

PATENT SPECIFICATION

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(54) *cis*-BICYCLOOCTYL-ALKYL-AMINE
 DERIVATIVES

(71) We, LILLY INDUSTRIES LIMITED, a British company of Henrietta House, Henrietta Place, London, W.1., 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 a novel class of 2-phenylbicyclooctane and octene derivatives having useful central nervous system activity. The invention also provides methods by which such novel compounds may be prepared, novel intermediates useful in the preparation of the active compounds of the invention and pharmaceutical compositions comprising said active compounds.

In the Applicants' W. German Offenlegungsschrift No. 2,354,931, there is described and claimed a class of *trans*-derivatives which also possess a 2-phenylbicyclooctane nucleus and which have activity in the central nervous system. United States Patent Specifications Nos. 3,308,160 and 3,362,878 also disclose bicyclooctanes having central nervous system activity.

According to the present invention there is provided an amine of formula (I):



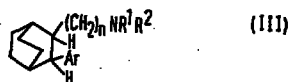
or an acid-addition salt thereof, wherein *n* is an integer from 1 to 3, R¹ is C₁₋₄ alkyl, R² is hydrogen or C₁₋₄ alkyl and R is a 2-phenylbicyclo group of formula:



wherein R³ and R⁴ each represent a hydrogen atom, said hydrogen atoms being in a *cis*-relationship, or taken together represent a single chemical bond; and wherein Ar

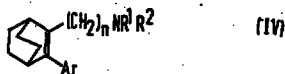
represents an optionally substituted phenyl group.

When R³ and R⁴ represent *cis*-hydrogen atoms the Ar and $-(CH_2)_nNR^1R^2$ groups will also be in a *cis*-relationship. Such *cis*-2-phenylbicyclooctanes of formula (I) may be represented by the formula (III):



Those skilled in the art will appreciate that the compounds of formula (III) may exist in two enantiomeric forms and it is to be clearly understood that the invention extends to both the (+) or (−) form, as well as to the racemic mixture thereof.

When R³ and R⁴ taken together represent a single chemical bond the 2-phenylbicyclooct-2-ene of formula (I) may be represented by the formula (IV):



Preferably, the optionally substituted phenyl group Ar in the compounds of formula (I) has the formula:



wherein R⁵ and R⁶ individually represent the same or different substituents selected from hydrogen, halogen, trifluoromethyl, nitro, amino, C₂₋₆ acylamino, mono- or di-C₁₋₄ alkylamino, C₁₋₄ alkyl or C₁₋₄ alkoxy; or taken together represent C₁₋₈ alkylenedioxy.

Preferred compounds of the formula (I) are those having one or more of the following features:



- (a) n is 1;
 (b) R^1 is C_{1-3} alkyl and R^2 is hydrogen, methyl or ethyl;
 (c) R^1 and R^2 are the same or different C_{1-3} alkyl groups;
 (d) R^1 and R^2 are methyl;
 (e) R^3 and R^4 are *cis*-hydrogen atoms;
 (f) Ar is phenyl substituted by halogen in the 2,6; 2,5; 2,4; 2,3; 3,5; or 3,4-positions;
 (g) Ar is phenyl singly or doubly substituted by halogen;
 (h) Ar is a *p*-chloro or *p*-bromophenyl group;
 (i) Ar is 3,4-dichlorophenyl; or
 (j) R^3 and R^4 are *cis*-hydrogen atoms and the compound of formula (I) is the (+)-enantiomer.
- Most advantageously, the compounds of formula (I) have the features (a), (b), (e) and (g); (a), (b) and (f); (a), (d), (g) and (j); (a), (d) and (h); or (a), (d), (i) and (j).
- For the avoidance of doubt, the term " C_{1-4} alkyl" as used herein, whether explicitly or implicitly as in the term " C_{2-3} acylamino", is intended to encompass any straight or branched chain alkyl group having from 1 to 4 carbon atoms. Thus R^1 and/or R^2 may be a methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *s*-butyl or *t*-butyl group. Similarly, the term "halogen" refers to fluorine, chlorine, bromine or iodine.
- Presently preferred compounds of the inventions are:
- cis* - 3 - N,N - dimethylaminomethyl - 2 - (*p* - chlorophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminomethyl - 2 - (*p* - chlorophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminomethyl - 2 - (*p* - bromophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminomethyl - 2 - (*p* - bromophenyl) - bicyclo[2,2,2]octane; and their (+)-enantiomers;
 3 - N - methylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]oct - 2 - ene; and
 3 - N,N - dimethylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]oct - 2 - ene.
- Other illustrative Examples of compounds of the invention are:
- cis* - 3 - N - methylaminomethyl - 2 - (*p* - nitrophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminomethyl - 2 - (*p* - nitrophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminomethyl - 2 - (*p* - aminophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminomethyl - 2 - (*p* - aminophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminomethyl - 2 - (*m* - chloro - *p* - nitrophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - diethylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - ethylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminomethyl - 2 - (*p* - acetylaminophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminomethyl - 2 - (*m* - acetylaminophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - methylethylaminomethyl - 2 - (*p* - methylamino - phenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminomethyl - 2 - (*p* - dimethylamino - phenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminomethyl - 2 - (*p* - methoxyphenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminomethyl - 2 - (*p* - methoxyphenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminoethyl - 2 - phenylbicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminoethyl - 2 - phenylbicyclo[2,2,2]octane;
cis - 3 - N - methylaminoethyl - 2 - (*p* - chlorophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminoethyl - 2 - (*p* - chlorophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminoethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminoethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminoethyl - 2 - (3,4 - difluorophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminoethyl - 2 - (*m* - trifluoromethylphenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminoethyl - 2 - (*m* - trifluoromethylphenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminoethyl - 2 - (*m* - nitrophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminoethyl - 2 - (*p* - nitrophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminoethyl - 2 - (*m* - aminophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminoethyl - 2 - (*p* - aminophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminoethyl - 2 - (*m* - acetylaminophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminoethyl - 2 - *p* - acetylaminophenyl - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminoethyl - 2 - (*m* - methylamino - phenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminoethyl - 2 - (*p* - dimethylamino - phenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminoethyl - 2 - (*p* - methylphenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminoethyl - 2 - (*m* - methoxyphenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminoethyl - 2 - (*o* - methoxyphenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminopropyl - 2 - phenylbicyclo[2,2,2]octane;

- cis* - 3 - N,N - dimethylaminopropyl - 2 - phenylbicyclo[2,2,2]octane;
cis - 3 - N - methylaminopropyl - 2 - (*o* - chloro - *p* - nitrophenyl) - bicyclo[2,2,2] - 5 octane;
cis - 3 - N,N - dimethylaminopropyl - 2 - (*o* - bromo - *m* - chlorophenyl) - bicyclo - [2,2,2]octane;
cis - 3 - N,N - dimethylaminopropyl - 2 - (*p* - aminophenyl) - bicyclo[2,2,2]octane;
cis - 3 - N - methylaminopropyl - 2 - (*o* - methyl - *p* - acetylaminophenyl) - bicyclo - [2,2,2]octane;
cis - 3 - N,N - dimethylaminopropyl - 2 - (*o* - methoxy - *m* - methylphenyl) - bicyclo - [2,2,2]octane;
cis - 3 - N - methylaminopropyl - 2 - (*p* - methylamino - phenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminopropyl - 2 - (*p* - dimethylamino - phenyl) - bicyclo - [2,2,2]octane;
cis - 3 - N,N - dimethylaminopropyl - 2 - (*p* - methylamino - phenyl) - bicyclo[2,2,2] - 25 octane;
cis - 3 - N,N - dimethylaminopropyl - 2 - (*p* - methylphenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminopropyl - 2 - (*p* - methoxyphenyl) - bicyclo[2,2,2]octane;
cis - 3 - N,N - dimethylaminoethyl - 2 - 30 (3,4 - methylenedioxyphenyl) - bicyclo[2,2,2] - octane;
cis - 3 - N - methylaminopropyl - 2 - (3,4 - methylenedioxyphenyl) - bicyclo[2,2,2]octane; and their (+) and (-) enantiomers;
3 - N - methylaminomethyl - 2 - phenyl- 35 bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminomethyl - 2 - phenyl- bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminomethyl - 2 - (*p* - 40 nitrophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N - methylaminomethyl - 2 - (*p* - aminophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminomethyl - 2 - (*p* - aminophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N - methylaminomethyl - 2 - (*m* - 45 chloro - *p* - nitrophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - diethylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N - ethylaminomethyl - 2 - (3,4 - di- 50 chlorophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N - methylaminomethyl - 2 - (*p* - acetylaminophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminomethyl - 2 - (*m* - 55 acetylaminophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - methylethylamino - 2 - (*p* - methylamino - phenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N - methylaminomethyl - 2 - (*p* - di- 60 methylamino - phenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N - methylaminomethyl - 2 - (*p* - methoxyphenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminomethyl - 2 - (*p* - methoxyphenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N - methylaminoethyl - 2 - phenyl- bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminoethyl - 2 - (*p* - chlorophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminoethyl - 2 - (*p* - chlorophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N - methylaminoethyl - 2 - (3,4 - di- 75 chlorophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminoethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminoethyl - 2 - (3,4 - difluorophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminoethyl - 2 - (*m* - trifluoromethylphenyl) - bicyclo[2,2,2]oct - 2 - 80 ene;
3 - N - methylaminoethyl - 2 - (*m* - trifluoromethylphenyl) - bicyclo[2,2,2]oct - 2 - 85 ene;
3 - N - methylaminoethyl - 2 - (*m* - nitrophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminoethyl - 2 - (*p* - nitrophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N - methylaminoethyl - 2 - (*m* - amino- 90 phenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminoethyl - 2 - (*p* - aminophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N - methylaminoethyl - 2 - (*m* - acetylaminophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminoethyl - 2 - (*p* - acetylaminophenyl) - bicyclo[2,2,2]oct - 2 - 95 ene;
3 - N - methylaminoethyl - 2 - (*m* - methylamino - phenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminoethyl - 2 - (*p* - dimethylamino - phenyl) - bicyclo[2,2,2]oct - 2 - 100 ene;
3 - N,N - dimethylaminoethyl - 2 - (*p* - methylphenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N - methylaminoethyl - 2 - (*p* - methylphenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminoethyl - 2 - (*m* - methoxyphenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N - methylaminoethyl - 2 - (*o* - methoxyphenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N - methylaminopropyl - 2 - phenyl- bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminopropyl - 2 - phenylbicyclo[2,2,2]oct - 2 - ene;
3 - N - methylaminopropyl - 2 - (*o* - chloro - *p* - nitrophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminopropyl - 2 - (*o* - bromo - *m* - chlorophenyl) - bicyclo[2,2,2] - 120 oct - 2 - ene;
3 - N,N - dimethylaminopropyl - 2 - (*p* - aminophenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N - methylaminopropyl - 2 - (*o* - methyl - *p* - acetylaminophenyl) - bicyclo - [2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminopropyl - 2 - (*o* - 125 methyl - *p* - acetylaminophenyl) - bicyclo - [2,2,2]oct - 2 - ene;

- methoxy - *m* - methylphenyl) - bicyclo -
[2,2,2]oct - 2 - ene;
3 - N - methylaminopropyl - 2 - (*p* -
methylamino - phenyl) - bicyclo[2,2,2]oct -
2 - ene;
3 - N,N - diethylaminopropyl - 2 - (*p* - di-
methylamino - phenyl) - bicyclo[2,2,2]oct -
2 - ene;
3 - N,N - dimethylaminopropyl - 2 - (*p* -
methylamino - phenyl) - bicyclo[2,2,2]oct -
2 - ene;
3 - N,N - dimethylaminopropyl - 2 - (*p* -
methylphenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminopropyl - 2 - (*p* -
methoxyphenyl) - bicyclo[2,2,2]oct - 2 - ene;
3 - N,N - dimethylaminomethyl - 2 - (3,4 -
methylenedioxyphenyl) - bicyclo[2,2,2]oct -
2 - ene;
3 - N,N - dimethylaminoethyl - 2 - (3,4 -
methylenedioxyphenyl) - bicyclo[2,2,2]oct -
2 - ene;
3 - N,N - dimethylaminopropyl - 2 - (3,4 -
methylenedioxyphenyl) - bicyclo[2,2,2]oct -
2 - ene;
and their acid-addition salts, especially their
pharmaceutically-acceptable salts.

The compounds of formula (I) may be pre-
pared by any of the normal methods for pre-
paring substituted alkyl amines.

According to one aspect of the present
invention there is provided a method of pre-
paring a compound of formula (I), or an acid-
addition salt thereof, which comprises

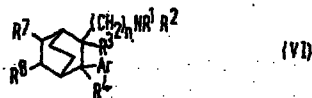
(A) reducing:

(i) a compound of formula (V):



where *m* is 0, 1 or 2 and *Z* is $-\text{CONR}^1\text{R}^2$,
 $-\text{CH}=\text{NR}^1$ or $-\text{C}(\text{OR}^1)=\text{NR}^2$; or

(ii) an olefin of formula (VI):



where R^7 and R^8 taken together represent a
single bond or, when R^3 and R^4 taken together
represent a single bond, independently repre-
sent hydrogen atoms;

(B) alkylating a compound of formula
(VII):



or

(C) condensing an amine of formula:



with a compound of formula (VIII):



where *Q* is a leaving group; optionally followed

when R^3 and R^4 represent *cis*-hydrogen atoms
by (D) resolution of the product of formula
(I) formed in reaction (A), (B) or (C), into its
(+) or (−) enantiomeric form.

The preferred methods of preparation
according to the present invention involve the
use of an intermediate of formula (IX):



where *m* is as defined above, i.e. *n*−1, and *Z*'
represents *Z* or $-\text{CHO}$, $-\text{CN}$, COCl ,
 CONH_2 , $-\text{CH}_2\text{NCO}$ or $-\text{COOR}^9$ where R^9
is C_{1-4} alkyl, which may, if convenient, be
reacted *in situ* in the reaction medium in
which it is formed.

When *R* is a bicyclooctane nucleus, use of
the nitrile intermediate is much preferred
since the *cis*-nitrile is thermally stable and
the nitrile group is a good activating group
in the Diels-Alder reaction by which this class
of intermediates is prepared. When *R* is a
bicyclooctene nucleus, use of the aldehyde
intermediate is preferred.

The compounds of formula (IX) are readily
converted to compounds of formula (I), or
primary amino analogues thereof, by reduc-
tion, although, when R^3 and R^4 represent a
single bond, precautions must be taken to avoid
reduction of the olefinic moiety. In the case
of the nitriles and amides of formula (IX),
the reduction is preferably carried out using
a complex hydride reducing agent such as
lithium aluminium hydride or sodium boro-
hydride, whilst in the case of the isocyanates
of formula (IX), treatment with a concen-
trated mineral acid such as hydrochloric acid
produces the desired conversion. The alde-
hydes and esters of formula (IX) may be
reductively aminated to the desired com-
pounds of formula (I) by reduction to the
corresponding alcohols, for example, using a
complex hydride reducing agent, conversion of
the alcohols to the corresponding alkyl or aryl
sulphonates (by reaction with an alkyl or aryl
sulphonyl chloride such as methyl sulphonyl
chloride or *p*-toluene sulphonyl chloride) and
reaction of the sulphonates with an amine of
formula HNR^1R^2 . Reductive amination of the
aldehydes of formula (IX) may also be carried
out by catalytic hydrogenation in the presence
of ammonia or an amine of formula HNR^1R^2 .

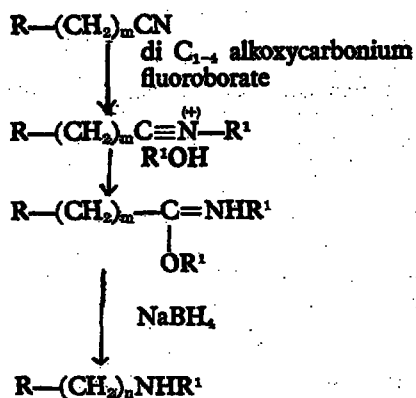
Alternatively, compounds of formula (IX)
where *Z*' is $-\text{CHO}$ may be condensed directly
with an amine to give the corresponding
Schiffs base which can be reduced with a
complex hydride, preferably sodium boro-
hydride, to give a compound of formula (I) in
which R^2 is hydrogen.

Where *Z*' is $-\text{CN}$, $-\text{CONH}_2$ or CH_2NCO
or the above-mentioned reductive amination
is carried out in the presence of ammonia, the
resultant product is a primary amine of
formula $R-(CH_2)_n\text{NH}_2$ which can then be
alkylated to produce a compound of formula

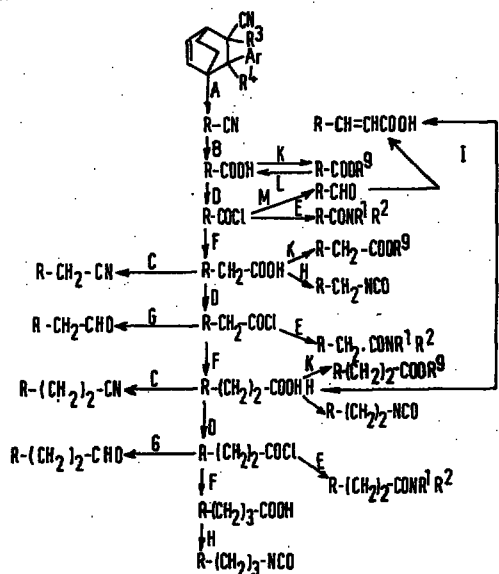
(I) in which R^1 and/or R^2 is C_{1-4} alkyl. Compounds of the formula $R-(CH_2)_nNH_2$ and acid-addition salts thereof, wherein R and n have the values stated above, provided that when R^3 and R^4 represent *cis*-hydrogen atoms and n is 1, Ar cannot be *p*-chlorophenyl, are included in the invention. The alkylation may be carried out in conventional manner, for example by reductive alkylation, reaction with an alkyl halide or sulphate, reaction with an alkyl chloroformate followed by reduction of the resultant urethane or, when methylation is to be carried out, by reaction with formic acid/formaldehyde. Similarly, monoalkylated products of formula (I), i.e. compounds of formula (I) where R^2 is hydrogen, can be alkylated to form dialkylated products of formula (I) where R^2 is C_{1-4} alkyl.

In the case where Z' is CN, the compound of formula (I) in which R^1 is hydrogen and R^2 is C_{1-4} alkyl can be obtained by treatment with the corresponding oxonium salt followed by addition of the corresponding alcohol and reduction with sodium borohydride (see J. Org. Chem. 34, 627 (1969)).

This reaction may be schematically illustrated:



The above intermediates of formula (IX), with the exception of the compound in which R is a bicyclooctane nucleus, m is 0, Z' is $-CN$ and Ar is *p*-chlorophenyl, are novel. They may be obtained from the nitrile of formula (X) according to the following reaction sequences in which R , R^1 , R^2 , and R^3 are as defined above.



When R^3 and R^4 are *cis*-hydrogen atoms, the *cis*-6-phenylbicyclo[2,2,2]oct-2-ene-5-carbonitrile of formula (X) can be prepared by a Diels-Alder reaction between the appropriate *cis*-cinnamonitrile and 1,3-cyclohexadiene. The *cis*-cinnamonitrile may be prepared by the route described in J. Pharm. Sci., 54, 1110 (1965) or by decarboxylation of the corresponding benzalcyanoacetic acid.

When R^3 and R^4 represent a single bond, the nitrile of formula (X) may be prepared from the corresponding aldehyde of formula (XI):



(XI)

by reaction with hydroxylamine followed by dehydration of the oxime thus formed with any suitable dehydrating agent, for example, P_2O_5 or cyanuric chloride.

Alternatively, and preferably, the aldehyde of formula (XI) is directly converted to the acid of formula $RCOOH$ by selective hydrogenation followed by treatment of the partially reduced aldehyde with Jones Reagent ($Na_2Cr_2O_7/H_2SO_4$).

The aldehyde of formula (XI) may be prepared by a Diels-Alder reaction between the

appropriate phenyl propargyl aldehyde and 1,3-cyclohexadiene.

Reaction A above involves the reduction of the compound of formula (X) using, for example, hydrogen in the presence of a suitable catalyst such as palladium on charcoal, to produce the nitrile of formula (IX) in which m is 0. Clearly, when R^3 and R^4 represent a single bond, selective hydrogenation must be employed, the reaction being stopped after uptake of one mole of hydrogen. Reaction B is accomplished by hydrolysis as is well known in the art and the resultant carboxylic acid may then be converted to the corresponding acid chloride—reaction D—in conventional manner, for example, by reaction with thionyl chloride. The latter may then be converted by the Arndt-Eistert synthesis—reaction F—to a substituted acetic acid and, by repetition of reactions D and F, the correspondingly substituted propionic and butyric acid may be obtained. The aforementioned substituted propionic acid may also be prepared from the aldehyde $R-CHO$ by reactions I and J, reaction I being the well-known Knoevenagel reaction to produce a 3-substituted acrylic acid and reaction J involving the reduction of the acrylic acid using, for example, hydrogen over a palladium catalyst to produce the desired propionic acid.

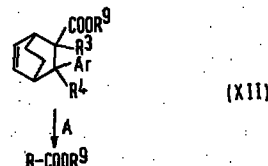
By reaction C, the aforementioned carboxylic acid, substituted acetic acid or substituted propionic acid may be converted to the corresponding nitriles of formula (IX) in which m is 0, 1 or 2. Reaction C may be carried out by treatment of the acid with ammonia at elevated temperatures in the presence of alumina.

The acid chlorides produced by reaction D above are readily converted—reaction E—to the desired amides of formula (IX) by reaction with the appropriate amine of formula HNR^1R^2 . Additionally by reduction of substituted acetyl and propionyl chlorides produced above—reaction G—the required aldehydes of formula (IX) in which m is 1 or 2 may be obtained. The well known Rosenmund reaction provides one means of accomplishing this reduction.

The above-mentioned substituted acetic, propionic and butyric acids may also be converted—reaction H—to the desired isocyanates of formula (IX) in which m is 0, 1 or 2. This conversion may be accomplished by forming the corresponding acid azide either by treatment of the corresponding acid chloride with sodium azide or by formation of the corresponding acid hydrazide and treatment of the latter with nitrous acid, and then heating the acid azide in benzene or chloroform solution.

Reaction K involves the conventional esterification of the corresponding acid, for example, by reaction with an alcohol R^2-OH . The esters of formula (IX) in which m is 0 can

also be prepared by the following reaction sequence:



wherein reaction A is as described above, the compound of formula (IX) where R is a bicyclooctane nucleus being obtained by a Diels-Alder reaction between the appropriate *cis*-cinnamitrile and 1,3-cyclohexadiene, followed by hydrolysis and subsequent esterification. The resultant ester may then be hydrolysed—reaction L—to yield the corresponding acid.

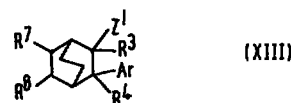
Reaction M can be accomplished by the well-known Rosenmund reduction.

As stated above, reaction A involves reduction, for example, by means of catalytic hydrogenation, and it will therefore be appreciated by those skilled in the art that, if Ar is substituted with a nitro group, the latter may be partially or entirely reduced to the corresponding amino substituted product. Accordingly, if a nitro substituted end product is desired, the appropriate intermediate of formula (IX) is preferably obtained by nitration after reaction A has been carried out and the subsequent conversion of the nitrated intermediate to the desired compound of formula (I) carried out under conditions which will not reduce the nitro substituent.

The compounds of formula (I) may also be prepared by the reduction of an olefin of formula (VI) as hereinbefore defined.

This reduction may be effected using hydrogen over a catalyst such as a group VIII metal, for example, platinum or palladium. The catalyst may be supported on an inert carrier, for example, charcoal. To carry out the reaction the unsaturated compound of formula (VI) may be dissolved in a suitable inert solvent, for example, ethanol or ethyl acetate. When it is desired to form a compound of formula (I) in which R^3 and R^4 represent a single bond, selective hydrogenation of the R^7/R^8 olefinic group must be accomplished.

Compounds of formula (VI) are novel. They may be prepared from compounds of formula (XIII):



where R^7 and R^8 are as defined for formula (VI) and wherein Z' is $-CHO$, CO_2H , CO_2R^9 or CN by any of the methods described above for converting the same Z' groups, in the

compound of formula (IX) to $\text{—NR}^1\text{R}^2$, provided, of course, that such manipulations do not destroy the unsaturated nature of the bicyclooctene moiety.

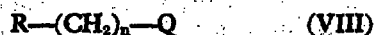
Compounds of formula (XIII) in which R^3 and R^4 taken together represent a single bond, R^7 and R^8 represent hydrogen atoms and Z' represents an aldehyde group may be prepared:

1. By a Diels-Alder reaction between the appropriate *trans*-cinnamaldehyde and 1,3-cyclohexadiene followed by catalytic reduction, bromination with cupric bromide, and subsequent dehydrobromination, preferably with a lithium chloride-lithium carbonate mixture; or
2. By a Diels-Alder reaction between the appropriate phenyl propargyl aldehyde and 1,3-cyclohexadiene followed by catalytic reduction.

Compounds of formula (XIII) where R^7 and R^8 taken together represent a single bond and Z' is CHO may be prepared by a Diels-Alder reaction between 1,3-cyclohexadiene and an aldehyde of formula $\text{ArR}^4\text{C}=\text{CR}^3\text{CHO}$.

The acid, acid chloride, ester and nitrile analogues may be similarly prepared using appropriate modifications of the above synthetic procedures. Preparation of the compounds of formula (XIII) in which R^7 and R^8 represent a single bond, R^3 and R^4 represent *cis*-hydrogen atoms and Z' is nitrile, has already been described hereinabove. Such compounds can be converted into the corresponding acid, ester derivatives, etc., by the methods indicated previously for the compound of formula (X) except, of course, that the reduction step A should be omitted.

A further method of preparing the amines of formula (I) involves the condensation of a compound of formula (VIII):



where Q is a leaving group being a reactive atom such as a halogen atom, e.g. an iodine atom, or a reactive group such as a sulphonate, e.g. mesyl or tosyl, group, with an amine of formula:



where R , R^1 and R^2 are as defined above.

The above type of reaction is well-known in the art and any skilled art worker will immediately appreciate the nature of the reaction conditions necessary to effect the reaction and the identity of suitable Q radicals. However, in passing, it may be mentioned that since the reaction proceeds with elimination of HQ , presence of a proton acceptor such as a base is advisable. If desired, the reaction may be carried out in the presence of a suitable solvent such as methylene dichloride, or dimethyl sulphoxide.

The compounds of formula (VIII) may be

derived from the corresponding alcohols of formula (XIV):



For example, to obtain a compound of formula (VIII) in which Q is chlorine the above alcohol may be reacted with phosphorous pentachloride or oxychloride and to obtain such a compound in which Q is tosyl or mesyl, the alcohol may be reacted with *p*-toluene sulphonyl chloride or methyl sulphonyl chloride.

The alcohols of formula (XIV) may be derived from aldehydes of formula:



by reduction using an alkali metal borohydride such as sodium borohydride or lithium aluminium hydride.

It will also be appreciated by those skilled in the art that a resultant compound of formula (I) in which Ar is substituted by an amino group can be converted to other compounds of formula (I) in conventional manner. Thus, the amino substituted compound may be acylated to produce a desired product of formula (I) in which Ar is substituted by a C_{2-5} acylamino group or mono- or di-alkylated to produce a desired compound in which Ar is substituted by a mono- or di- C_{1-4} alkyl-amino group. Further the amino substituted product may be diazotized and the resultant diazonium salt converted to a variety of other products, for example, by decomposition in an alcohol to yield the corresponding C_{1-4} alkoxy substituted compound or by reaction with a cuprous halide to yield the corresponding halo substituted compound of formula (I).

The compounds of formula (I) produced by the foregoing processes may be isolated *per se* or in acid-addition salt form.

The acid-addition salts are preferably the pharmaceutically acceptable, non-toxic addition salts with suitable acids, such as those with inorganic acids, for example, hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example, glycolic, maleic, hydroxymaleic, malic, tartaric, citric, salicylic, *o*-acetoxybenzoic, nicotinic or isonicotinic acid, or organic sulphonic acids for example methane sulphonc, ethane sulphonc, 2-hydroxyethane sulphonc, toluene-*p*-sulphonc, or naphthalene-2-sulphonc acid. Apart from pharmaceutically acceptable acid-addition salts, other salts are also included within the scope of acid-addition salts such as, for example, those with picric or oxalic acid; they may serve as intermediates in the purification of the compounds or in the preparation of other, for example, pharmaceutically acceptable, acid-addition salts, or are useful for identification, characterization or purification of the bases.

(16)

A resulting acid-addition salt may be converted into the free compound according to known methods, for example, by treating it with a base, such as with a metal hydroxide or alkoxide, for example, an alkali metal or alkaline earth metal hydroxide, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide or calcium hydroxide; with a metal carbonate, such as an alkali metal or an alkaline earth metal carbonate or hydrogen carbonate, for example, sodium potassium or calcium carbonate or hydrogen carbonate; with ammonia; or with a hydroxyl ion exchange preparation, or with any other suitable reagent.

A resulting acid-addition salt may also be converted into another acid-addition salt according to known methods; for example, a salt with an inorganic acid may be treated with a metal salt, for example a sodium, barium or silver salt, of an acid in a suitable diluent, in which a resulting inorganic salt is insoluble and is thus removed from the reaction medium. An acid-addition salt may also be converted into another acid-addition salt by treatment with an anion exchange preparation.

As stated previously, when R^3 and R^4 represent *cis*-hydrogen atoms, the compound of formula (I) may exist in two enantiomeric forms. Although the racemate possesses antidepressant activity in its own right, in certain circumstances it may be desirable to resolve the racemate into its dextrorotatory (+) and laevorotatory (-) forms. The resolution may be effected by any method conventionally used in the resolution of optically active bases, such as by reaction with optically active acids of known stereochemistry, followed by fractional crystallisation of the salts formed. Suitable optically active acids which may be mentioned are (+) or (-) tartaric, malic, mandelic or camphor sulphonic acid, use of the latter acid being preferred. It has been found that the (+)-enantiomers of the compounds of formula (I) have particularly specific CNS activity.

The compounds of formula (I), and pharmaceutically-acceptable acid-addition salts thereof, possess antidepressant activity and hence are useful for the treatment of various depressive states in mammals. Their usefulness has been demonstrated in well-known test procedures such as antagonism of reserpine hypothermia in mice and inhibition of reuptake of noradrenaline (NA) and 5-hydroxytryptamine (5HT) in mouse brain synaptosomes. They have low toxicity.

As noted above, the active compounds of the present invention form acid-addition salts and, where such salts are pharmaceutically-acceptable, they are equally useful for the treatments mentioned herein. The active compounds and the pharmaceutically-acceptable acid-addition salts thereof of this invention are effective over a wide dosage range, the actual

dose administered being dependent on such factors as the particular compound being used, the condition being treated and the type and size of mammal being treated. However, the dosage per day required will normally fall within the range of 0.1 to 20 mg/Kg., for example, in the treatment of adult humans, single dosages of from 0.1 to 5 mg/Kg. may be used whilst, in the treatment of test animals such as mice and rats, single dosages of from 1 to 50 mg/Kg. may be employed.

The active compounds and salts of the present invention will normally be administered orally or by injection and, for this purpose, said compounds and salts will usually be utilised in the form of a pharmaceutical composition. Such compositions are prepared in a manner well known in the pharmaceutical art and normally comprise at least one active compound or salt of the invention in association with a pharmaceutically-acceptable carrier therefor. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Some examples of suitable carriers are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydroxybenzoate, talc, magnesium stearate or mineral oil. The compositions of the invention may, as is well known in the art, be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

Depending on the route of administration, the foregoing compositions may be formulated as tablets, capsules or suspensions for oral use and injection solutions for parenteral use. Preferably the compositions are formulated in a dosage unit form, each dosage containing from 1 to 500 mg., more usually 5 to 250 mg., of the active ingredient.

Accordingly, in one aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically-acceptable acid-addition salt thereof, associated with a pharmaceutically-acceptable carrier therefor.

In a further aspect of the invention there is provided a method of preparing a pharmaceutical composition as described above which comprises admixing a compound of formula (I), or a pharmaceutically-acceptable acid-addition salt thereof, with a pharmaceutically-acceptable carrier therefor.

It is to be clearly understood that the preferred features set out below the initial discussion of the compounds of formula (I) here-

inbefore, apply *mutatis mutandis* to all other aspects of the invention.

The invention will now be illustrated with references to the following Examples.

EXAMPLE 1

cis-3-N,N-Dimethylaminomethyl-2-(*o*-chlorophenyl)-bicyclo[2,2,2]octane hydrochloride

(a) *cis*-*o*-Chlorocinnamionitrile

o-Chlorobenzalcyanoacetic acid (40 g; 0.193 m) was intimately mixed with copper powder (3 g) and cuprous oxide (1 g) and heated *in vacuo* at a temperature of 240°C with vigorous evolution of carbon dioxide. The distillate was a pale yellow oil which was shown to contain 71% *cis*-nitrile by NMR assay. Fractional distillation of the mixture was carried out collecting early fractions containing pure *cis*-isomer, b.p. 90–92°C. at 1.2 mm/Hg.

(b) *cis*-5-(*o*-Chlorophenyl)-6-cyano-bicyclo[2,2,2]oct-2-ene

cis-*o*-Chlorocinnamionitrile (13 g; 80 mmole) and 1,3-cyclohexadiene (11.43 ml; 120 mmols) were added to a sealed tube with a trace of hydroquinone and 1,2-dichlorobenzene, and heated at 150–160°C. for 2 weeks. The product oil was washed several times with cold 40–60°C. petrol, after having highly boiling solvents initially removed, and then repeatedly washed with hot 60–80°C. petrol. These latter washings were collected and reduced to a viscous oil (15 g. crude; 77%). Crystallisation of a small part of this oil gave a white crystalline solid (m.p. 105–106°C). The remainder was used in the next reaction.

(c) *cis*-2-(*o*-Chlorophenyl)-3-cyano-bicyclo[2,2,2]octane

Crude *cis*-5-(*o*-chlorophenyl)-6-cyano-bicyclo[2,2,2]oct-2-ene (5.9 g; 243 mmole) was dissolved in absolute ethanol (40 ml) and reduced at atmospheric pressure over 5% Palladium/charcoal (0.6 g; 10% by weight). After the theoretical amount of hydrogen uptake, the catalyst was filtered off and the solution reduced to an oil (4.72 g; 80%). Recrystallisation from ethanol yielded a white crystalline solid (m.p. 96–98°C).

(d) *cis*-3-Aminomethyl-2-(*o*-chlorophenyl)-bicyclo[2,2,2]octane hydrochloride

cis-2-(*o*-Chlorophenyl)-3-cyano-bicyclo[2,2,2]octane (4.0 g; 16.4 mm) in dry tetrahydrofuran (10 ml) was added dropwise to a chilled and stirred solution of lithium aluminium hydride (0.87 g; 23.2 mm) in dry tetrahydrofuran (20 ml). After the addition, the solution was allowed to warm to room temperature and was stirred overnight. After the addition of water, the solution was decanted from solid material which was

washed with ether. The solutions were combined then washed with 2N HCl. The aqueous layer was separated, basified with 2N NaOH solution, and the amine extracted using ethyl acetate. After drying the combined extracts over magnesium sulphate, filtration and removal of solvent produced an oil which on dissolving in ethanolic hydrochloric acid and slowly adding ether gave the title compound (2.8 g) m.p. 220–223°C.

(e) *cis*-3-N,N-Dimethylaminomethyl-2-(*o*-chlorophenyl)-bicyclo[2,2,2]octane hydrochloride

To *cis*-3-aminomethyl-2-(*o*-chlorophenyl)-bicyclo[2,2,2]octane (2.3 g; 8.1 mm) was added sodium hydrogen carbonate (1.55 g; 18.5 mmole) and dimethyl formamide (50 ml). The flask was cooled in ice and a mixture of formic acid 90% (2.03 ml; 45 mm) and formaldehyde (3.87 ml; 45 mmole) added slowly. After the addition, the solution was slowly heated to reflux. After 4 hours, the solution was cooled, added to water (50 ml), made alkaline (pH=8) with solid potassium hydroxide and extracted with ethyl acetate. The combined ethyl acetate layer was washed with water, dried over magnesium sulphate, filtered and subjected to reduced pressure so as to yield a brown oil (2.2 g). The salt was formed from ethanolic hydrochloric acid and recrystallised from ethanol/ether mixture (1.7 g; m.p. 215–217°C).

EXAMPLES 2 and 3

The following bicyclo[2,2,2]octylamines were similarly prepared:

cis-3-N,N-Dimethylaminomethyl-2-(*m*-chlorophenyl)-bicyclo[2,2,2]octane, hydrochloride, m.p. 206–7°C.

cis-3-N,N-Dimethylaminomethyl-2-phenylbicyclo[2,2,2]octane, hydrochloride, m.p. 220–3°C.

EXAMPLE 4

cis-3-N,N-Dimethylaminomethyl-2-(*p*-fluorophenyl)-bicyclo[2,2,2]octane, hydrochloride

cis-3-Aminomethyl-2-(*p*-fluorophenyl)-bicyclo[2,2,2]octane (3 g; 0.0128 m) (prepared as in Example 1(d)), (except that the *p*-fluorocinnamionitrile was prepared from *p*-fluorobenzaldehyde and cyanoacetic acid by the procedure outlined in *Organic Reactions*, 15 374–381), acetic acid (30 ml), ethanol (30 ml), 40% formaldehyde in water (10 ml, 0.051 m) and 5% Palladium on charcoal (1 g) were hydrogenated in a Parr apparatus (60 lbs/inch²). After four hours, the catalyst was filtered off and the filtrate evaporated. The oil was dissolved in dilute hydrochloric acid and extracted with ether. The acid extracts were basified (5N NaOH) and extracted with ether. The ether was washed, (H₂O), dried (MgSO₄) and evaporated to give

an oil 2.6 g (80.4%) which, on dissolving in ethanolic hydrogen chloride and adding ether, produced the hydrochloride salt. Yield 1.9 g, (50%) m.p. 232—4°C.

EXAMPLE 5

cis-2-(*p*-Fluorophenyl)-3-*N*-methylaminoethyl-bicyclo[2,2,2]octane, hydrochloride

To a mixture of *cis*-3-aminomethyl-2-(*p*-fluorophenyl)-bicyclo[2,2,2]octane (1.34 g; 0.006 m) prepared in a similar manner to Example 1(d), and sodium carbonate (7.92 g; 0.078 m) in ether (25 ml) at 0°C, was added trifluoroacetic anhydride (12.0 g; 0.06 m) dropwise. After stirring at room temperature for two hours, the mixture was poured into ice/water and extracted with chloroform. The chloroform was washed (water), dried (MgSO₄) and evaporated to give an oil (2 g). After dissolving the oil in acetone (50 ml), methyl iodide (4.6 g; 0.03 m) then potassium hydroxide (1.4 g; 0.03 m) were added followed by reflux for one hour. After evaporation, the residue was to water (50 ml) and refluxed for twenty minutes. After extracting with ether, the ether was washed, dried, evaporated to give an oil which, on dissolving in ethanolic hydrogen chloride and adding ether, produced white crystals. Yield 0.4 g (24.6%) m.p. 236—8°C.

EXAMPLE 6

(a) *cis*-3,4-Dichlorocinnamionitrile

3,4-Dichlorobenzaldehyde (175 gms; 1 m), cyanoacetic acid (100 g; 1.15 m), and pyridine were refluxed for one day. Evaporation produced an oil which was fractionally distilled using a column (1 ft. long, ½ inch diameter) filled with glass helices. Overall yield 88.9 g (45%, 30% *cis*/70% *trans*).

Yield of isolated pure *cis* isomer 17 g (9%) m.p. 60—60.5°C. b.p. 110°C. at 0.15 mm.

Only pure *cis*-isomer was used in the next stage (b).

(b) *cis*-6-Cyano-5-(3,4-dichlorophenyl)-bicyclo[2,2,2]oct-2-ene

1,3-Cyclohexadiene (60% solution, 13.8 g, 0.17 m), *cis*-3,4-dichlorocinnamionitrile (17 g, 0.085 m) and benzene (10 ml) were heated in a sealed tube in the presence of a few crystals of hydroquinone at 160°C. After 17 days, the solution was evaporated and the residue was extracted with hot petrol (60—80°C). The petrol was evaporated to give a solid which was recrystallised from ethanol to give large crystals of the title compound. Yield 12.3 g (51.5%) m.p. 115—116°C.

(c) *cis*-3-Cyano-2-(3,4-dichlorophenyl)-bicyclo[2,2,2]octane

cis-6-Cyano-5-(3,4-dichlorophenyl)-bicyclo[2,2,2]oct-2-ene (12 g; 0.043 m) in ethanol (50 ml) and chloroform (30 ml) was hydrogenated at 60 lb/inch² in the presence of 5% Palladium on charcoal (1.2 g). The

catalyst was filtered off and the filtrate evaporated to give the title compound as a solid (12 g) which was recrystallised from ethanol. Yield 8.4 g (70%), m.p. 82—83°C.

(d) *cis*-3-Aminomethyl-2-(3,4-dichlorophenyl)-bicyclo[2,2,2]octane, hydrochloride

To lithium aluminium hydride (0.8 g; 0.021 m) in ether (50 ml), *cis*-3-cyano-2-(3,4-dichlorophenyl)-bicyclo[2,2,2]octane (4 g; 0.014 m) in tetrahydrofuran (30 ml) was added dropwise at 0°C. After four hours, 5N NaOH (1 ml) then water (4 ml) was added cautiously to produce a fine white precipitate which was filtered. The filtrate was dried and evaporated to produce an oil. On adding ethanolic hydrogen chloride, white crystals of the hydrochloride salt were produced. Yield 3 g (65.6%) m.p. 274—277°C.

(e) *cis*-2-(3,4-Dichlorophenyl)-3-*N*-methylaminomethyl-bicyclo[2,2,2]octane hydrochloride

cis-3-Cyano-2-(3,4-dichlorophenyl)-bicyclo[2,2,2]octane (0.9 g; 0.0032 m), dimethoxycarbonium fluoroborate (0.8 g; 0.0128 m) and dichloromethane (25 ml) were refluxed with stirring for one day. The mixture was cooled to 0°C. and ethanol (4 ml) added followed by evaporation. The residue was dissolved in methanol (15 ml) and, at 0°C. sodium borohydride (0.75 g, 0.02 m) added carefully. After 1 hour at 0°C. the mixture was acidified with 5N HCl and evaporated. The residue was diluted with water and extracted with ether. The aqueous part was basified (5N NaOH) and extracted with ether. The ether was washed, dried and evaporated to give an oil which on dissolving in ethanolic hydrogen chloride gave the title product as white needles. Yield 0.72 g; (67%) m.p. 247—248°C.

EXAMPLE 7

cis-3-*N*-Methylaminomethyl-2-phenylbicyclo[2,2,2]octane, hydrochloride

cis-3-Cyano-2-phenyl-bicyclo[2,2,2]octane (2.1 g; 0.01 m) prepared as in Example 1(c), dimethoxycarbonium fluoroborate (3.2 g; 0.02 m) and dichloromethane (25 ml) were refluxed with stirring for one day. The mixture was cooled to 0°C. and ethanol (3 ml) added followed by evaporation. The residue was dissolved in methanol (25 ml) and, at 0°C, sodium borohydride (2 g; 0.05 m) added carefully. After 1 hour at 0°C. the mixture was acidified with 5N HCl and evaporated. The residue was diluted with water and extracted with ether. The aqueous part was basified with 5N NaOH and extracted with ether. The ether was washed, dried (MgSO₄) and evaporated to give an oil which on dissolving in ethanolic hydrogen chloride gave white needles. Yield 1 g (38%) m.p. 213—215°C.

EXAMPLE 8

3-N,N-Dimethylaminomethyl-2-phenyl-bicyclo[2,2,2]oct-2-ene, hydrochloride

(a) 3 - Formyl - 2 - phenyl - bicyclo[2,2,2] - oct - 2,5 - diene

1,3-Cyclohexadiene (70% solution, 10 ml, 0.09 m) and phenylpropargyl aldehyde (4 g; 0.03 m) were refluxed in the presence of a few crystals of hydroquinone for 5 days. The solution was evaporated and the residue distilled. Yield 3.8 g (61%) b.p. 110–120°C. at 0.1 mm. NMR showed the mixture to contain 75% of the required product.

(b) 3 - Formyl - 2 - phenyl - bicyclo[2,2,2] - oct - 2 - ene

3 - Formyl - 2 - phenyl - bicyclo[2,2,2] - octa - 2,5 - diene (3.7 g; 0.018 m) 5% Palladium on charcoal (0.3 g) and ethyl acetate (100 ml) were hydrogenated for 1 week. The catalyst was filtered off and the filtrate evaporated, then the residue distilled twice; Yield 1.9 g (51%) b.p. 160°C. at 0.2 mm/Hg.

(c) 3 - Formyl - 2 - phenyl - bicyclo[2,2,2] - oct - 2 - ene (alternative method)

trans - 3 - Formyl - 2 - phenyl - bicyclo[2,2,2]octane (10.7 g; 0.05 m) in chloroform (50 ml) was added to cupric bromide (22.3 g; 0.1 m) in ethyl acetate (50 ml). The mixture was refluxed for four hours, left overnight at room temperature, treated with charcoal and evaporated to give 3 - bromo - 3 - formyl - 2 - phenyl - bicyclo[2,2,2]octane as a brown oil. (m.p.)=65–66°C. after crystallisation from ethanol). The oil was dissolved in dimethylformamide (50 ml) and lithium bromide (5 g; 0.057 m) and lithium carbonate (5 g; 0.078 m) were added, refluxing the mixture for 2 hours. After pouring in water (600 ml) and extracting with ether, the ether was washed, dried (MgSO₄) and evaporated to give an oil which was distilled. Yield 8.3 g. (76%) b.p. 160°C. at 0.2 mm/Hg.

(d) 3 - Hydroxymethyl - 2 - phenyl - bicyclo[2,2,2]oct - 2 - ene

To lithium aluminium hydride (1 g; 0.03 m) in ether (50 ml) was added 3 - formyl - 2 - phenyl - bicyclo[2,2,2]octane (4.2 g; 0.02 m) in ether (40 ml) dropwise at 0°C. After 1 hour, 5N sodium hydroxide (1 ml) followed by water (5 ml) was added cautiously. After filtering, the filtrate was evaporated to give an oil which was used directly in (e) below.

(e) 3 - N,N - Dimethylaminomethyl - 2 - phenyl - bicyclo[2,2,2]oct - 2 - ene, hydrochloride

To 3 - Hydroxymethyl - 2 - phenyl - bicyclo[2,2,2]oct - 2 - ene (1.4 g; 0.008 m) in dichloromethane (20 ml) and triethylamine (5 ml) at 0°C. methane sulphonyl chloride (2.4 ml, 20% excess) was added dropwise. After one day at 0°C, the mixture was poured

into ice and extracted with dichloromethane. The dichloromethane was dried (MgSO₄) and evaporated to give an oil (1.7 g). The oil was dissolved in dichloromethane (20 ml) and added to dimethylamine (15 ml. of 30% solution in ethanol) at 0°C. After stirring at room temperature for 3 days, the solution was evaporated and the residue dissolved in 5N HCl and extracted with ether. The ether was dried (MgSO₄) and evaporated to give an oil (0.5 g) which on dissolving in ethanolic hydrogen chloride produced white needles. Yield 0.48 g (26%) m.p. 236–237°C.

EXAMPLE 9

cis-2-(3,4-Dichlorophenyl)-3-N,N-dimethylaminomethyl-bicyclo[2,2,2]octane, hydrochloride

cis - 3 - Aminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]octane hydrochloride (4 g; 0.012 m) acetic acid (30 ml), ethanol (30 ml), 40% formaldehyde in water (20 ml, 0.1 m) and 5% Palladium on charcoal (1 g) were hydrogenated in a Parr apparatus (60 lbs./inch²). After five hours the catalyst was filtered off and the filtrate evaporated. The oil was dissolved in dilute hydrochloric acid and extracted with ether. The aqueous extracts were basified (5N NaOH) and extracted with ether. The ether was washed (H₂O), dried (MgSO₄) and evaporated to give an oil which, on dissolving in ethanolic hydrogen chloride and adding ether, produced the title compound. Yield 3.2 g; (74%), m.p. 223–225°C.

EXAMPLE 10

(+) and (–) *cis*-2-(3,4-Dichlorophenyl)-3-N,N-dimethylaminomethylbicyclo[2,2,2]octane, hydrochloride

The amine hydrochloride product of Example 9 was dissolved in hot water containing sufficient ethanol for solubilisation. Excess potassium carbonate solution was then added and the mixture agitated. The free base thus liberated was then extracted with ether, the ether extracts dried with magnesium sulphate, filtered and evaporated to yield an oil which crystallised on standing for a few days.

The crystalline free base was then dissolved in cold ethyl acetate (2.63 g; in 25 ml) containing ethanol (2.5 ml). D-(+)-Camphorsulphonic acid (1.95 g) dissolved in hot ethyl acetate (25 ml) was added to this solution. The combined solution was stirred slowly until white crystals of the acid/amine salt came out of solution. The reaction mixture was then allowed to stand for 24 hours and the salt recovered by filtration. This salt was repeatedly recrystallised from ethyl acetate and ethanol until a constant melting point and specific rotation were obtained.

$[\alpha]_D^{25} = +81^\circ$ (C=0.5%, EtOH)
m.p. 219°C.

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The pure camphorsulphonic acid/amine salt was then dissolved in hot water and excess potassium carbonate added to liberate the free base, which was extracted with ether. The combined ether extracts were dried, filtered and evaporated to an oil. This oil was dissolved in ethanol. HCl was then added to the solution followed by sufficient ether to allow crystallisation of the hydrochloride salt overnight. The white HCl salt which formed was (+) - *cis* - 2 - (3,4 - dichlorophenyl) - 3 - N,N - dimethylaminomethylbicyclo[2,2,2] - octane, hydrochloride.

$[\alpha]_D^{25} = +99^\circ$ (C=0.4%, EtOH)
m.p. 224—6°C.

Similarly, using a modification of the above resolution method there was obtained:

(-) - *cis* - 2 - (3,4 - dichlorophenyl) - 3 - N,N - dimethylaminomethylbicyclo[2,2,2] octane, hydrochloride.

$[\alpha]_D^{25} = -99^\circ$ (C=0.4%, EtOH)

EXAMPLE 11

3-N-methylaminomethyl-2-(3,4-dichlorophenyl)-bicyclo[2,2,2]oct-2-ene, hydrochloride)

(a) *trans* - 3 - Formyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]oct - 5 - ene - *trans* - 3,4 - Dichlorocinnamaldehyde (J. Med. Chem. 14, 797 (1971))

(71.9 g; 0.36 m), 1,3-cyclohexadiene (56 ml of a 70% solution, 0.45 m) and benzene (25 ml) were heated in a sealed tube in the presence of a few crystals of hydroquinone at 180°C. After 4 days, the solution was evaporated and the residue purified by bulb to bulb distillation to give the title compound as a yellow oil, yield 62 g; b.p. 200°C. at 0.1 mm/Hg.

(b) *trans* - 3 - Formyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]octane

trans - 3 - Formyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]oct - 5 - ene (62 g; 0.218 m) was hydrogenated in ethyl acetate (400 ml) at atmospheric pressure in the presence of 5% Pd/C (6.2 g). After 3 hours the catalyst was filtered off and the filtrate evaporated to give the title compound as an oil which was crystallised from petroleum ether (60—80°C.), yield 51.3 g (81%) m.p. 73—74°C.

(c) 3 - Formyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]oct - 2 - ene

Cupric bromide (45.7 g; 0.205 m) was added to *trans* - 3 - formyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]octane (29 g; 0.102 m) dissolved in a mixture of chloroform (355 ml) and ethyl acetate (355 ml). After refluxing for 2 hours the solution was filtered and the filtrate evaporated to give 3 - bromo -

2 - (3,4 - dichlorophenyl) - 3 - formyl - bicyclo[2,2,2]octane as a brown oil. This oil was dissolved in dimethylformamide (350 ml) and lithium bromide (17.8 g; 0.204 m) and lithium carbonate (15.2 g; 0.204 m) added, refluxing the mixture for 2 hours. After pouring the solution into water (3 litres) and extracting with dichloromethane, the dichloromethane extract was washed, dried (MgSO₄) and evaporated to give an oil (31 g) which was purified by bulb to bulb distillation. Yield 25.3 g (88%) b.p. 190°C. 0.1 mm/Hg. m.p. 71—71.5°C. (after crystallisation from petroleum ether (60—80°C.)).

(d) N - {2 - (3,4 - Dichlorophenyl) - bicyclo[2,2,2]oct - 2 - ene - 3 - yl} - methylenemethylamine

A 33% solution of methylamine in ethanol (250 ml) was added in one lot to 3 - formyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]oct - 2 - ene (25 g; 0.089 m) in dichloromethane (50 ml) at 0°C. After 1 hour, the solution was evaporated to yield an oil. Yield 26 g. (100%). An infra-red spectrum showed complete loss of the carbonyl group. A peak at 1630 cm⁻¹ indicated the presence of an imine (—CH=N—Me group). M⁺ 293/295.

(e) 3 - N - Methylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]oct - 2 - ene, hydrochloride

Sodium borohydride (6 g, 0.162 m) was added to N - {2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]oct - 2 - ene - 3 - yl} - methylenemethylamine (26 g; 0.089 m) in methanol (250 ml) at 0°C. over a period of forty-five minutes, the mixture being stirred at room temperature overnight. The methanol was evaporated off, the residue dissolved in dilute hydrochloric acid and the mixture extracted with ether. The aqueous parts were basified (5N NaOH) and extracted with ether. The ether was washed (H₂O), dried (MgSO₄) and evaporated to give a colourless oil 21.4 g (81.3%). A sample of the product was dissolved in ethanolic hydrogen chloride and, ether added to give the title compound, m.p. 247.0—249°C.

(f) 3 - N,N - Dimethylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2] - oct - 2 - ene hydrochloride

A mixture of 90% formic acid (18.5 ml, 0.36 m) and 37% formaldehyde (29.3 ml, 0.036 m) was added at 0°C. to 3 - N - methylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]oct - 2 - ene (0.072 m, 21.4 g) in dimethylformamide (36 ml). After refluxing for 5 hours, evaporation produced a colourless residue to which water (1 litre) then 5N HCl was added. After extraction with ether, the aqueous part was basified (5N NaOH) and again extracted with ether. The ether was washed, dried (MgSO₄) and evaporated to give

- 5 a colourless oil which, on dissolving in ethanolic hydrogen chloride followed by addition of ether, gave the title product which was crystallised from an IPA/hexane mixture, yield 15.8 g (63%) m.p. 204—7°C.

EXAMPLES 12 to 27

The following further compounds of the invention were prepared using procedures similar to those described above.

- 10 *cis* - 3 - N - Methylaminomethyl - 2 - (p - tertiarybutylphenyl) - bicyclo[2,2,2]octane, hydrochloride, (m.p. 273—276°C).
- 15 *cis* - 3 - N,N - Dimethylaminomethyl - 2 - (2,4 - dichlorophenyl) - bicyclo[2,2,2] - octane.
- cis* - 3 - N - Methylaminomethyl - 2 - (2,4 - dichlorophenyl) - bicyclo[2,2,2]octane, hydrochloride, (m.p. 265—7°C).
- 20 *cis* - 3 - N,N - Dimethylaminomethyl - 2 - (p - bromophenyl) - bicyclo[2,2,2]octane, hydrochloride, (m.p. 238°C).
- cis* - 3 - N - Methylaminomethyl - 2 - (p - bromophenyl) - bicyclo[2,2,2]octane, hydrochloride, (m.p. 241°C).
- 25 *cis* - 3 - N - Methylaminomethyl - 2 - (4 - chloro - 3 - trifluoromethylphenyl) - bicyclo - [2,2,2]octane, hydrochloride, (m.p. 223°C).
- cis* - 3 - N,N - Dimethylaminomethyl - 2 - (2,3 - dichlorophenyl) - bicyclo[2,2,2]octane.
- 30 *cis* - 3 - N - Methylaminomethyl - 2 - (2,3 - dichlorophenyl) - bicyclo[2,2,2]octane.
- cis* - 3 - N,N - Dimethylaminomethyl - 2 - (2,5 - dichlorophenyl) - bicyclo[2,2,2] - octane.
- 35 *cis* - 3 - N - Methylaminomethyl - 2 - (2,5 - dichlorophenyl) - bicyclo[2,2,2]octane.
- cis* - 3 - N,N - Dimethylaminomethyl - 2 - (3,5 - dichlorophenyl) - bicyclo[2,2,2]octane.
- 40 *cis* - 3 - N - Methylaminomethyl - 2 - (3,5 - dichlorophenyl) - bicyclo[2,2,2]octane.
- cis* - 3 - N,N - Dimethylaminomethyl - 2 - (3,4 - methylenedioxyphenyl) - bicyclo[2,2,2] - octane, maleate, (m.p. 124—5°C).
- 45 3 - N - Methylaminomethyl - 2 - (4 - nitro - phenyl) - bicyclo[2,2,2]oct - 2 - ene, hydro - chloride, (m.p. 246—7°C).
- 3 - N - Methylaminomethyl - 2 - (4 - chlorophenyl) - bicyclo[2,2,2]oct - 2 - ene, hydrochloride, (m.p. 251—3°C).
- 50 3 - N,N - Dimethylaminomethyl - 2 - (4 - chlorophenyl) - bicyclo[2,2,2]oct - 2 - ene, hydrochloride, (m.p. 195°C).

The following Examples illustrate pharmaceutical formulations containing compounds of formula (I). The active ingredient used was *cis* - 3 - N,N - dimethylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]octane, hydrochloride; however, this compound may be replaced by other active solid compounds of the invention.

EXAMPLE 28

Tablets each containing 5 mg. of active ingredient were made up as follows:

Active ingredient	5 mg.	
Potato starch	20 mg.	65
Lactose	20 mg.	
Polyvinylpyrrolidone (as 10% solution in water)	2 mg.	
Sodium starch glycolate	2 mg.	
Magnesium stearate	0.5 mg.	70
Talc	0.5 mg.	
Total	50 mg.	

The starch, lactose and active ingredient were passed through a sieve and thoroughly mixed. The solution of polyvinylpyrrolidone was mixed with the resultant mixture and the combination passed through a No. 12 mesh B.S. sieve. The granules so produced were dried at approximately 55°C. and passed through a No. 16 mesh B.S. sieve. The magnesium stearate, sodium starch glycolate and talc, previously passed through a No. 60 mesh B.S. sieve, were then added to the granules which, after mixing, were compressed on a tablet machine to yield tablets each weighing 50 mg.

EXAMPLE 29

Capsules each containing 10 mg of medication were made as follows:

Active ingredient	10 mg.	90
Starch	44 mg.	
Lactose	45 mg.	
Magnesium stearate	1 mg.	
Total	200 mg.	

The lactose, starch, magnesium stearate and active ingredient were passed through a No. 44 mesh B.S. sieve and filled into hard gelatin capsules in 100 mg. quantities.

EXAMPLE 30

Suppositories each containing 25 mg. of active ingredient were made as follows:

Active ingredient	25 mg.
Saturated fatty acid glycerides to	2,000 mg.

The active ingredient was passed through a No. 60 mesh B.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture was then poured into a suppository mould of nominal 2 g. capacity and allowed to cool.

WHAT WE CLAIM IS:—

1. A process of preparing an amine of formula (I):





* C L M S *

a colourless oil which, on dissolving in ethanolic hydrogen chloride followed by addition of ether, gave the title product which was crystallised from an IPA/hexane mixture, yield 15.8 g (63%) m.p. 204—7°C.

EXAMPLES 12 to 27

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- 10 *cis* - 3 - N - Methylaminomethyl - 2 - (*p* - tertiarybutylphenyl) - bicyclo[2,2,2]octane, hydrochloride, (m.p. 273—276°C).
- 15 *cis* - 3 - N,N - Dimethylaminomethyl - 2 - (2,4 - dichlorophenyl) - bicyclo[2,2,2] - octane.
- 20 *cis* - 3 - N - Methylaminomethyl - 2 - (2,4 - dichlorophenyl) - bicyclo[2,2,2]octane, hydrochloride, (m.p. 265—7°C).
- 20 *cis* - 3 - N,N - Dimethylaminomethyl - 2 - (*p* - bromophenyl) - bicyclo[2,2,2]octane, hydrochloride, (m.p. 238°C).
- 25 *cis* - 3 - N - Methylaminomethyl - 2 - (*p* - bromophenyl) - bicyclo[2,2,2]octane, hydrochloride, (m.p. 241°C).
- 30 *cis* - 3 - N - Methylaminomethyl - 2 - (4 - chloro - 3 - trifluoromethylphenyl) - bicyclo[2,2,2]octane, hydrochloride, (m.p. 223°C).
- 30 *cis* - 3 - N,N - Dimethylaminomethyl - 2 - (2,3 - dichlorophenyl) - bicyclo[2,2,2]octane.
- 30 *cis* - 3 - N - Methylaminomethyl - 2 - (2,3 - dichlorophenyl) - bicyclo[2,2,2]octane.
- 35 *cis* - 3 - N,N - Dimethylaminomethyl - 2 - (2,5 - dichlorophenyl) - bicyclo[2,2,2]octane.
- 40 *cis* - 3 - N - Methylaminomethyl - 2 - (3,5 - dichlorophenyl) - bicyclo[2,2,2]octane.
- 40 *cis* - 3 - N,N - Dimethylaminomethyl - 2 - (3,4 - methylenedioxyphenyl) - bicyclo[2,2,2] - octane, maleate, (m.p. 124—5°C).
- 45 3 - N - Methylaminomethyl - 2 - (4 - nitrophenyl) - bicyclo[2,2,2]oct - 2 - ene, hydrochloride, (m.p. 246—7°C).
- 50 3 - N - Methylaminomethyl - 2 - (4 - chlorophenyl) - bicyclo[2,2,2]oct - 2 - ene, hydrochloride, (m.p. 251—3°C).
- 50 3 - N,N - Dimethylaminomethyl - 2 - (4 - chlorophenyl) - bicyclo[2,2,2]oct - 2 - ene, hydrochloride, (m.p. 195°C).

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Magnesium stearate	0.5 mg.	70
Talc	0.5 mg.	
Total	50 mg.	

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Lactose	45 mg.	
Magnesium stearate	1 mg.	
Total	200 mg.	

The lactose, starch, magnesium stearate and active ingredient were passed through a No. 44 mesh B.S. sieve and filled into hard gelatin capsules in 100 mg. quantities.

EXAMPLE 30

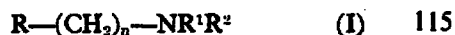
Suppositories each containing 25 mg. of active ingredient were made as follows:

Active ingredient	25 mg.	
Saturated fatty acid glycerides to	2,000 mg.	

The active ingredient was passed through a No. 60 mesh B.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture was then poured into a suppository mould of nominal 2 g. capacity and allowed to cool.

WHAT WE CLAIM IS:—

1. A process of preparing an amine of formula (I):





or an acid-addition salt thereof, wherein n is an integer from 1 to 3, R^1 is C_{1-4} alkyl, R^2 is hydrogen or C_{1-4} alkyl and R is a 2-phenyl-bicyclo group of formula:

5

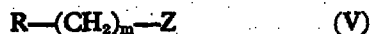


(II)

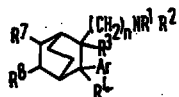
wherein R^3 and R^4 each represent a hydrogen atom, said hydrogen atoms being in a *cis*-relationship, or taken together represent a single chemical bond; and wherein Ar represents an optionally substituted phenyl group; which process comprises:

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- (A) reducing:
(i) a compound of formula (V):



- 15 where m is 0, 1 or 2 and Z is $-\text{CONR}^1\text{R}^2$, $-\text{CH}=\text{NR}^1$ or $-\text{C}(\text{OR}^1)=\text{NR}^2$; or
(ii) an olefin of formula (VI):



(VI)

- 20 where R^7 and R^8 taken together represent a single bond or, when R^3 and R^4 taken together represent a single bond, independently represent hydrogen atoms;

- (B) alkylating a compound of formula (VII):

25



or

- (C) condensing an amine of formula:



with a compound of formula (VIII):

30



where Q is a leaving group as hereinbefore defined; optionally followed when R^3 and R^4 represent *cis*-hydrogen atoms by (D) resolution of the product of formula (I) formed in reaction (A), (B) or (C) into its (+) or (-) enantiomeric form.

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2. A process according to claim 1, wherein the optionally substituted phenyl group Ar has the formula:

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wherein R^5 and R^6 individually represent the same or different substituents selected from hydrogen, halogen, trifluoromethyl, nitro, amino, C_{2-3} acylamino, mono- or di- C_{1-4} alkylamino, C_{1-4} alkyl or C_{1-4} alkoxy; or taken together represent C_{1-3} alkylendioxy.

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3. A process according to claim 1 or 2, wherein n is 1.

4. A process according to claim 1, 2 or 3, wherein R^1 and R^2 are methyl.

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5. A process according to any one of claims 1 to 4, wherein Ar is phenyl singly or doubly substituted by halogen.

6. A process according to claim 5, wherein Ar is 3,4-dichlorophenyl.

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7. A process according to any one of claims 1 to 6, wherein R^3 and R^4 represent *cis*-hydrogen atoms.

8. A process according to claim 7, wherein the (+)-enantiomer is obtained by resolution of the product of formula (I).

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9. An amine of formula (I), or an acid-addition salt thereof, whenever prepared by a process according to any one of claims 1 to 8.

10. An amine of formula (I):

65



or an acid-addition salt thereof, wherein n is an integer from 1 to 3, R^1 is C_{1-4} alkyl, R^2 is hydrogen or C_{1-4} alkyl and R is a 2-phenyl-bicyclo group of formula:

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(II)

wherein R^3 and R^4 either each represent a hydrogen atom, said hydrogen atoms being in a *cis*-relationship, or taken together represent a single chemical bond; and wherein Ar represents an optionally substituted phenyl group.

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11. An amine of formula (I), or an acid-addition salt thereof, as claimed in claim 10, wherein Ar represents an optionally substituted phenyl group of formula:

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wherein R^5 and R^6 individually represent the same or different substituents selected from hydrogen, halogen, trifluoromethyl, nitro, amino, C_{2-3} acylamino, mono- or di- C_{1-4} alkylamino, C_{1-4} alkyl or C_{1-4} alkoxy; or taken together represent C_{1-3} alkylendioxy.

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12. An amine of formula (I), or an acid-addition salt thereof, as claimed in claim 10 or 11, wherein n is 1.

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13. An amine of formula (I), or an acid-addition salt thereof, as claimed in claim 10, 11 or 12, wherein R^1 is C_{1-3} alkyl and R^2 is hydrogen, methyl or ethyl.

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14. An amine of formula (I), or an acid-addition salt thereof, as claimed in claim 13 wherein R^1 and R^2 are methyl.

15. An amine of formula (I), or an acid-addition salt thereof, as claimed in any one of claims 10 to 14, wherein Ar is phenyl singly or doubly substituted by halogen.

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16. An amine of formula (I), or an acid-



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addition salt thereof, as claimed in claim 15 wherein Ar is *p*-chloro or *p*-bromophenyl.

17. An amine of formula (I), or an acid-addition salt thereof, as claimed in claim 15 wherein Ar is 3,4-dichlorophenyl.

18. An amine of formula (I), or an acid-addition salt thereof, as claimed in any one of claims 10 to 17, wherein R³ and R⁴ together represent a single chemical bond.

19. An amine of formula (I), or an acid-addition salt thereof, as claimed in any one of claims 10 to 17, wherein R³ and R⁴ both represent *cis*-hydrogen atoms.

20. An amine of formula (I), or an acid-addition salt thereof, as claimed in claim 19 which is the (+)-enantiomer.

21. An acid-addition salt as claimed in any one of claims 10 to 20, which is a pharmaceutically-acceptable salt.

22. *cis* - 3 - N,N - Dimethylaminomethyl - 2 - (*p* - chlorophenyl) - bicyclo[2,2,2]octane.

23. *cis* - 3 - N - Methylaminomethyl - 2 - (*p* - chlorophenyl) - bicyclo[2,2,2]octane.

24. *cis* - 3 - N,N - Dimethylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2] - octane.

25. *cis* - 3 - N,N - Dimethylaminomethyl - 2 - (*p* - bromophenyl) - bicyclo[2,2,2]octane.

26. *cis* - 3 - N - Methylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]octane.

27. (+) - *cis* - 3 - N,N - Dimethylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]octane.

28. 3 - N - Methylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]oct - 2 - ene.

29. 3 - N,N - Dimethylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]oct - 2 - ene.

30. A pharmaceutically-acceptable acid-addition salt of the compound claimed in any one of claims 22 to 29.

31. A pharmaceutically-acceptable acid-addition salt as claimed in claim 21 or 30 which is the hydrochloride salt.

32. *cis* - 3 - N,N - Dimethylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2] - octane, hydrochloride.

33. (+) - *cis* - 3 - N,N - Dimethylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]octane, hydrochloride.

34. An amine of formula:



or an acid-addition salt thereof, wherein R and n are as defined in any one of claims 10 to 20; provided that when R³ and R⁴

represent *cis*-hydrogen atoms and n is 1, Ar cannot be *p*-chlorophenyl.

35. A method of preparing a pharmaceutical composition which comprises admixing a compound of formula (I) as defined in any one of claims 9 to 33, or a pharmaceutically-acceptable acid-addition salt thereof, with a pharmaceutically-acceptable carrier therefor.

36. A method according to claim 35, wherein (+) - *cis* - 3 - N,N - dimethylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]octane, hydrochloride is admixed with a pharmaceutically-acceptable carrier therefor.

37. A pharmaceutical composition which comprises as an active ingredient a compound of formula (I) as defined in any one of claims 9 to 33, or a pharmaceutically-acceptable acid-addition salt thereof, associated with a pharmaceutically-acceptable carrier therefor.

38. A pharmaceutical composition as claimed in claim 37 containing from 1 to 250 mg. of the compound of formula (I), or a pharmaceutically - acceptable acid - addition salt thereof, as the active ingredient.

39. A pharmaceutical composition as claimed in claim 37 or 38, wherein the active ingredient is a pharmaceutically-acceptable acid-addition salt of *cis* - 3 - N,N - dimethylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]octane.

40. A pharmaceutical composition as claimed in claim 39, wherein the active ingredient is (+) - *cis* - 3 - N,N - dimethylaminomethyl - 2 - (3,4 - dichlorophenyl) - bicyclo[2,2,2]octane, hydrochloride.

41. An amine of formula (I), as claimed in claim 10, or an acid-addition salt thereof, substantially as herein described with reference to any one of the foregoing Examples.

42. An amine as claimed in claim 34, or an acid-addition salt thereof, substantially as herein described with reference to the foregoing Examples.

43. A method according to claim 1 substantially as herein described with reference to any one of the foregoing Examples.

44. An amine of formula (I), or an acid-addition salt thereof, whenever prepared by a method according to claim 43.

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