent is evaporated to leave a residual oil which is 6 - (3 - methylaminopropyl) - 1,1a,6,10b - tetrahydrodibenzo [a,e] cyclopropa [c] heptene. This oil is dissolved in ethanol and mixed with a saturated ethanol solution of oxalic acid. The precipitate which forms is separated by filtration to give 6 - (3 - methyl-

hours. The resulting mixture is triturated with water and then extracted with ether. The combined ether extracts are washed with water and dried over potassium carbonate.

- 5 Evaporation of the ether solvent leaves an amber oil which is 1,1 - dichloro - 6 - [3 - (4 - methyl - 1 - piperazinyl)propylidene] - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene. The oil is dissolved in ethanol and mixed with an excess of hydrogen chloride in 2-propanol. The precipitate which forms is separated by filtration and recrystallized from ethanol to give 1,1 - dichloro - 6 - [3 - (4 - methyl - 1 - piperazinyl)propylidene] - 1,1a,6,10b - tetrahydrodibenzo [a,e] cyclopropa [c] cycloheptene dihydrochloride melting at about 215—225°C.

EXAMPLE 14

- 20 3.0 Parts of 6 - (3 - chloropropylidene) - 1,1 - dichloro - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene and 2.6 parts of 1 - (2 - hydroxyethyl)piperazine is heated at 100—110°C. for 18 hours. Cooling of this mixture gives an oil which is triturated with water and extracted with ether. The combined ether extracts are washed with water and dried over potassium carbonate, and the solvent is evaporated to leave a residual oil which is 1,1 - dichloro - 6 - [3 - [4 - (2 - hydroxyethyl) - 1 - piperazinyl]propylidene] - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene. This oil is dissolved in a minimum amount of ethanol and mixed with an excess of hydrogen chloride in 2-propanol. The precipitate which forms is separated by filtration and recrystallized from ethanol to give 1,1 - dichloro - 6 - [3 - [4 - (2 - hydroxyethyl) - 1 - piperazinyl]propylidene] - 1,1a,6,10b - tetrahydrodibenzo [a,e] cyclopropa [c] cycloheptene dihydrochloride melting at about 226—228°C.

EXAMPLE 15

- 45 To 2.43 parts of magnesium in a dry flask there is added, with stirring, 9 parts of tetrahydrofuran, 0.5 part of ethyl bromide, and a crystal of iodine, followed by the portionwise addition of a solution of 15 parts of freshly distilled 3 - dimethylaminopropyl chloride in 18 parts of tetrahydrofuran. At the end of the addition, almost all of the magnesium has reacted. To this solution is then added a solution of 10 parts of 1,1 - dichloro - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene - 6 - one in 90 parts of tetrahydrofuran portionwise. The mixture is refluxed for 2 hours and then poured into 500 parts of water containing 20 parts of ammonium chloride. The solid which forms is separated by filtration and washed with water to give 1,1 - dichloro - 6 - (3 - dimethylaminopropyl) - 1,1a,6,10b -

tetrahydrodibenzo [a,e] cyclopropa [c] cyclohepten - 6 - ol melting at about 170—171°C. 65

EXAMPLE 16

A solution of 1.0 part of 1,1 - dichloro - 6 - (3 - dimethylaminopropyl) - 1,1a,6,10b - tetrahydrodibenzo [a,e] cyclopropa [c] cyclohepten - 6 - ol, 4 parts of 47% hydriodic acid, 5 parts of acetic acid, and 1 part of concentrated hydrochloric acid is refluxed for 2 hours. The resulting mixture is poured into an aqueous potassium carbonate solution. This is extracted with ether and the combined ether extracts are washed with water and dried over potassium carbonate. Evaporation of the solvent leaves a colorless oil which is 1,1 - dichloro - 6 - (3 - dimethylaminopropylidene) - 1,1a,6,10b - tetrahydrodibenzo [a,e] cyclopropa [c] cycloheptene. The oil is dissolved in ethanol and treated with an ethanol solution of oxalic acid. The precipitate which forms is separated by filtration and recrystallized from ethanol to give 1,1 - dichloro - 6 - (3 - dimethylaminopropylidene) - 1,1a,6,10b - tetrahydrodibenzo [a,e] cyclopropa [c] cycloheptene oxalate melting at about 166—167°C. 70 75 80

EXAMPLE 17

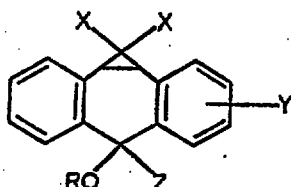
3 - Dimethylaminopropylmagnesium chloride is prepared from 12 parts of 3 - dimethylaminopropyl chloride according to the procedure described in Example 15. To the resulting tetrahydrofuran solution is added, portionwise, a solution of 11.5 parts of 1,1,3 - trichloro - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - one in 90 parts of tetrahydrofuran and the resulting solution is refluxed for 2 hours. It is then cooled and poured into an excess of water containing 20 parts of ammonium chloride. A crystalline material forms on standing and this is separated by filtration and recrystallized from ethanol to give 6 - (3 - dimethylaminopropyl) - 1,1,3 - trichloro - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - ol melting at about 168—170°C. 90 95 100 105

EXAMPLE 18

A solution of 2.0 parts of 6 - (3 - dimethylaminopropyl) - 1,1,3 - trichloro - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten - 6 - ol in 10 parts of acetic acid containing 8 parts by volume of 48% hydriodic acid and 2 parts of concentrated hydrochloric acid is refluxed for 2 hours. The resultant mixture is poured into water, made alkaline with potassium carbonate, and extracted with ether. The ether extracts are dried over potassium carbonate and the solvent is evaporated to leave a residual yellow oil which solidifies on standing. This is dissolved in hot ethanol and cooled and the precipitate which first forms is separated by 110 115 120 125

aminopropyl) - 1,1a,6,10b - tetrahydrodibenzo [a,e] cyclopropa [c] cycloheptene oxalate melting at about 207—209°C.

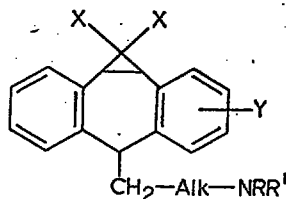
- 5 The products of Examples 15, 17 and 19 are claimed in our co-pending application No. 27417/69 (Serial No. 1214270) which relates to cycloheptenol derivatives of the formula



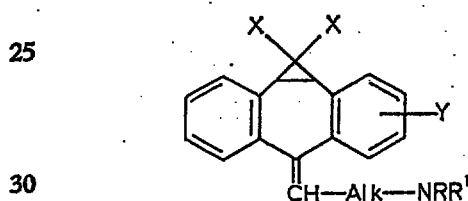
- 10 in which X is hydrogen or chlorine; Y is hydrogen or chlorine; R is hydrogen or lower alkanoyl; and Z is 1 - methyl - 4 - piperidyl or —Alk—NR'R'' wherein Alk is lower alkylene and —NR'R'' is di(lower alkyl)-amino, piperidino or 4 - methyl - 1 - piperazinyl.

WHAT WE CLAIM IS:—

1. Compounds of the formula



- 20 and



- 30 wherein the radicals X, which may be the same or different, are hydrogen or halogen; Y is hydrogen or halogen; Alk is a lower alkylene radical; and —NRR' is (lower alkyl)-amino, di(lower alkyl)amino, piperidino, carbamoylpiperidino, 4 - methyl - 1 - piperazinyl, or 4 - (2 - hydroxyethyl) - 1 - piperazinyl.

- 40 2. Compounds as claimed in claim 1, wherein X is hydrogen or chlorine, Y is hydrogen or chlorine and Alk is ethylene or propylene.

- 45 3. 6 - (3 - Dimethylaminopropyl) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene.

4. 6 - (3 - Methylaminopropylidene) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene.

5. 6 - (3 - Dimethylaminopropylidene) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene. 50

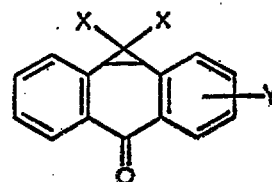
6. 1,1 - Dichloro - 6 - (3 - dimethylaminopropylidene) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene. 55

7. 1,1 - Dichloro - 6 - [3 - (4 - carbamoylpiperidino)propylidene] - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene.

8. Compounds as claimed in claim 1, substantially as hereinbefore described with reference to examples 8 to 14, 16, 18 and 20 to 22.

9. Acid addition salts of the compounds claimed in any of claims 1 to 8 with inorganic or strong organic acids.

10. A process for the preparation of compounds as claimed in claim 1 which comprises contacting a compound of the general formula



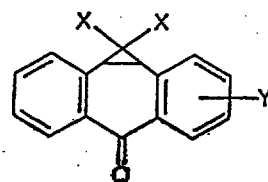
- in which X and Y are as defined in claim 1 with an aminoalkyl Grignard reagent of the general formula 60



- in which Alk and —NRR' are as defined in claim 1 and X' is bromine or chlorine; followed by dehydration of the 6 - amino alcohol formed. 65

11. A process as claimed in claim 10 wherein the 6 - amino alcohol is dehydrated by treatment with hydriodic acid.

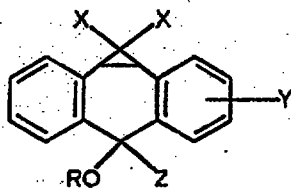
12. A process for the preparation of compounds as claimed in claim 1 which comprises contacting a compound of the general formula 70



- in which X and Y are as defined in claim 1 with cyclopropylmagnesium bromide; rearranging the resulting 6 - cyclopropylalcohol to give a compound of formula 80

aminopropyl) - 1,1a,6,10b - tetrahydrodibenzo [a,e] cyclopropa [c] cycloheptene oxalate melting at about 207-209°C.

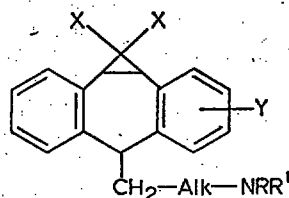
- 5 The products of Examples 15, 17 and 19 are claimed in our co-pending application No. 27417/69 (Serial No. 1214270) which relates to cycloheptenol derivatives of the formula



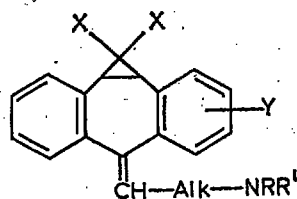
- 10 in which X is hydrogen or chlorine; Y is hydrogen or chlorine; R is hydrogen or lower alkanoyl; and Z is 1 - methyl - 4 - piperidyl or —Alk—NR'R'' wherein Alk is lower alkylene and —NR'R'' is di(lower alkyl)-
- 15 amino, piperidino or 4 - methyl - 1 - piperazinyl.

WHAT WE CLAIM IS:—

1. Compounds of the formula



- 20 and



- 25 wherein the radicals X, which may be the same or different, are hydrogen or halogen; Y is hydrogen or halogen; Alk is a lower alkylene radical; and —NRR' is (lower alkyl)-
- 30 amino, di(lower alkyl)amino, piperidino, carbamoylpiperidino, 4 - methyl - 1 - piperazinyl, or 4 - (2 - hydroxyethyl) - 1 - piperazinyl.

- 40 2. Compounds as claimed in claim 1, wherein X is hydrogen or chlorine, Y is hydrogen or chlorine and Alk is ethylene or propylene.

- 45 3. 6 - (3 - Dimethylaminopropyl) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene.

4. 6 - (3 - Methylaminopropylidene) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene.

5. 6 - (3 - Dimethylaminopropylidene) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene. 50

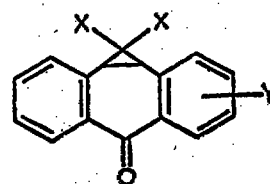
6. 1,1 - Dichloro - 6 - (3 - dimethylaminopropylidene) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene. 55

7. 1,1 - Dichloro - 6 - {3 - (4 - carbamoylpiperidino)propylidene} - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene.

8. Compounds as claimed in claim 1, substantially as hereinbefore described with reference to examples 8 to 14, 16, 18 and 20 to 22.

9. Acid addition salts of the compounds claimed in any of claims 1 to 8 with inorganic or strong organic acids.

10. A process for the preparation of compounds as claimed in claim 1 which comprises contacting a compound of the general formula



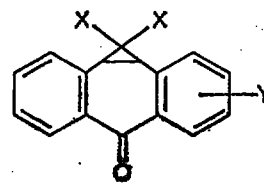
- in which X and Y are as defined in claim 1 with an aminoalkyl Grignard reagent of the general formula



- in which Alk and —NRR' are as defined in claim 1 and X' is bromine or chlorine; followed by dehydration of the 6 - amino alcohol formed.

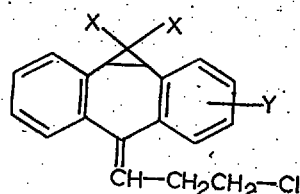
11. A process as claimed in claim 10 wherein the 6 - amino alcohol is dehydrated by treatment with hydriodic acid.

12. A process for the preparation of compounds as claimed in claim 1 which comprises contacting a compound of the general formula



- in which X and Y are as defined in claim 1 with cyclopropylmagnesium bromide; rearranging the resulting 6 - cyclopropylalcohol to give a compound of formula

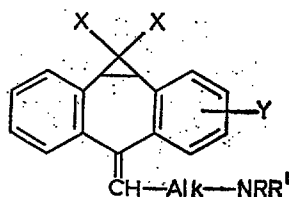




and contacting this compounds with an amine of the formula



- 5 wherein $\text{—NRR}'$ is as defined in claim 1.
 13. A process as claimed in claim 12 wherein the rearrangement of the 6 - cyclopropyl alcohol is effected by treatment with hydrochloric acid.
 10 14. A process for the preparation of compounds as claimed in claim 1 which are saturated in the 6 position which comprises contacting a compound of the general formula



- 15 in which X, Y, Alk and $\text{—NRR}'$ are as defined in claim 1, with a reducing agent.
 15. A process as claimed in claim 14 wherein the reducing agent is lithium and *t*-butyl alcohol.
 20 16. A process for the preparation of 6 - (3 - dimethylaminopropyl) - 1, 1a, 6, 10b - tetrahydrodibenzo [a,e] cyclopropa [c] cycloheptene which comprises contacting 1,1 - dichloro - 6 - (3 - dimethylamino-
 25 propylidene) - 1,1a,6,10b - tetrahydro-

dibenzo[a,e]cyclopropa[c]cycloheptone with lithium and *t*-butyl alcohol.

17. A process for the preparation of 6 - (3 - methylaminopropylidene) - 1,1a,6,10b - tetrahydrodibenzo [a,e] cyclopropa [c] cycloheptene which comprises contacting 6 - (3 - chloropropylidene) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene with methylamine.

18. A process for the preparation of 6 - (3 - dimethylaminopropylidene) - 1,1a,6,10b - tetrahydrodibenzo [a,e] cyclopropa [c] cycloheptene which comprises contacting 6 - (3 - chloropropylidene) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene with dimethylamine.

19. A process for the preparation of 1,1 - dichloro - 6 - (3 - dimethylaminopropylidene) - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene which comprises contacting 1,1 - dichloro - 6 - (3 - dimethylaminopropyl) - 1,1a,6,10b - tetrahydrodibenzo [a,e] cyclopropa [c] cyclohepten - 6 - ol with hydriodic acid.

20. A process for the preparation of 1,1 - dichloro - 6 - [3 - (4 - carbamoylpiperidino)propylidene] - 1,1 - dichloro - 1,1a,6,10b - dibenzo[a,e]cyclopropa[c]cycloheptene which comprises contacting 6 - (3 - chloropropylidene) 1,1 - dichloro - 1,1a,6,10b - tetrahydrodibenzo [a,e] cyclopropa [c] cycloheptene with 4 - piperidine carboxylic acid amide.

21. A process for the preparation of compounds as claimed in claim 1 substantially as hereinbefore described with reference to Examples 8 to 14, 16, 18 and 20 to 22.

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