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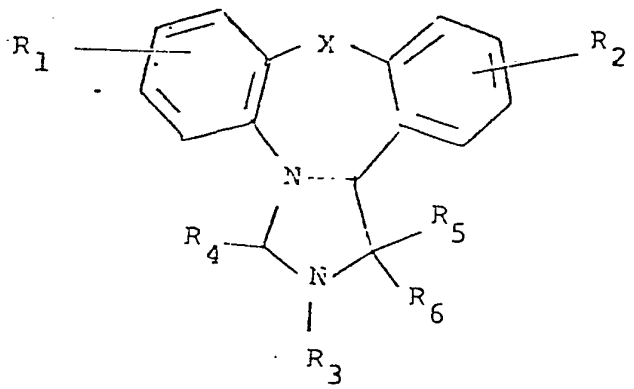
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(54) Title: TETRACYCLIC COMPOUNDS




(I)

(57) Abstract

Compounds of formula (I) or a pharmaceutically acceptable salt thereof wherein: X is $CH_2$, O, S, or NR where R is $C_{1-4}$ alkyl; $R_1$ and $R_2$ are independently selected from hydrogen, hydroxy, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, halogen or $CF_3$; $R_3$ is $C_{1-7}$ alkyl, $C_{2-5}$ alkynyl, $C_{3-7}$ cycloalkyl, $C_{4-7}$ cycloalkenyl or $C_{1-6}$ alkyl substituted by $C_{2-7}$ alkenyl, $C_{2-7}$alkynyl, $C_{3-7}$ cycloalkyl, hydroxy, thiol, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio, carboxy, $C_{1-6}$ alkoxycarbonyl, $C_{2-7}$ alkanoyl, amino optionally substituted by one or two $C_{1-4}$ alkyl or by $C_{4-6}$ polymethylene optionally containing an oxygen or nitrogen atom, aminocarbonyl optionally N-substituted by one or two $C_{1-6}$ alkyl groups, or benzoyl or phenyl either being optionally ring-substituted by one or two $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, halogen or trifluoromethyl; and one of $R_4$, $R_5$ and $R_6$ is $C_{1-6}$ alkyl and the other two are independently hydrogen or $C_{1-6}$ alkyl, having anti-depressant and/or anxiolytic activity, a process for their preparation and their use.

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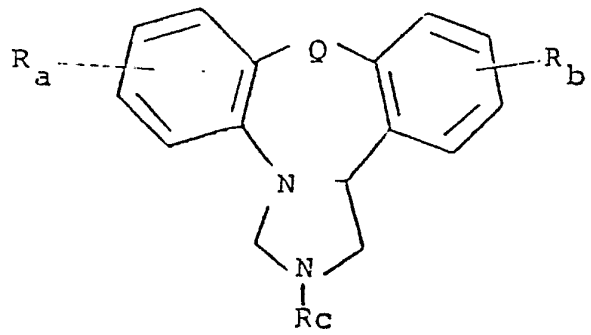
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# TETRACYCLIC COMPOUNDS

This invention relates to novel tetracyclic compounds having mood-modifying, particularly anti-depressant and/or anxiolytic activity, to pharmaceutical compositions containing them, and to a process for their preparation.

UK Patent 1,404,642 describes compounds of the formula (A):




(A)

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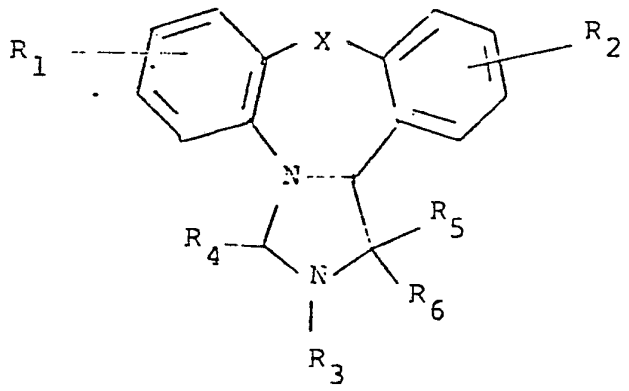
in which $R_a$ and $R_b$ are hydrogen, hydroxy, halogen, alkyl or alkoxy with 1-6 carbon atoms, acyloxy with 1-8 carbon atoms, or a trifluoromethyl group;

$R_c$ is hydrogen, an alkyl group with 1-6 carbon atoms, an aryl group or an aralkyl group with 7-9 carbon atoms; and

Q is a single bond, a $-CH_2-CH_2-$ group, a $-CH=CH-$ group or a $-CHR-$ group where R is hydrogen or an alkyl group 1-6 carbon atoms.

A class of tetracyclic compounds has now been discovered to have useful mood-modifying, particularly anti-depressant activity and/or anxiolytic activity.

Accordingly, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

X is $CH_2$, O, S or NR where R is $C_{1-4}$ alkyl;

$R_1$ and $R_2$ are independently selected from hydrogen, hydroxy, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, halogen or $CF_3$;

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$R_3$ is $C_{1-7}$ alkyl, $C_{2-5}$ alkenyl, $C_{2-5}$ alkynyl, $C_{3-7}$ cycloalkyl, $C_{4-7}$ cycloalkenyl or $C_{1-6}$ alkyl substituted by $C_{2-7}$ alkenyl, $C_{2-7}$ alkynyl, $C_{3-7}$ cycloalkyl, hydroxy, thiol, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio, carboxy, $C_{1-6}$ alkoxycarbonyl, $C_{2-7}$ alkanoyl, amino optionally substituted by one or two $C_{1-4}$ alkyl or by $C_{4-6}$ polymethylene optionally containing an oxygen or nitrogen atom, aminocarbonyl optionally N-substituted by one or two $C_{1-6}$ alkyl groups, or benzoyl or phenyl either being optionally ring-substituted by one or two $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, halogen or trifluoromethyl; and

one of $R_4$, $R_5$ and $R_6$ is $C_{1-6}$ alkyl and the other two are independently hydrogen or $C_{1-6}$ alkyl.

When X is NR, suitable examples of R include methyl, ethyl, n- or iso-propyl, n, sec- or tert-butyl.

Suitable examples of $R_1$ and $R_2$ include hydrogen, hydroxy, methyl, ethyl; methoxy and ethoxy; fluoro, chloro, bromo; and $CF_3$. Often $R_1$ and $R_2$ will be hydrogen or 7-halo, such as chloro bromo. Preferably $R_1$ and $R_2$ are both hydrogen.

When $R_3$ is $C_{1-4}$ alkyl substituted by phenyl optionally substituted as hereinbefore defined, examples of such optional substituents include methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo or trifluoromethyl. Preferably, phenyl is unsubstituted.

When $R_3$ is $C_{1-4}$ alkyl substituted by amino optionally substituted as hereinbefore defined, examples of such optional substituents include methyl and ethyl and, together with the nitrogen atom, piperidino and morpholino.

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Preferably, $R_3$ is $C_{1-4}$ alkyl, such as methyl and ethyl, most preferably methyl.

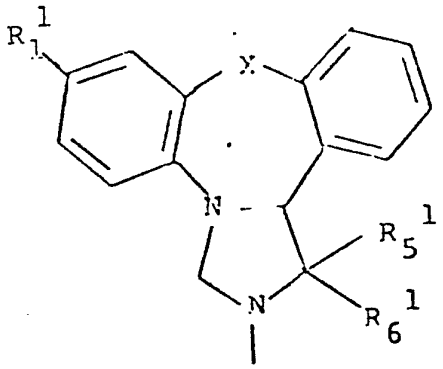
When $R_4$, $R_5$ or $R_6$ are hydrogen or $C_{1-6}$ alkyl suitable values include hydrogen, methyl, ethyl, n- and iso-propyl, n, sec- and tert-butyl. In such cases $R_4$, $R_5$ or $R_6$ will often be hydrogen or methyl or ethyl. Preferably, at least one of $R_5$ and $R_6$ is hydrogen.

Suitable examples of salts of the compounds of formula (I) include acid addition salts with pharmaceutically acceptable inorganic and organic acids, such as hydrochloric, hydrobromic, sulphuric, maleic and succinic acids.

The compounds of formula (I) have asymmetric centres and are capable of existing in a number of stereoisomeric forms. The invention extends to each of these forms and to mixtures thereof.

There is a group of compounds within formula (I) wherein $R_3$ is $C_{1-6}$ alkyl, $C_{2-5}$ alkenyl, $C_{2-5}$ alkynyl, $C_{3-7}$ cycloalkyl, $C_{5-7}$ cycloalkenyl or $C_{1-4}$ alkyl substituted by $C_{3-7}$ cycloalkyl or phenyl or $C_{1-6}$ alkyl substituted by hydroxy, $C_{1-6}$ alkoxy, carboxy, $C_{2-7}$ alkanoyl, benzoyl or aminocarbonyl or amino optionally substituted by one or two $C_{1-6}$ alkyl groups and the remaining variables are as defined in formula (I).

A group of compounds within formula (I) is of formula (II):




(II)

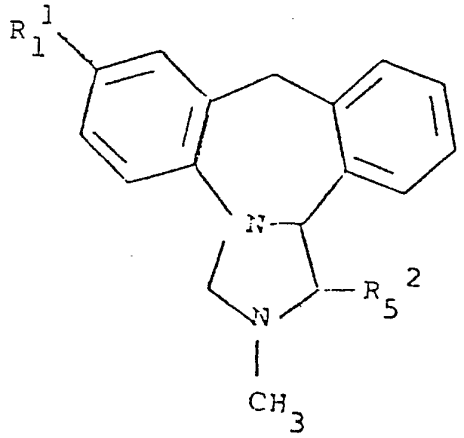
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wherein $R_1^1$ is hydrogen or halogen, one of $R_5^1$ and $R_6^1$ is $C_{1-6}$ alkyl and the other is hydrogen or $C_{1-6}$ alkyl; and X is as defined in formula (I).

Suitable values for $R_1^1$, $R_5^1$ and $R_6^1$ are as described under formula (I) for relevant $R_1$, $R_5$ and $R_6$.

Preferably one of $R_5^1$ and $R_6^1$ is hydrogen and the other is $C_{1-6}$ alkyl. Preferably $R_1$ is hydrogen.

A sub-group of compounds within formula (II) is of formula (III):



(III)

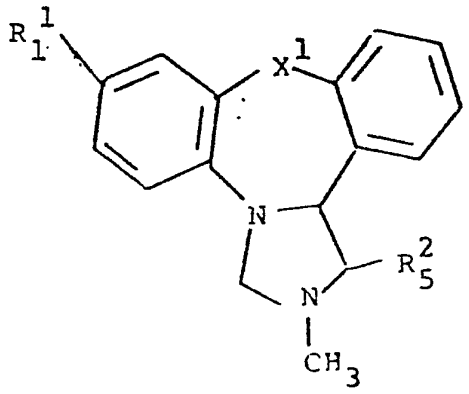
wherein $R_5^2$ is $C_{1-6}$ alkyl and $R_1^1$ is as defined in formula (II).

Suitable values for $R_5^2$ are as described for relevant $R_5$ under formula (I).

Preferably $R_5^2$ is methyl or ethyl, most preferably methyl.

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A further sub-group of compounds within formula (II) is of formula (IV):



(IV)

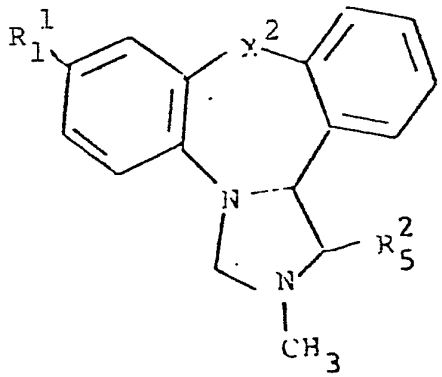
wherein $X^1$ is oxygen or sulphur; and

$R_1^1$ and $R_5^2$ are as defined in formula (III).

Suitable and preferred values for $R_1^1$ and $R_5^2$ are as described for relevant $R_1$ and $R_5$ under formula (I).

Preferably $R_5^2$ is methyl or ethyl, most preferably methyl.

There is another sub-group of compounds within formula (II) of formula (V):



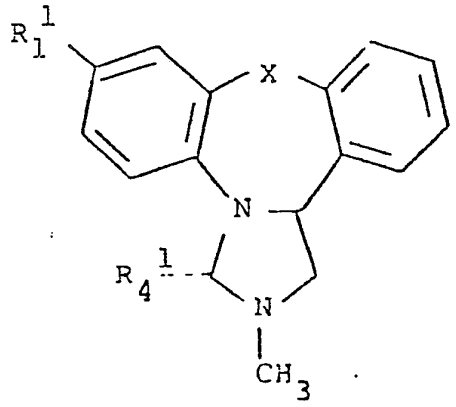
(V)

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wherein $X^2$ is NR as defined in formula (I) and $R_1^1$ and $R_5^2$ are as defined in formula (III).

Suitable and preferred values for $R_1^1$ and $R_5^2$ are as described for the corresponding variables under formula (I).

There is another group of compounds within formula (I) of formula (VI):



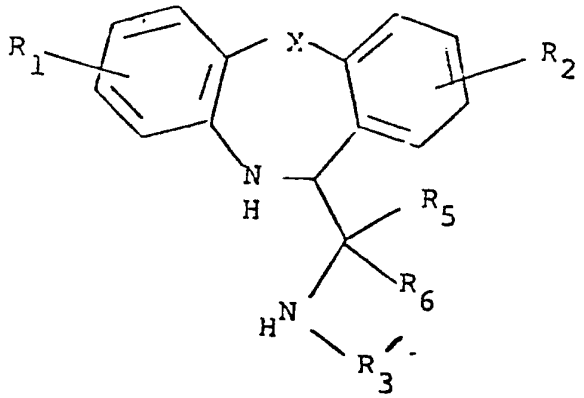
(VI)

wherein $R_4^1$ is $C_{1-6}$ alkyl and $R_1^1$ is as defined in formula (II).

Suitable values for $R_1^1$ and $R_4^1$ include those described under formula (I) for relevant $R_1$ and $R_4$.

Preferably $R_4^1$ is methyl.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises the reaction of a compound of formula (VII):

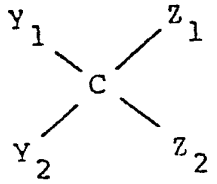


(VII)



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with a compound of formula (VIII):



(VIII)

wherein $R_3'$ is $R_3$ or a group convertible thereto, $R_1$, $R_2$, $R_5$ and $R_6$ are as defined in formula (I), one of $Y_1$ and $Y_2$ is hydrogen and the other is $R_4$ as defined or (when $R_4$ in formula (I) is hydrogen), $Y_1$ and $Y_2$ together form an oxo or thiocarbonyl group; and $Z_1$ and $Z_2$ are leaving groups, and thereafter reducing the resulting compound formed when $Y_1$ and $Y_2$ together form an oxo or thiocarbonyl group, and/or converting $R_3'$ to $R_3$ and/or forming a pharmaceutically acceptable salt.

$Z_1$ and $Z_2$ are suitably groups which are readily displaceable by a secondary amino nucleophile.

Favourable values for $Z_1$ and $Z_2$ when $Y_1/Y_2$ are hydrogen and $R_4$, include halo or hydroxy. When $Y_1$ and $Y_2$ are both hydrogen, reagents therefore include methylene chloride, methylene bromide and methylene diol (aqueous or ethanolic formaldehyde).

Favourable values for $Z_1$ and $Z_2$ when $Y_1$ and $Y_2$ together are oxo or thiocarbonyl include halo, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio, amino optionally substituted by one or two $C_{1-6}$ alkyl or $C_{1-6}$ acyl groups.

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Such reagents of formula (VIII) therefore include phosgene, thiophosgene, haloformic esters, such as ethyl chloroformate, carbonic acid esters, such as diethyl carbonate, urea derivatives, such as urea, thiourea or N, N$^1$-carbonyl-di-imidazole.

When $R_4$ is hydrogen, the compound of of formula (VII) is preferably methylene diol.

The reaction may be carried out in a suitable solvent. Aprotic, polar solvents such as dimethyl-sulphoxide, sulfolane or acetonitrile are suitable.

Alternatively, the reagent may act as the solvent such as methylene chloride. If urea is used as the reagent the reaction can be carried out in a melt.

If $Z_1$ and/or $Z_2$ are halo, an agent capable of binding the hydrogen halide released in the condensation, is usually added. Suitable agents include pyridine and triethylamine.

It will be appreciated that, if $R_3'$ is a carbonyl containing group, the carbonyl group is preferably protected, for example as the ketal during the reaction between compounds (VII) and (VIII).

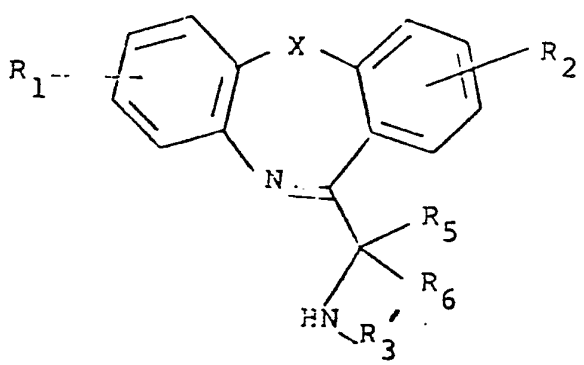
The subsequent reduction of the compound formed between a compound of formula (VI) and a compound of formula (VII) wherein $Y_1/Y_2$ are oxo or thio is normally carried out using a conventional reducing agent, such as metal hydrides eg. sodium borohydride, sodium cyanoborohydride, lithium aluminium hydride or diborane. Catalytic hydrogenation is also suitable. It will be appreciated that, if $R_3'$ is a group susceptible to reducing agents,

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suitable protection or selection of reagents and reaction conditions must be selected.

Examples of an optional conversion of $R_3$ in a compound of formula (I) into another $R_3$ include the conversion of $C_{1-6}$ alkyl substituted by hydroxy into $C_{1-6}$ alkyl substituted by thiol by, for example, first forming a $C_{1-6}$ halide, such as the chloride, and then reacting the $C_{1-6}$ alkyl halide with potassium hydrogen sulphide, or into $C_{1-6}$ alkyl subsituted by $C_{1-6}$ alkoxy using, for example, sodium hydride and a $C_{1-6}$ alkyl halide; the conversion of $C_{1-6}$ alkyl substituted by thiol into $C_{1-6}$ alkyl substituted by $C_{1-6}$ alkylthio using, for example, a base and a $C_{1-6}$ alkyl halide; the conversion of $C_{1-6}$ alkyl substituted by $C_{1-6}$ alkoxycarbonyl into $C_{1-6}$ alkyl substituted by carboxy by hydrolysis; the conversion of $C_{1-6}$ alkyl substituted by carboxy into $C_{1-6}$ alkyl substituted by aminocarbonyl optionally N-substituted by one or two $C_{1-6}$ alkyl by,for example, first forming the carboxylic acid halide, such as the chloride, and then reacting the acid halide with ammonia optionally substituted by one or two $C_{1-6}$ alkyl; and the conversion of $C_{1-5}$ alkyl substituted by aminocarbonyl optionally N-substituted by one or two $C_{1-6}$ alkyl into $C_{1-6}$ alkyl substituted by amino optionally substituted by one or two $C_{1-6}$ alkyl by reduction.

Compounds of the formula (VII) may be prepared by reduction of a compound of formula (IX):




(IX)



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wherein $R_1$, $R_2$, $R_3'$, $R_5$ and $R_6$ are as hereinbefore defined.

The reduction may be carried out using either catalytic hydrogenation or by complex metal hydride reduction or using other conventional reducing agents such as diborane or sodium cyanoborohydride.

Conventional reaction conditions may be used. For example with sodium borohydride, the reaction temperature is suitably around 0°C, and a solvent such as ethanol is suitably used; and with lithium aluminium hydride low temperatures such as -80°C to 0°C are suitably used, in a solvent such as ether or THF.

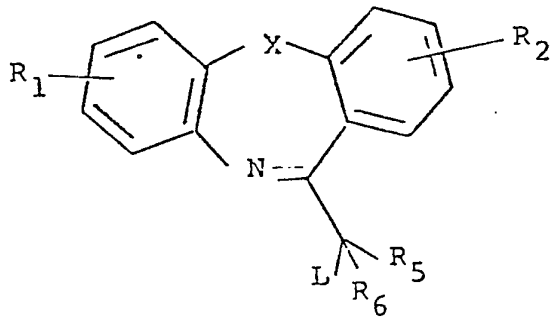
Sodium cyanoborohydride reduction is suitably carried out at ambient temperatures using methanol or ethanol as solvent, suitably at pH 3-4. When catalytic hydrogenation is used, acetic acid (or other conventional solvent plus acid catalyst) using platinum as catalyst may be used; and the reaction effected at slightly above atmospheric pressure at non-extreme temperatures such as 0°C to 40°C. The choice of reducing agent will of course be affected by the desired stereochemistry in the reaction product, since for example diborane and $LiAlH_4$ are stereoselective in their mode of action. It will also be appreciated that the selection of reducing agent will depend upon the nature of $R_3$. It may be necessary to protect any carbonyl or thiocarbonyl groups during the reduction step.

After the processes of the invention it will be appreciated that $R_1$ and $R_2$ groups may be varied. For

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example a compound of formula (I) wherein $R_1$ and $R_2$ are hydrogen may be halogenated.

Compounds of the formula (IX) may be prepared from a compound of the formula (X), which is known or prepared analogously to known compounds:



(X)

wherein L is a group readily displaceable by a nucleophile, and other variables are as hereinbefore defined, by treatment with $HNR_3'$.

Suitable examples of L include halide, such as chloride or bromide or activated ester such as mesyl- or tosyloxy.

Intermediates of the formula (VII) and (IX) are novel and thus form an aspect of the present invention.

Compounds of the formula (I) have useful pharmacological activity, in that they have mood-modifying in particular anti-depressant and anxiolytic activity.

The invention therefore also provides a pharmaceutical composition comprising a compound of the formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

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The compositions may be in the form of tablets, capsules, powders, granules, lozenges or liquid preparations.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, fillers, tabletting lubricants, distintegrants, and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilising the compound of the formula (I) and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved for injection and filter sterilised before filing into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents can be dissolved in the vehicle. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration.

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The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant of wetting agent is included in the composition to facilitate uniform distribution of the compound.

Preferred unit dosage forms include tablets, capsules and their equivalents.

The compositions of this invention may be formulated by conventional methods of blending, filling and compressing.

Suitable carriers for use in this invention include diluents, binders, disintegrants, colouring agents, flavouring agents and preservatives. These agents may be utilized in conventional manner, for example in a manner similar to that already used for other mood-modifying agents such as anti-depressants and anxiolytics.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

Mood-modifying compositions will most suitably be presented as oral or parenteral unit dose compositions containing from 1 to 100 mg, more usually from 5 to 50 mg, for example 10 to 25 mg, such as 12.5, 15 and 20 mg. Such compositions will normally be taken from 1 to 6 times daily, for example 2, 3 or 4 times daily, so that the total amount of active agent administered is usually within the range 5 to 400 mg.

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Preferred unit dosage forms include tablets, capsules and their equivalents, such as granules or lozenges.

The invention also provides a method of treatment of CNS disorders in mammals including man which method comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof to the sufferer.

The invention also provides a compound of the formula (I) or a pharmaceutically acceptable salt thereof for use in treating CNS disorders in mammals.

The following Examples illustrate the invention; the following Descriptions intermediates thereto.

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Description 1

2-Chloro-N-[2-(phenylmethyl)-phenyl]propanamide (D1)

2-Chloropropionyl chloride (41.91g, 0.33 mol) in sodium-dry toluene (70ml) was added over 3 hours, at such a rate that the reaction temperature did not exceed 9°, to an ice-cooled, stirred, solution of 2-benzyl-aniline (54.9g, 0.30 mol) in dry toluene (600 ml) containing pyridine (25 ml). After 1 hour at 18°, water (6 ml) was added and the mixture kept at 18° for a further 1 hour. The resultant precipitate was removed by filtration, washed well with water and then dissolved in dichloromethane. The solution was washed with water, saturated brine, dried ($Na_2SO_4$) and concentrated under reduced pressure to yield a solid residue. Recrystallisation from ethanol gave the title compound (63.6g, 78%). m.p. 142-5°.

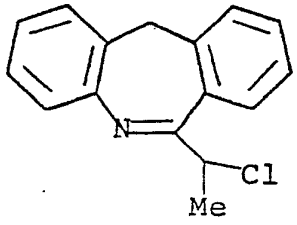
$\nu_{max}$ (nujol): 3250 (N-H) and 1663 ($\overset{H}{N}$.CO) $cm^{-1}$.

NMR $\delta_H$ ($CDCl_3$): 6.90-7.40 (8H, m, aromatic);
4.30 (1H, q, 7Hz, $\underline{CH}CH_3$);
3.90 (2H, s, $CH_2$);
1.60 (3H, d, 7Hz, $CH_3$).

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Description 2

6-(1-Chloroethyl)-11H-dibenzo[b,e]azepine (D2)




(D2)

The anilide D1 (40.95g, 0.15 mol) was added to polyphosphoric acid (409.5g) and the mixture was warmed to 125° over 1 hour and stirring continued at this temperature for a further 6 hours. The mixture was allowed to cool to room temperature, poured onto crushed ice and stirred for 1 hour. The product was extracted into dichloromethane (3 x 1 litre) and the combined organic extracts were washed with brine and dried ($Na_2SO_4$). Evaporation under reduced pressure gave crude 6-(1-chloroethyl)-11H-dibenzo[b,e]azepine which on trituration with ether gave a product (34.7g, 91%) of sufficient purity for further reaction (see Description 3).

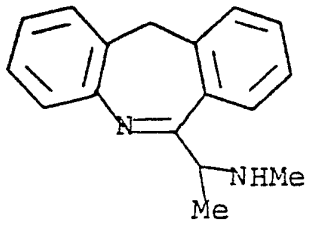
$\nu_{max}$ (nujol): 1618 (C=N) $cm^{-1}$.

NMR $\delta_H$ ($CDCl_3$): 6.9-7.6 (8H, m, aromatic);
5.2 (1H, q, 6.5Hz, CH);
3.45 (2H, s, $CH_2$);
1.88 (3H, d, 6.5Hz, CH.$CH_3$).

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Description 3

6-[1-(Methylamino)ethyl]-11H-dibenzo[b,e]azepine (D3)




(D3)

A solution of the chloroethyl compound D2 (2.55g, 10 mmol) in methylamine (100 ml, 33% solution w/v in IMS) was kept at 18° for 7 days in the dark. The reaction mixture was concentrated under reduced pressure and the residue dissolved in dichloromethane, washed with 10% aqueous sodium carbonate solution (2x100ml), brine (100ml) and dried ($Na_2SO_4$). Evaporation in vacuo gave crude 6-[1-(methylamino)ethyl]-11H-dibenzo[b,e]azepine in 92% yield and this was used immediately without further purification as shown in Descriptions 4 and 5.

NMR $\delta_H$ ($CDCl_3$): 6.8-7.7 (8H, m, aromatic);
3.9 (1H, q, 7Hz, $\underline{CH}CH_3$);
4.5 (2H, s, $CH_2$);
2.5 (3H, s, $NCH_3$);
1.3 (3H, d, 7Hz, $CH_3$).

This was converted to the monomaleate salt, m.p. 163-171° (recrystallised from acetone).

Found: C, 68.70; H, 6.06; N, 7.56%; $C_{21}H_{12}N_2O_4$.

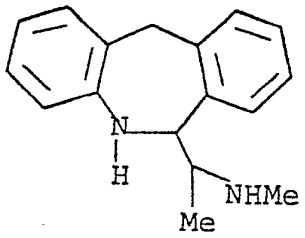
requires: C, 68.84; H, 6.05; N, 7.65%.

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Description 4

5,6-Dihydro-6-[1-(methylamino)ethyl]-11H-dibenzo[b,e] azepine

Diastereoisomer A (D4)




(D4)

A solution of 6-[1-(methylamino)ethyl]-11H-dibenzo[b,e] azepine (10 mmol) in dry ether (20 ml) and dichloromethane (10 ml) was added to a stirred suspension of lithium aluminium hydride (190 mg, 5 mmol) in dry ether at -78°, under nitrogen. After 45 minutes, the temperature of the reaction mixture was raised to -20° over 1 hour. Wet ether was then carefully added, followed by water and the resultant granular precipitate removed by filtration. The residue was washed with dichloromethane and the combined organic phases were washed with brine, dried ($Na_2SO_4$) and evaporation in vacuo gave the product (1.99g, 77%). This was shown by t.l.c. and n.m.r. to be a single isomer - diastereoisomer A.

NMR $\delta_H$ ($CDCl_3$): 6.2-7.4 (8H, m, aromatic)
4.5 (1H, d, 14Hz, H-11)
4.3 (1H, d, 5Hz, H-6)
3.35 (1H, d, 14Hz, H-11)
2.7-3.2 (1H, m, C<u>H</u>-$CH_3$)
2.35 (3H, s, N-$CH_3$)
1.1 (3H, d, 6Hz, CH-C<u>H</u>$_3$)

Conversion to a monomaleate salt followed by recrystallisation from acetone-ether gave the title compound m.p. 151-55°.



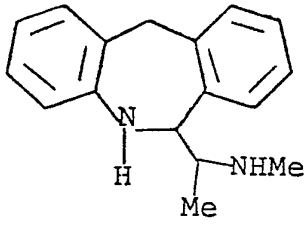
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Found: C, 68.46; H, 6.57; N, 7.60%. $C_{21}H_{24}N_2O_4$ requires: C, 68.33; H, 6.70; N, 7.27%.

Description 5

5,6-Dihydro-6-[1-(methylamino)ethyl]-11H-dibenzo[b,e] azepine

Diastereisomer B (D5)




(D5)

Sodium cyanoborohydride (3.16g, 50 mmol) in methanol (30 ml) was added dropwise to a solution of 6-[1-(methylamino)ethyl]-11H-dibenzo[b,e]azepine (12.5g, 50 mmol) in methanol (150 ml) maintained at pH 3-4 by the addition of methanolic HCl as appropriate. The reaction was allowed to proceed until all the starting material had been consumed and then pH of the solution was lowered to 0. When effervesence had ceased, the solution was concentrated under reduced pressure and the residue dissolved in dichloromethane (300 ml). The solution was washed with saturated sodium carbonate solution (2 x 250 ml), brine (250 ml) and dried ($Na_2SO_4$). Evaporation in vacuo gave a 45:55 mixture of the two diastereoisomers A and B. ($R_f$ 0.17 and 0.04 on $SiO_2$/EtOAc respectively). Trituration of the crude product with ether-pentane gave diastereoisomer B as a solid (3.0g, 24%).

NMR $\delta_H$ ($CDCl_3$): 6.25-7.2 (8H, m, aromatic);
4.2 (1H, d, 9Hz, C-6 CH);
3.9 (2H, s, $CH_2$);
2.9-3.3 (1H, m, CH $CH_3$);
2.4 (3H, s, $NCH_3$);
0.9 (3H, d, 7Hz, $CH_3$);

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Conversion into a monomaleate salt followed by recrystallisation from acetone-ether gave 5,6-dihydro-6-[1(methylamino)ethyl]-11H-dibenzo[b,e]azepine monomaleate diastereoisomer B, m.p. 170-173°.

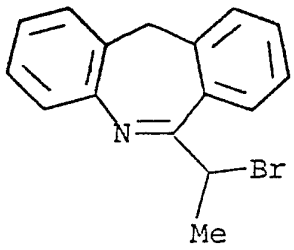
Found: C, 68.37; H, 6.54; N, 7.61%. $C_{21}H_{24}N_2O_4$ requires: C, 68.46; H, 6.57; and N, 7.60%

The soluble fraction from the foregoing trituration was chromatographed on Kieselgel 60 (200g) in 10% 60:80 petroleum ether-ether and gradually increasing the polarity of the eluant to 10% methanol-ether. Combination of appropriate fractions gave pure diastereoisomer B (3.12g, 25%) and pure diastereoisomer A (4.44g, 35%). The latter was shown to be identical with the compound obtained in Description 4.

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Description 6

6-(1-Bromoethyl)-11H-dibenzo[b,e]azepine (D6)

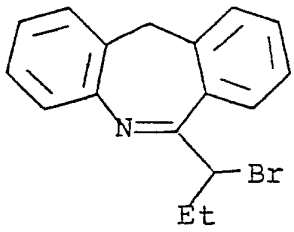



(D6)

The title compound was prepared from 2-bromopropionyl chloride using a method similar to that in Descriptions 1 and 2. 83% yield, m.p. 92-94 (from ether/60:80° petrol).

Description 7

6-(1-Bromopropyl)-11H-dibenzo[b,e]azepine (D7)



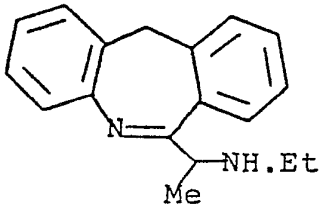

(D7)

The title compound was prepared in 55% yield using a method similar to that in Descriptions 1 and 2.

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Description 8

6-[1-(Ethylamino)ethyl]-11H-dibenzo[b,e]azepine (D8)



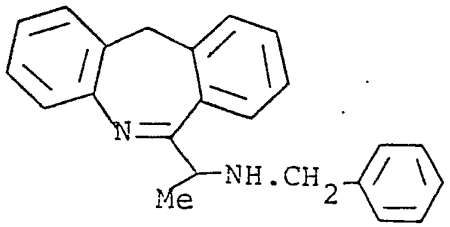
(D8)

6-(1-Bromoethyl)-11H-dibenzo[b,e]azepine D6 (1.37g; 4.5 mmol) in ethylamine (50ml; 33% solution v/v in ethanol) was kept at 18° for 1 day in the dark. The solvent was removed, water and ether added and organic layer separated, dried ($MgSO_4$) and evaporated in vacuo. Column chromatography on Kieselgel 60 eluted with ether gave the title compound in 58% yield. This was converted to the monomaleate salt, m.p. 160-161° (from acetone).

Found: C, 69.18; H, 6.29; N, 7.31% $C_{22}H_{24}N_2O_4$
requires: C, 69.46; H, 6.36; N, 7.36%

Description 9

6-[1-(Phenylmethylamino)ethyl]-11H-dibenzo[b,e]azepine (D9)



(D9)

The bromoethyl compound D6 (1g, 3.3mmol) was dissolved in DMF (20ml) and potassium carbonate (0.54g, 3.9mmol) added. Benzylamine (0.42g, 0.46ml, 3.9mmol) was then added and the mixture stirred at 18° for 2.5 hours. Water was then added and product extracted into ether. Organic

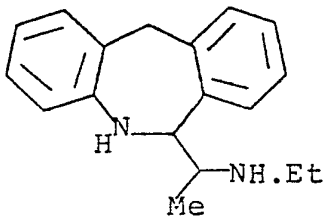
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phase washed well with water, dried ($MgSO_4$) and evaporated in vacuo. Chromatography on Kieselgel 60 eluted with 50% ether in petrol, gave the title compound in 70% yield. This was converted to the monomaleate salt, m.p. 141-143° (from acetone/ether).

Found: C, 73.29; H, 5.92; N, 6.29% $C_{27}H_{26}N_2O_4$
requires: C, 73.29; H, 5.92; N, 6.33%

Description 10

5,6-Dihydro-6-[1-(ethylamino)ethyl]-11H-dibenzo[b,e]azepine Diastereoisomer A (D10)




(D10)

The title compound was prepared in 60% yield from the imine D8 using a method similar to that in Description 4. This was converted to the monomaleate salt m.p. 165-167° - diastereoisomer A.

Found: C, 68.97; H, 6.82; N, 7.33% $C_{22}H_{26}N_2O_4$

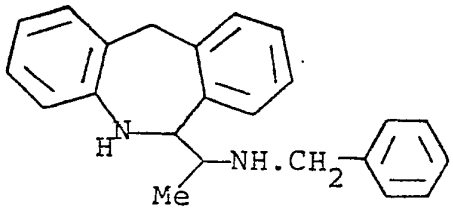
requires: C, 69.09; H, 6.85; N, 7.32%.

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Description 11

5,6-Dihydro-6-[1-(phenylmethylamino)ethyl]-11H-dibenzo [b,e]azepine

Diastereoisomer A (D11)



(D11)

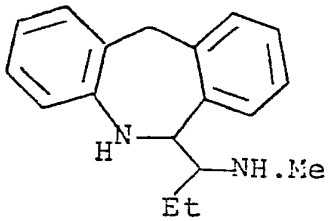
The title compound was obtained from D9, using a method similar to Description 4, in 77% yield after column chromatography on silica gel eluted with ether. After recrystallisation from acetone/ether the monomaleate salt had m.p. 184-186° - diastereoisomer A.

Found: C, 73.09; H, 6.39; N, 6.27% $C_{27}H_{28}N_2O_4$
requires: C, 72.95; H, 6.35; N, 6.30%

Description 12

5,6-Dihydro-6-[1-(methylamino)propyl]-11H-dibenzo[b,e] azepine

Diastereoisomer A (D12)



(D12)

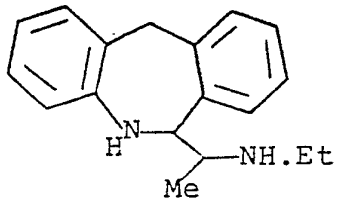
The title compound was obtained from the bromopropyl compound D7 in 35% yield using a method similar to that in Descriptions 3 and 4.

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Description 13

5,6-Dihydro-6-[1-(ethylamino)ethyl]-11H-dibenzo[b,e]azepine

Diastereoisomer B (D13)




(D13)

Using a similar procedure to that in Description 5 a 1:2 mixture of the two diastereoisomers A and B was obained from the imine D8. Column chromatography on Kieselgel 60 eluted with ether gave:

Diastereoisomer A - identical to the compound obtained in Description 10.

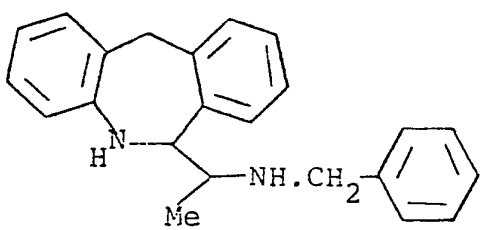
Diastereoisomer B (D13) converted to monomaleate salt m.p. 171-173°.

Found: C, 68.76; H, 6.92; N, 7.25% $C_{22}H_{26}N_2O_4$
requires: C, 69.09; H, 6.85; N, 7.32%

Description 14

5,6-Dihydro-6-[1-(phenylmethylamino)ethyl]-11H-dibenzo [b,e]azepine

Diastereoisomer B (D14)




(D14)

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Using a similar method to that in Description 5 a mixture of the two diastereoisomers was obtained from the imine D9. Column chromatography on Kieselgel 60 eluted with ether gave:

Diastereoisomer A (D11) obtained in 58% yield. A sample converted to the monomaleate salt, recrystallised from acetone/ether had m.p. 184-186°.

Found: C, 73.09; H, 6.39; N, 6.27% $C_{27}H_{28}N_2O_4$
requires: C, 72.95; H, 6.35; N, 6.30%

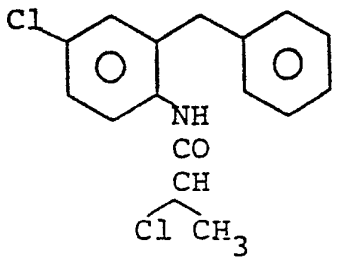
Diastereoisomer B (D14) obtained in 32% yield. Conversion to the monomaleate salt, recrystallisation from acetone/ether had m.p. 151-154°.

Found: C, 72.51; H, 6.34; N, 6.43% $C_{27}H_{28}N_2O_4$
requires: C, 72.95; H, 6.35; N, 6.30%

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Description 15

2-Chloro-N-[4-chloro-2-(phenylmethyl)phenyl]propanamide (D15)



(D15)

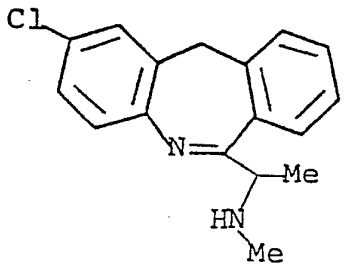
A solution of chlorine in acetic acid (0.57M, 177ml, 101 mmol) was added to a stirred solution of the anilide D1 (25g, 92 mmol) in acetic acid (1.5 litre) containing sodium acetate (8.25g, 101 mmol) and left at 20°C for 21h. Acetic acid was then removed under reduced pressure, the residue taken up in ethyl acetate (500ml), washed with aqueous sodium carbonate (10%, 3 x 200ml) brine, (200ml) and dried ($MgSO_4$). Evaporation in vacuo gave a crude reaction product which was purified by chromatography on silica gel, eluting with dichloromethane in pentane, initially using 25% and gradually increasing to 50%. Combination of appropriate fractions gave the title compound (20.3g; 72%) m.p. 150-151°.

NMR $\delta_H$ ($CDCl_3$): 7.85 (1H, d, 10Hz, aromatic); 7.0-7.4 (8H, m, aromatic); 4.38 (1H, q, 7.5Hz, CHCl); 3.97 (2H, s, $CH_2$); 1.65 (3H, d, 7.5Hz, $CH_3$).

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Description 16

2-Chloro-6-[1-(methylamino)ethyl]-11H-dibenzo[b,e]azepine (D16)



(D16)

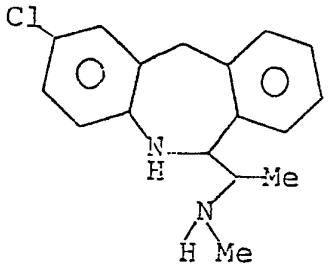
The chlorocompound D15 was converted into the title compound in 59% yield using a method similar to that in Descriptions 2 and 3.

NMR $\delta_H$ ($CDCl_3$): 7.0-7.4 (7H, m, aromatic), 3.9 (1H, q, 7Hz, $\underline{CH}CH_3$), 3.4 (2H, s), 2.3 (3H, s), 1.25 (3H, d, 7Hz, $CH\underline{CH_3}$).

Description 17

2-Chloro-5,6-dihydro-6-[1-(methylamino)ethyl]-11H-dibenzo [b,e]azepine

Diastereoisomer A (D17)



(D17)

The title compound was prepared from D16 by a similar method to Description 4. The crude reaction product was chromatographed on silica, using 4% methanol-ethylacetate. Combination of the appropriate fractions followed by trituration with methanol gave a light yellow solid in 50% yield.

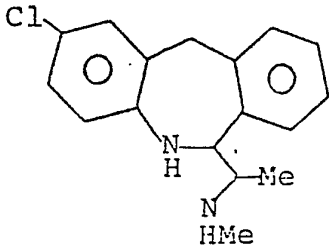
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NMR $\delta_H$ ($CDCl_3$) 6.95-7.4 (6H, m, aromatic), 6.74 (1H, d, 5Hz, aromatic), 4.6 (1H, d, 14Hz, H-11), 4.4 (1H, d, 4.7Hz, H-6), 3.45 (1H, d, 14Hz, H-11), 2.9-3.25 (1H, m, $\underline{CH}CH_3$), 2.55 (3H, s), 1.27 (3H, d, 6Hz, $CH\underline{CH_3}$).

Description 18

2-Chloro-5,6-dihydro-6-[1-(methylamino)ethyl]-11H-dibenzo [b,e]azepine

Diastereoisomer B (D18)




(D18)

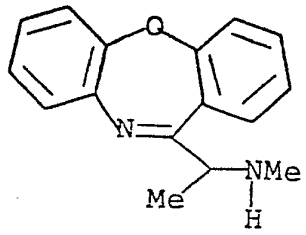
Using a procedure similar to that of Description 5, treatment of D16 gave a 40:60 mixture of the two diasterioisomers A and B (Rf's 0.3 and 0.1 respectively on $SiO_2$ 5% methanol-ethyl acetate). Trituration of the crude product with ether gave pure diastereoisomer B as a solid (38% yield).

NMR $\delta_H$ ($CDCl_3$): 6.85-7.35 (7H, m, aromatic), 6.48 (1H, d, 8.7Hz), 4.4 (1H, d), 4.25 (1H, d, 15Hz), 3.9 (1H, d, 15Hz), 3.0-3.4 (1H, m), 2.56 (3H, s, $NCH_3$), 1.1 (3H, d, 6Hz, $CH\underline{CH_3}$).

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Description 19

11-(1-Methylaminoethyl)dibenzo[b,f][1,4]oxazepine (D19)




(D19)

11-(1-Methylaminoethyl)dibenzo[b,f][1,4]oxazepine was obtained in a similar manner to that in Descriptions 1, 2 and 3. The crude free base was converted to a monomaleate salt m.p. 152-62°.

Purification was limited to thoroughly washing the crystals with acetone.

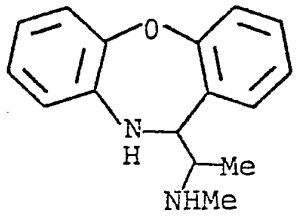
NMR $\delta_H$ ($d_6$-DMSO): 7.2-7.9 (8H, m, aromatic);
(monomaleate salt) 6.0 (2H, s);
4.95 (1H, q, 9Hz);
2.80 (3H, s);
1.42 (3H, d, 9Hz);

Found: C, 64.67; H, 5.51; N, 7.57%. $C_{20}H_{20}N_2O_5$ requires: C, 65.21; H, 5.47; N, 7.60%.

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Description 20

10, 11-Dihydro-11-(1-methylaminoethyl)dibenzo[b,f][1,4]oxazepine diastereoisomer A (D20)




(D20)

11-(1-methylaminoethyl)dibenzo[b,f][1,4]oxazepine (5g, 20 mmol) in ethanol (200 ml) containing platinum oxide (200 mg) was hydrogenated at atmospheric pressure until uptake of hydrogen ceased. Catalyst was removed by filtration through Celite and the solution concentrated under reduced pressure to give a product which was shown by t.l.c. and n.m.r. to be a single isomer-diastereoisomer A.

NMR $\delta_H$ ($CDCl_3$): 6.3-7.2 (8H, m, aromatic), 3.9 (1H, d, 9Hz), 3.5 (1H, m), 2.32 (3H, s), 1.46 (3H, d, 6.5Hz).

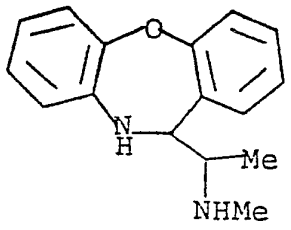
This was converted into a monomaleate salt and recrystallisation from methanol/ether gave 10, 11-dihydro-11-(1-methylaminoethyl)dibenzo[b,f][1,4]oxazepine monomaleate diastereoisomer A, m.p. 176-82°.

Found: C, 64.51; H, 5.83; N, 7.63%. $C_{20}H_{22}N_2O_5$ requires: C, 64.85; H, 5.99; N, 7.63%.

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Description 21

10,11-Dihydro-11-(1-methylaminoethyl)dibenzo[b,f][1,4]-oxazepine diastereoisomer B (D21)




(D21)

According to the method given in Description 5, 11-(1-methylaminoethyl)dibenzo[b,f][1,4]oxazepine was treated with sodium cyanoborohydride to give a 40:60 mixture of the two diastereoisomers A and B [$R_f$ 0.15 and 0.07 on $SiO_2$/EtOAc/MeOH (95:5)] and these were isolated by chromatography on silica gel, eluting with ethyl acetate. The first to elute, diastereoisomer A, was shown to be identical with the compound obtained in Description 5. The second to elute was diastereoisomer B and this was obtained in 31% yield.

NMR $\delta_H$ ($CDCl_3$): 6.15-7.3 (8H, m, aromatic), 3.75 (1H, d, 9Hz), 3.25-3.6 (1H, m), 2.3 (3H, s), 0.85 (3H, d, 6Hz).

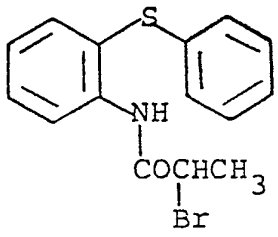
This was converted to a monomaleate salt. Recrystallisation from methanol gave 10,11-dihydro-11-(1-methylaminoethyl)dibenzo[b,f][1,4]oxazepine monomaleate diastereoisomer B, m.p. 169-73°.

Found: C, 65.16; H, 6.18; N, 7.63%. $C_{20}H_{22}N_2O_5$ requires: C, 64.85; H, 5.99; N, 7.56%.

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Description 22

2-Bromo-N-[2-(phenylthio)phenyl]propanamide (D22)



(D22)

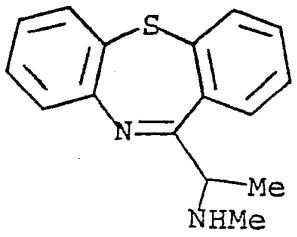
The title compound was prepared from 2-phenylthiobenzenamine and 2-bromopropionyl bromide in 65% yield using a method similar to that of Description 1.

NMR $\delta_H$ ($CDCl_3$): 8.45 (1H, m, aromatic), 7.05-7.8 (8H, m, aromatic), 4.40 (1H, q, 10Hz, CHBr), 1.78 (3H, d, 10Hz, $CH\underline{CH_3}$).

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Description 23

11-[1-(Methylamino)ethyl]dibenzo[b,f][1,4]thiazepine (D23)




(D23)

The title compound was prepared in 27% yield from 2-bromo-N-[2-(phenylthio)phenyl]propanamide D22 using a method similar to that in Descriptions 2 and 3.

NMR $\delta_H$ ($CDCl_3$): 7.04-7.50 (8H, m, aromatic), 3.90 (1H, q, 7Hz, $\underline{CH}CH_3$), 2.65 (3H, s, $NCH_3$), 1.30 (3H, d, 7Hz, $CH\underline{CH_3}$).

A portion of the title compound was converted into a mono-maleate salt, m.p. 179.5-184.5° (dec.) (from acetone).

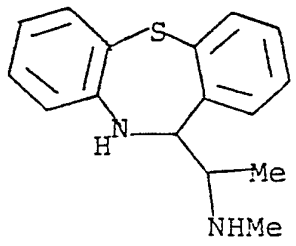
Found: C, 61.97; H, 5.06; N, 7.20 $C_{20}H_{20}N_2O_4S$
requires: C, 62.48; H, 5.24; N, 7.29%.

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Description 24

10,11-Dihydro-11-[1-(methylamino)ethyl]dibenzo[b,f][1,4] thiazepine

Diastereoisomer A (D24)




(D24)

The title compound was prepred from the imine D23 in 79% yield using a procedure similar to the one outlined in Description 4.

Purification was carried out on silica gel using ether and increasing the polarity of the eluent to 1% methanol ether.

NMR $\delta_H$ ($CDCl_3$): 6.50-7.60 (8H, m, aromatic), 6.60 (1H, d, 8Hz, H-6), 3.50-3.85 (1H, m, $C\underline{H}-CH_3$), 2.45 (3H, s, $NHC\underline{H}_3$), 1.30 (3H, d, 6Hz, $CHC\underline{H}_3$).

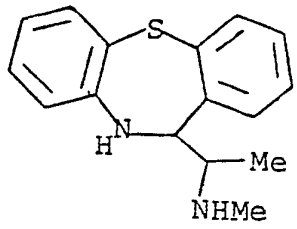
A portion of the title compound was converted to a mono-maleate salt, m.p. 165-168° (from acetone).

Found: C, 62.21; H, 5.86; N, 7.25%, $C_{20}H_{22}N_2O_4S$
requires: C, 62.16, H, 5.74, N, 7.25%.

Description 25

10,11-Dihydro-11-[1-(methylamino)ethyl]dibenzo[b,f]thiazepine

Diastereoisomer B (D25)



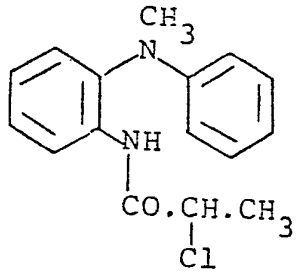

(D25)

The imine D23 was reduced using sodium cyanoborohydride according to the procedure outlined in Description 5 to give a 64:36 mixture of the two diastereoisomers A and B. Chromatography on silica gel using 5% methanol-ethyl acetate as eluent separated the diastereoisomers to give the title compound.

NMR $\delta_H$ ($CDCl_3$): 6.40-7.60 (8H, m, aromatic), 6.55 (1H, d, 8Hz, H-6), 3.35-3.65 (1H, m, $CHCH_3$), 2.40 (3H, s, $NHCH_3$), 1.07 (3H, d, 6Hz, $CHCH_3$).

Description 26

2-Chloro-N-[2-(N'-methyl-N'-phenyl)aminophenyl]propanamide (D26)




(D26)

A solution of N-methyl-N-phenyl-1,2-benzenediamine (16.13g, 0.081 mol) in dry toluene (100ml) containing pyridine (10ml) was immediately cooled in an ice-bath and

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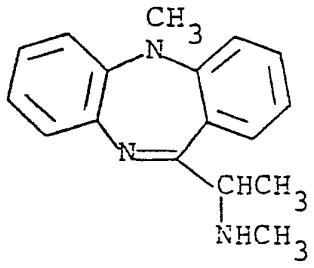
2-chloropropionyl chloride (11.38g, 0.090mol) added over 0.5h at such a rate that the reaction temperature did not exceed 5°.

After stirring for ca 18h, solvent was evaporated under reduced pressure and the solid residue partitioned between dichloromethane and water. The organic phase was washed with 1N hydrochloric acid, water, saturated brine, and dried ($MgSO_4$). Removal of solvent in vacuo afforded a crude product which was purified on silica gel using 5% ether - 60-80 petroleum ether as eluent to give the title compound (7.86g, 30%).

NMR $\delta_H$ ($CDCl_3$): 6.40-7.27 (9H, m, aromatic), 4.27 (1H, q, 7Hz, $C\underline{H}CH_3$), 3.13 (3H, s, $NCH_3$), 1.60 (3H, d, 7Hz, $CHC\underline{H}_3$).

Description 27

5-Methyl-11-[(1-methylamino)ethyl]-5H-dibenzo[b,e][1,4-]diazepine (D27)



(D27)

The title compound was prepared from D26 in 64% yield using a procedure similar to the one outlined in Descriptions 2 and 3.

NMR $\delta_H$ ($CDCl_3$): 6.70-7.27 (8H, m, aromatic), 3.37 (1H, q, 6Hz, $C\underline{H}CH_3$), 3.10 (3H, s, $NCH_3$), 2.47 (3H, s, $NHC\underline{H}_3$), 1.22 (3H, d, 6Hz, $CHC\underline{H}_3$).

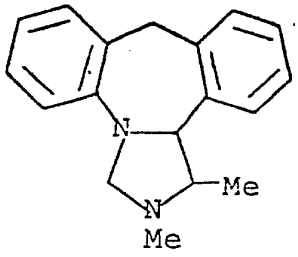
A portion of the title compound was converted into the monomaleate salt, m.p. 145-155° (dec.) (from acetone).

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Example 1

1,2-Dimethyl-2,3,9,13b-tetrahydro-1H-dibenzo[c,f]imidazo [1,5-a]azepine

Diastereoisomer A (E1)




(E1)

Formaldehyde (1.9 ml of 37% solution in water, 15mmol) was added to the amine D4 diastereoisomer A (2.5g, 10 mmol) in ethanol (40 ml) with ice-cooling. After 1h, ethanol was removed under reduced pressure and the residue partitioned between dichloromethane (50 ml) and water (30 ml). The aqueous layer was extracted with dichloromethane (2x10ml) and the combined dichloromethane extracts washed with brine (25 ml) and dried ($MgSO_4$). Evaporation in vacuo, followed by filtration through a silica gel column (20g), eluting with ether, gave the title compound (2.6g, 98%).

NMR $\delta_H$ ($CDCl_3$): 6.60-7.20 (8H, m, aromatic);
4.65 (1H, d 13Hz, H-9);
4.35 (1H, d 7Hz);
4.20 (1H, d 3.5Hz);
3.80 (1H, d 3.5Hz);
3.45 (1H, d 13Hz, H-9);
2.85-3.35 (1H, m, H-1);
2.52 (3H, s, $NCH_3$);
0.95 (3H, d 7Hz, $CHCH_3$).

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This was converted to a monomaleate salt, m.p. 182-4° (recrystallisation from acetone).

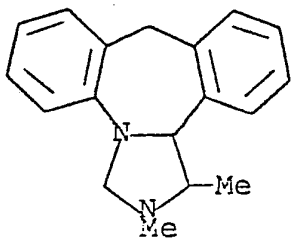
Found: C, 69.50; H, 6.26; N, 7.14%. $C_{22}H_{24}N_2O_4$

requires: C, 69.46; H, 6.36; N, 7.36%.

Example 2

1,2-Dimethyl-2,3,9,13b-tetrahydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine

Diastereoisomer B (E2)




(E2)

This was prepared as outlined for Example 1 from the amine D5 diastereoisomer B in 98% yield.

NMR $\delta_H$ ($CDCl_3$): 6.1-7.3 (8H, m, aromatic);
5.22 (1H, d 9Hz);
4.89 (1H, d 14Hz, H-8);
4.39 (1H, d 4Hz);
3.78 (1H, d 4Hz);
3.36 (1H, d 14Hz, H-9);
2.9-3.3 (1H, m, H-1);
2.47 (3H, s, N-$CH_3$);
1.37 (3H, d 6Hz, CHC$\underline{H}_3$);

Conversion to a monomaleate salt, followed by recrystallisation from acetone gave 1,2-dimethyl-2,3,9,13b-tetrahydro-dibenzo[c,f]imidazo[1,5-a]azepine monomaleate diastereoisomer B m.p. 169-73°.

Found: C, 69.55; H, 6.46; N, 7.27%. $C_{22}H_{24}N_2O_4$

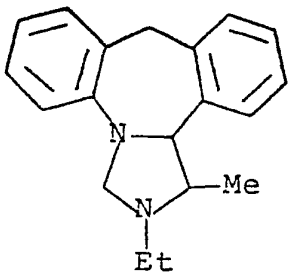
requires: C, 69.46; H, 6.36; N, 7.36%.

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Example 3

2-Ethyl-1-methyl-2,3,9,13b-tetrahydro-1H-dibenzo[c,f]imidazo [1,5-a]azepine

Diastereoisomer A (E3)




(E3)

The title compound was prepared from the amine D10 using a method similar to that in Example 1 and converted into a monohydrogen maleate, m.p. 173-175° (from acetone-ether).

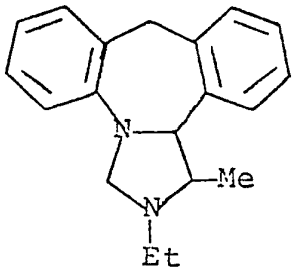
Found: C, 70.74; H, 6.68; N, 6.94 $C_{23}H_{26}N_2O_4$
requires: C, 70.03; H, 6.64 and N, 7.10%

Found: $M^+$ 278.1771 Calc. for $C_{19}H_{22}N_2$ 278.1783

Example 4

2-Ethyl-1-methyl-2,3,9,13b-tetrahydro-1H-dibenzo[c,f]imidazo [1,5-a]azepine

Diastereoisomer B (E4)




(E4)

The title compound was prepared from the amine D13 using a method similar to that in Example 1 and converted into a monohydrogen maleate, m.p. 108-110°.

Found: C, 66.93; H, 6.46; N, 6.71 $C_{23}H_{26}N_2O_4 \cdot H_2O$
requires: C, 66.99; H, 6.79 and N, 6.79%

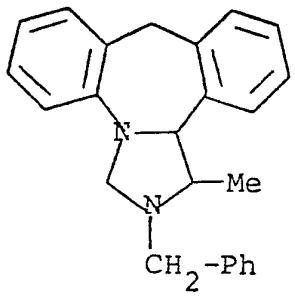
Found: $M^+$ 278.1774 Calc. for $C_{19}H_{22}N_2$ 278.1783

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Example 5

1-Methyl-2-(phenylmethyl)-2,3,9,13b-tetrahydro-1H-dibenzo [c,f]imidazo[1,5-a]azepine

Diastereoisomer A (E5)



(E5)

The title compound was prepared from the amine D11 using a method similar to that in Example 1 and converted into a monohydrogen maleate, m.p. 167-170° (from methanol-ether).

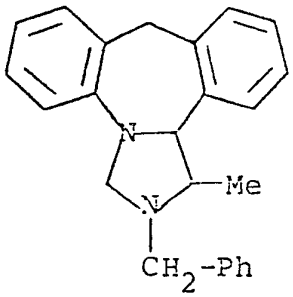
Found: C, 73.84; H, 6.27; N, 6.10 $C_{28}H_{28}N_2O_4$
requires: C, 73.66; H, 6.18 and N, 6.14%

Found: $M^+$ 340.1941 Calc. for $C_{24}H_{24}N_2$ 340.1939.

Example 6

1-Methyl-2-(phenylmethyl)-2,3,9,13b,tetrahydro-1H-dibenzo [c,f]imidazo[1,5-a]azepine

Diastereoisomer B (E6)



(E6)

The title compound was prepared from the amine D14 using a method similar to that in Example 1 and converted into a monohydrogen maleate, m.p. 99-101° (from acetone-ether).

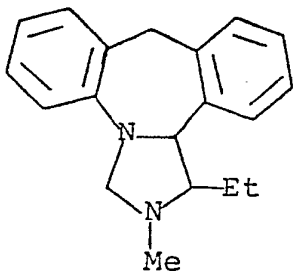
Found: $M^+$ 340.1941 Calc. for $C_{24}H_{24}N_2$ 340.1939

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Example 7

1-Ethyl-2-methyl-2,3,9,13b-tetrahydro-1H-dibenzo[c,f] imidazo[1,5-a]azepine

Diastereoisomer A (E7)




(E7)

The title compound was prepared from the amine D12 using a method similar to that in Example 1 and converted into a monohydrogen maleate, m.p. 188-190° (from methanol-ether).

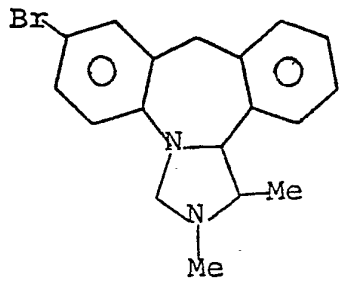
Found: C, 70.02; H, 6.72; N, 7.03 $C_{23}H_{26}N_2O_4$
requires: C, 70.03; H, 6.64 and N, 7.10%

Found: $M^+$ 278.1780 Calc. for $C_{19}H_{22}N_2$ 278.1783.

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Example 8

7-Bromo-1,2-dimethyl-2,3,9,13b-tetrahydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine (E8)




(E8)

Pyridine hydrobromide perbromide (1.54g, 48mmol) was added to an ice-cooled, stirred solution of Example 1 (1.06g; 4 mmol) in chloroform (40ml). After 1hr, 5% aqueous sodium carbonate (20ml) was added and the aqueous layer extracted with dichloromethane (2 x 10ml). The combined organic layers were washed with brine (20ml) and dried ($MgSO_4$). Evaporation in vacuo, followed by chromatography on silica gel, eluting with ether gave the title compound (860mg, 63%) as a light brown gum.

NMR $\delta_H$ ($CDCl_3$): 6.9-7.35 (6H, m, aromatic), 6.68 (1H, d, 9Hz), 4.63 (1H, d, 15Hz), 4.55 (1H, d, 7.5Hz), 4.25 (1H, d, 4Hz), 3.83 (1H, d, 4Hz), 3.5 (1H, d, 15Hz), 3.1-3.22 (1H, m), 2.6 (3H, s, N-$CH_3$), 0.98 (3H, d, 7Hz, CH$\underline{CH_3}$).

Found: $M^+$ 342.0721 Calc. for $C_{18}H_{19}N_2Br$ 342.0732.

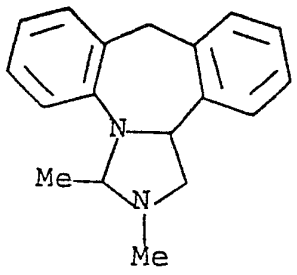
This was converted to a monomaleate salt, m.p. 160-4° (from methanol/ether).

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Example 9

2,3-Dimethyl-2,3,9-13b-tetrahydro-1H-dibenzo[c,f]imidazo [1,5-a]azepine

Diastereoisomer A (E9)




(E9)

Freshly distilled acetaldehyde (402mg, 510µl, 9.1mmol) was added to a stirred solution of 5,6-dihydro-N-methyl-11H-dibenz[b,e]azepine-6-methanamine (2g, 8.3mmol) in dichloromethane (30ml) at 0° containing p-toluenesulphonic acid (100mg). After 2hr at 0° and 30 min at 20°, water (20ml) and 10% aqueous sodium carbonate (10ml) were added and the aqueous layer extracted with dichloromethane (20 ml). The combined organic layers were washed with brine (30ml), dried ($MgSO_4$) and evaporation in vacuo gave a yellow gum. Trituration in ether gave a solid (436mg; 20%) which was shown by NMR to contain 95% diastereoisomer A plus 5% diastereoisomer B.

For Diastereoisomer A (E9):

NMR $\delta_H$ ($CDCl_3$): 6.85-7.3 (6H, m, aromatic), 6.3-6.7 (2H, m, aromatic), 5.52 (1H, m), 4.6 (1H, d, 14Hz), 4.2 (1H, q, 5Hz, $\underline{CH}CH_3$), 3.5 (1H, m), 3.35 (1H, d, 14Hz), 2.95 (1H, m), 2.57 (3H, s, $NCH_3$), 1.4 (3H, d, 5Hz, $CH\underline{CH_3}$).

Found: $M^+$ 264.1633 Calc. for $C_{18}H_{20}N_2$ 264.1626

For Diastereoisomer B:

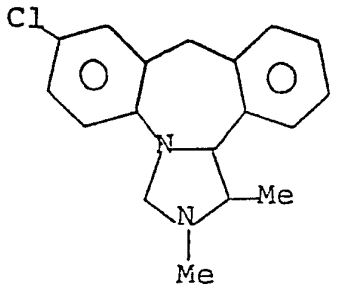
NMR $\delta_H$ ($CDCl_3$): 2.53 (3H, s, $NCH_3$), 1.25 (3H, d, $CH\underline{CH_3}$).

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Example 10

7-Chloro-1,2-dimethyl-2,3,9,13b-tetrahydro-1H-dibenzo [c,f]imidazo[1,5-a]azepine

Diastereoisomer A (E10)




(E10)

The title compound was obtained from Diastereoisomer A D17 in a similar manner to Example 1 in 90% yield.

NMR $\delta_H$ ($CDCl_3$):

The title compound was converted into a monomaleate salt.

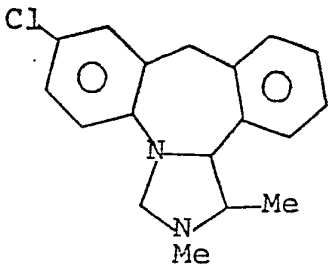
Found: C, 63.58; H, 5.59; N, 6.44; Cl, 8.62. $C_{22}H_{23}N_2O_4Cl$
Requires: C, 63.69; H, 5.59; N, 6.75 and Cl, 8.55%.

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Example 11

7-Chloro-1,2-dimethyl-2,3,9,13b-tetrahydro-1H-dibenzo [c,f]imidazo[1,5-a]azepine

Diastereoisomer B (E11)




(E11)

The title compound was obtained from Diastereoisomer B D18 in a similar manner to Example 1 in 84% yield.

NMR $\delta_H$ ($CDCl_3$):

The title compound was converted into a monomaleate salt.

Found: C, 63.38; H, 5.56; N, 6.44; Cl, 8.54. $C_{22}H_{23}N_2O_4Cl$ Requires: C, 63.69; H, 5.59; N, 6.75 and Cl, 8.55%.

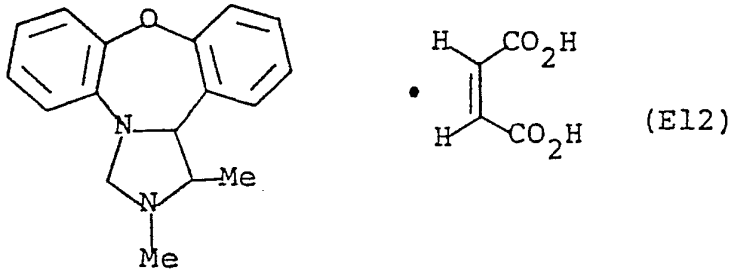
Found: $M^+$ 298.1242 Calc. for $C_{18}H_{19}N_2Cl$ 298.1236.

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Example 12

1,2-Dimethyl-1,2,3,13b-tetrahydro-dibenzo[b,f]imidazo [1,5-d][1,4]oxazepine monohydrogen maleate

Diastereoisomer A (E12)



(E12)

The title compound was prepared from the amine D20 using a method similar to that of Example 1, m.p. 147-149° (from acetone-ether).

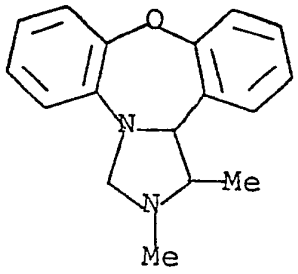
Found: C, 66.00; H, 5.93; N, 7.34 $C_{21}H_{22}N_2O_5$
requires: C, 65.96; H, 5.80; N, 7.32%.

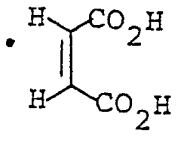
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Example 13

1,2-Dimethyl-1,2,3,13b-tetrahydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine monohydrogen maleate

Diastereoisomer B (E13)





(E13)

The title compound was prepared from the amine D21 using a method similar to that of Example 1, m.p. 148-149° (from acetone).

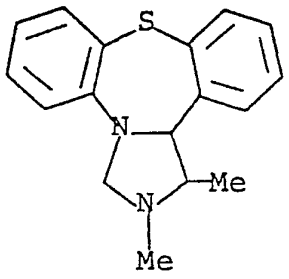
Found: C, 65.82; H, 5.84; N, 7.28 $C_{21}H_{22}N_2O_5$ requires: C, 65.96; H, 5.80; N, 7.32%.

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Example 14

1,2-Dimethyl-1,2,3,-3b-tetrahydrodibenzo[b,f]imidazo [1,5-d][1,4]thiazepine

Diastereoisomer A (E14)




(E14)

The title compound was prepared from D24 in 79% yield using a procedure similar to the one outlined in Example 1.

NMR $\delta_H$ ($CDCl_3$): 6.20-7.70 (8H, m, aromatic), 6.52 (1H, d, 5.9Hz), 4.27 (1H, d, 4Hz, H-3), 3.63 (1H, d, 4Hz, H-3), 2.80-3.1 (1H, m, H-1), 2.45 (3H, s, $NHCH_3$), 1.37 (3H, d, 7Hz, $CHCH_3$).

This was converted to a monomaleate salt, m.p. 160-165° (from acetone).

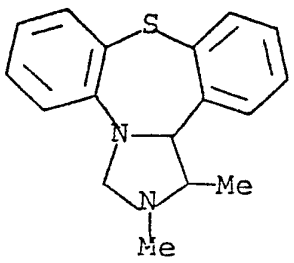
Found: C, 63.36; H, 5.58; N, 7.04% $C_{21}H_{22}N_2SO_4$ requires: C, 63.30; H, 5.57; N, 7.03%.

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Example 15

1,2-Dimethyl-1,2,3,13b-tetrahydrodibenzo[b,f]imidazo [1,5-d][1,4]thiazepine

Diastereoisomer B (E15)




(E15)

The title compound was prepared from D25 in 62% yield using a method similar to that of Example 1.

NMR $\delta_H$ ($CDCl_3$): 6.15-7.70 (8H, m, aromatic), 6.15 (1H, d, 8.6Hz), 4.32 (1H, d, 4Hz, H-3), 3.87 (1H, d, 4Hz, H-3), 2.90-3.30 (1H, m, $C\underline{H}CH_3$), 2.47 (3H, s, $NCH_3$), 1.26 (3H, d, 6Hz, $CH\underline{CH}_3$).

This was converted to a monomaleate salt, m.p. 149-154° (from acetone).

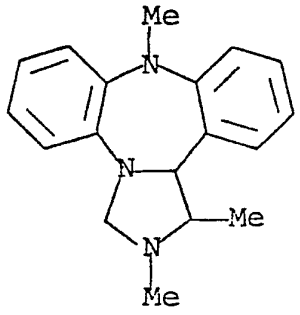
Found: C, 63.30; H, 5.62; N, 7.05% $C_{21}H_{22}N_2SO_4$ requires: C, 63.20; H, 5.57; N, 7.03%.

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Example 16

1,2,3,13b-Tetrahydro-1,2,9-trimethyl-5H-dibenzo[b,f]imidazo[1,5-d][1,4]diazepine

Diastereoisomer A (E16)



(E16)

The title compound was prepared from the imine from Description D27 using a combination of the procedures outlined in Description 5 and Example 1.

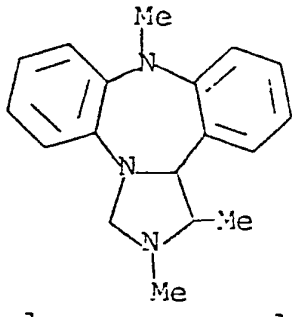
NMR $\delta_H$ ($CDCl_3$): 6.33-7.10 (8H, m, aromatic), 4.80 (1H, d, 7Hz, H-14), 4.17 (1H, d, 5Hz, H-3), 3.70 (1H, d, 5Hz, H-3), 3.22 (3H, s, ArN-$C\underline{H}_3$), 2.77-3.22 (1H, m, $C\underline{H}CH_3$), 2.63 (3H, s, $NC\underline{H}_3$), 1.06 (3H, d, 7Hz, $CHC\underline{H}_3$).

This was converted to a monomaleate salt.

Example 17

1,2,3,13b-Tetrahydro-1,2,9-trimethyl-5H-dibenzo[b,f]imidazo[1,5-d][1,4]diazepine

Diastereoisomer B (E17)



(E17)

The title compound was prepared from the imine Description D27 using a combination of the procedures outlined

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in Description 5 and Example 1.

NMR $\delta_H$ ($CDCl_3$): 6.10-7.90 (8H, m, aromatic), 5.45 (1H, d, 9.2Hz, H-14), 4.30 (1H, d, 4Hz, H-3), 3.83 (1H, d, 4Hz, H-3), 3.25 (3H, s, Ar N-C<u>H</u>$_3$), 2.85-3.30 (1H, m, C<u>H</u>CH$_3$), 2.45 (3H, s, NC<u>H</u>$_3$), 1.30 (3H, d, 7Hz, CHC<u>H</u>$_3$).

This was converted to a monomaleate salt.

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Pharmacological Data

Compounds of the invention inhibit the behavioural symptoms induced by 5-methoxy-N,N-dimethyl tryptamine (5-MDMT), a central 5-hydroxytryptamine agonist, and are central 5HT antagonists. As such they would be expected to possess antidepressant, (Ogren, S O, Fuxe, K, Agnati, L F, Gustafsson J A, Jonsson, G, and Holm A C, 1979, J Neural Trans, 46, 85-103) and/or anxiolytic (Stein, L, Kline, D, and Bellugi, J D, 1975, in Advances in Biochemical Psychopharmacology, ed Costa, E, and Greengard, P, Vol 14, 29-44, Raven Press, NY) activity.

Method

Mice (♂ CD-1 Charles River) are pretreated with the compounds (10 animals/group) under investigation and 1h later are injected with 10 mg/kg i.p. 5-methoxy-N,N-dimethyltryptamine (Sigma). The symptoms of fore-paw tapping movements, head jerks and splayed limbs are scored: 1, present; 0, absent, giving a maximum score of 3/mouse or 30/group. Results are expressed as the percentage inhibition compared to the group treated with 5-methoxy-N,N-dimethyl tryptamine alone. The dose of compound inhibiting the symptoms by 50% is determined graphically.

The results are shown in Table 1.

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Table 1

Inhibition of 5-MDMT induced symptoms in the mouse

| Compound | $ED_{50}$ mg/kg p.o. or % inhibition at dose |
|---|---|
| 1,2-Dimethyl-2,3,9,13b-tetrahydro-1H-dibenz[c,f]imidazo[1,5-a]azepine diastereo-isomer A (Compound E1) | 4.3 |
| 1,2-Dimethyl-2,3,9,13b-tetrahydro-1H-dibenz[c,f]imidazo[1,5-a]azepine diastereo-isomer B (Compound E2) | 10 |
| 2-Ethyl-1-methyl-2,3,9,13b-tetrahydro-1H-dibenz[c,f]imidazo[1,5-a]azepine diastereo-isomer A (Compound E3) | 1.6 |
| 2-Ethyl-1-methyl-2,3,9,13b-tetrahydro-1H-dibenz[c,f]imidazo[1,5-a]azepine, diastereo-isomer B (Compound E4) | 41% at 10 |
| 1-Methyl-2-(phenylmethyl)-2,3,9,13b-tetra-hydro-1H-dibenz[c,f]imidazo[1,5-a]azepine diastereoisomer A (Compound E5) | 46% at 10 |
| 1-Ethyl-2-methyl-2,3,9,13b-tetrahydro-1H-dibenz[c,f]imidazo[1,5-a]azepine, diastereo-isomer A (Compound E7) | 61% at 10 |

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Blockade of presynaptic $\alpha_2$-adrenoceptors on noradrenergic neurons effects an increase in intrasynaptic noradrenaline, and thus in the central nervous system could be expected to have an antidepressant effect.

$[^3H]$-clonidine binds to $\alpha_2$-adrenoceptor sites and inhibition of this binding correlates with the blockade of $\alpha_2$-adrenoceptors. In vitro inhibition by some of the present compounds of the binding of $[^3H]$-clonidine to isolated rat-brain synaptic membrane fragment was therefore determined to provide an indication of antidepressant activity. This was carried out using standard biochemical binding study techniques, by the method of Maggi et al., Eur. J. Pharm. 1980, 61, 91. The parameter determined was the concentration of $[^3H]$-clonidine binding. $K_i$ values have been determined, using the Cheng-Prusoff equation, from $IC_{50}$ values. The results are shown in Table 2 below.

Table 2

| Compound | $K_i$ nM |
|---|---|
| 1,2-Dimethyl-2,3,9,13b-tetrahydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine, diastereoisomer A (Compound E1) | 23 |
| 1,2-Dimethyl-2,3,9,13b-tetrahydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine, diastereoisomer B (Compound E2) | 126 |
| 1-Ethyl-2-methyl-2,3,9,13b-tetrahydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine, diastereoisomer A (Compound E7) | 67 |

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Pharmacological Data

Shock Induced Suppression of Drinking in the Rat

The shock induced suppression of drinking (SSD) test (adapted from Vogel et al., 1971) is considered a reliable and specific method for showing up potential anxiolytics.

20h water-deprived rats (♂ Hacking and Churchill, CFHB), familiarised to the test apparatus the day before test, are allowed to drink for 30 sec and then receive 0.5m sec. footshock, maximum 0.5mA, for every 5 sec of drinking time accumulated in a 3 min session. Drugs were administered, intraperitoneally, 30 min before test.

The number of shocks taken during a given test period are recorded and results expressed as percentage change from control. Anxiolytic drugs such as benzodiazepines release the behaviour of rats suppressed in this way, such that the number of shocks taken increases in a dose dependent manner.

J.R. Vogel et al., (1971) Psychopharmacologia (Berl.) 21, 1-7.

The results are shown in Table 3.

Toxicity

No toxic effects were observed in these tests.

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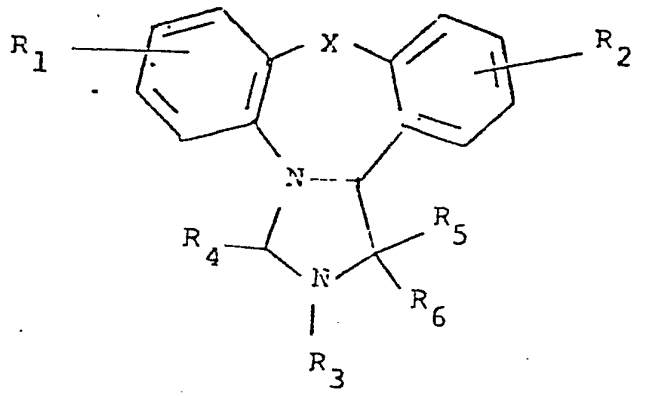
Table 3

| Compound | Dose mg/kg i.p. | % change from control no. of shocks taken |
|---|---|---|
| 1,2-Dimethyl-2, 3,9,13b-tetrahydro -1H-dibenzo[c,f] imidazo[1,5-a] azepine mono-maleate (Example 1) | 10 | + 103 |

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Claims

1. A compound of formula (I) or a phamaceutically acceptable salt thereof;



(I)

wherein:

X is $CH_2$, O, S or NR where R is $C_{1-4}$ alkyl;

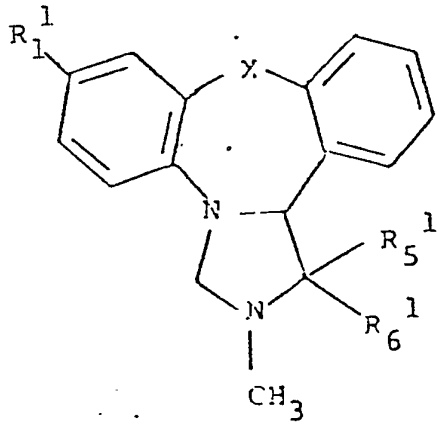
$R_1$ and $R_2$ are independently selected from hydrogen, hydroxy, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, halogen or $CF_3$;
$R_3$ is $C_{1-7}$ alkyl, $C_{2-5}$ alkenyl, $C_{2-5}$ alkynyl, $C_{3-7}$ cycloalkyl, $C_{4-7}$ cycloalkenyl or $C_{1-6}$ alkyl substituted by $C_{2-7}$ alkenyl, $C_{2-7}$ alkynyl, $C_{3-7}$ cycloalkyl, hydroxy, thiol, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio, carboxy, $C_{1-6}$ alkoxycarbonyl, $C_{2-7}$ alkanoyl, amino optionally substituted by one or two $C_{1-4}$ alkyl or by $C_{4-6}$ polymethylene optionally containing an oxygen or nitrogen atom, aminocarbonyl optionally N-substituted by one or two $C_{1-6}$ alkyl groups, or benzoyl or phenyl either being optionally ring-substituted by one or two $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, halogen or trifluoromethyl; and

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one of $R_4$, $R_5$ and $R_6$ is $C_{1-6}$ alkyl and the other two are independently hydrogen or $C_{1-6}$ alkyl.

2. A compound according to claim 1 wherein $R_3$ is $C_{1-6}$ alkyl, $C_{2-5}$ alkenyl, $C_{2-5}$ alkynyl, $C_{3-7}$ cycloalkyl, $C_{5-7}$ cycloalkenyl or $C_{1-4}$ alkyl substituted by $C_{3-7}$ cycloalkyl or phenyl or $C_{1-6}$ alkyl substituted by hydroxy, $C_{1-6}$ alkoxy, carboxy, $C_{2-7}$ alkanoyl, benzoyl or aminocarbonyl or amino optionally substituted by one or two $C_{1-6}$ alkyl groups and the remaining variables are as defined in claim 1.

3. A compound according to claim 1 or 2 of formula (II):

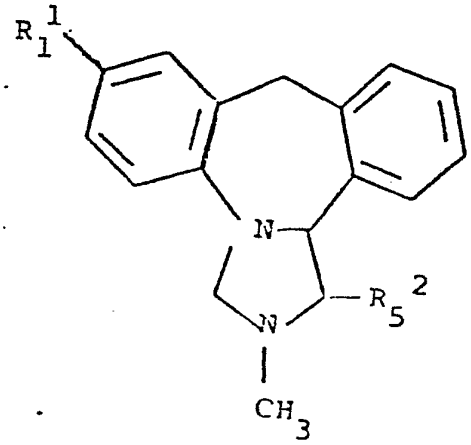


(II)

wherein $R_1^1$ is hydrogen or halogen, one of $R_5^1$ and $R_6^1$ is $C_{1-6}$ alkyl land the other is hydrogen or $C_{1-6}$ alkyl; and X is as defined in claim 1.

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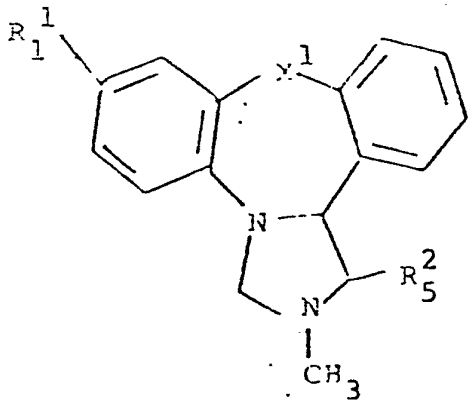
4. A compound according to claim 3 of formula (III):



(III)

wherein $R_5^2$ is $C_{1-6}$ alkyl and $R_1^1$ is as defined in claim 3.

5. A compound according to claim 3 of formula (IV):



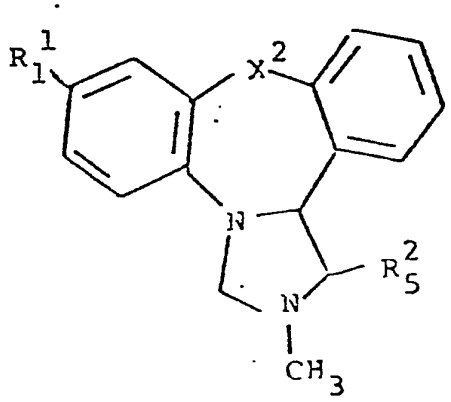
(IV)

wherein $X^1$ is oxygen or sulphur; and

$R_1^1$ and $R_5^2$ are as defined in claim 4.

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6. A compound according to claim 3 of formula (V):

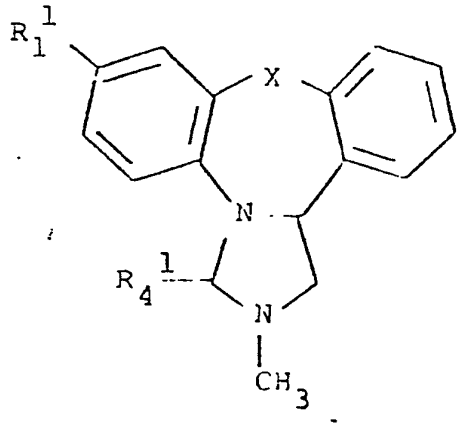


(V)

wherein $X^2$ is NR as defined in claim 1 and $R_1^1$ and $R_5^2$ are as defined in claim 4.

7. A compound according to any one of claims 4 to 6 wherein $R_5^2$ is methyl.

8. A compound according to claim 1 of formula (VI):



(VI)

wherein $R_4^1$ is $C_{1-6}$ alkyl and $R_1^1$ is as defined in claim 3.

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9. 2-Ethyl-1-methyl-2,3,9,13b-tetrahydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine,

1-Methyl-2-(phenylmethyl)-2,3,9,13b-tetrahydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine,

1-Ethyl-2-methyl-2,3,9,13b-tetrahydr-1H-dibenzo[c,f]imidazo[1,5-a]azepine,

7-Bromo-1,2-dimethyl-2,3,9,13b-tetrahydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine,

2,3-Dimethyl-2,3,9-13b-tetrahydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine,

7-Chloro-1,2-dimethyl-2,3,9,13b-tetrahydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine,

1,2-Dimethyl-1,2,3,13b-tetrahydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine,

1,2-Dimethyl-1,2,3,-3b-tetrahydrodibenzo[b,f]imidazo[1,5-d][1,4]thiazepine or

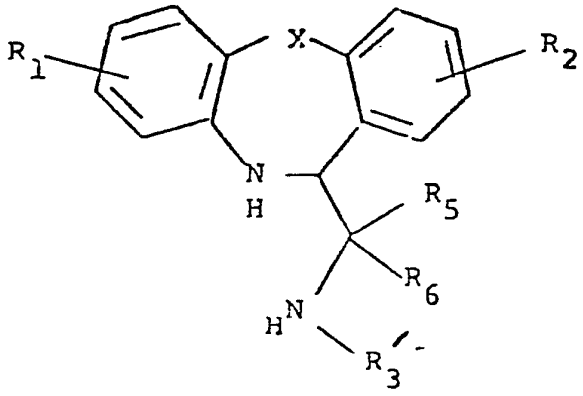
1,2,3,13b-Tetrahydro-1,2,9-trimethyl-5H-dibenzo[b,f]imidazo[1,5-b][1,4]diazepine, or a pharmaceutically acceptable salt thereof.

10. 1,2-Dimethyl-2,3,9,13b-tetrahydro-1H[c,f]imidazo[1,5-a]azepine, or a pharmaceutically acceptable salt thereof.

11. A process for the preparation of a compound according to any one of claims 1 to 10 or a

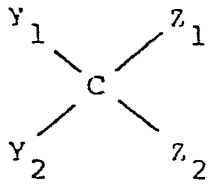
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pharmaceutically acceptable salt thereof which process comprises the reaction of a compound of formula (VII):



(VII)

with a compound of formula (VIII):

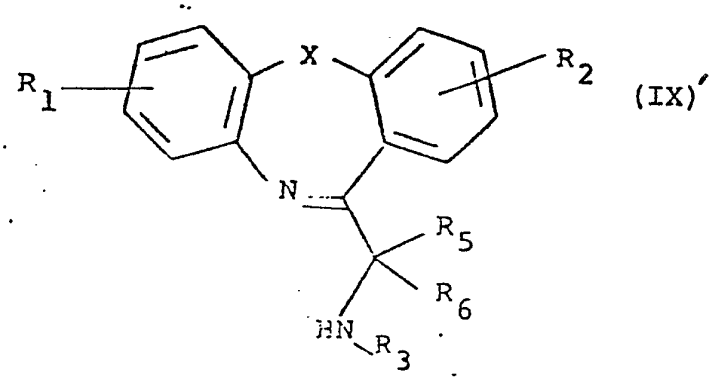


(VIII)

wherein $R_3'$ is $R_3$ or a group convertible thereto, $R_1$, $R_2$, $R_5$ and $R_6$ are as defined in formula (I), one of $Y_1$ and $Y_2$ is hydrogen and the other is $R_4$ as defined or (when $R_4$ in formula (I) is hydrogen), $Y_1$ and $Y_2$ together form an oxo or thiocarbonyl group; and $Z_1$ and $Z_2$ are leaving groups, and thereafter reducing the resulting compound formed when $Y_1$ and $Y_2$ together form an oxo or thiocarbonyl group, and/or converting $R_3'$ to $R_3$ and/or forming a pharmaceutically acceptable salt.

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12. A compound of formula (VII) as defined in claim 11 wherein $R_3'$ is $R_3$ as defined in claim 1 or a compound of formula (IX)':



(IX)'

wherein the variable groups are as defined in claim 1.

12. A compound according to claim 12 wherein $R_1$ (or $R_1^1$), $R_2$, $R_3$, $R_5$ (or $R_5^1$ or $R_5^2$), $R_6$ and X are as defined in any one of claims 1 to 9.

13. 6-[1-(Methylamino)ethyl]-11H-dibenzo[b,e]azepine,

5,6-Dihydro-6-[1-(methylamino)ethyl]-11H-dibenzo[b,e] azepine,

6-[1-(Ethylamino)ethyl]-11H-dibenzo[b,e,]azepine,

6-[1-(Phenylmethylamino)ethyl]-11H-dibenzo[b,e]azepine,

5,6-Dihydro-6-[1-(ethylamino)ethyl]-11H-dibenzo[b,e] azepine,

5,6-Dihydro-6-(phenylmethylamino)wthyl]-11H-dibenzo [b,e]azepine,

2-Chloro-6-[1-methylamino)ethyl]-11H-dibenzo[b,e] azepine,



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2-Chloro-5,6-dihydro-6-[1-methylamino)ethyl]-11H-dibenzo[b,e]azepine,

11-(1-Methylaminoethyl)dibenzo[b,f][1,4]oxapine,

10,11-Dihydro-11-(1-methylaminoethyl)dibenzo[b,f][1,4]oxazepine,

11-[1-(Methylamino)ethyl]dibenzo[b,f][1,4]thiazepine,

10,11Dihydro-11-[1-(methylamino)ethyl]dibenzo[b,f][1,4]thiazepine or

5-Methyl-11-[(1-methylamino)ethyl]-5H-dibenzo[b,e][1,4-]diazepine.

14. A pharmaceutical composition comprising a compound according to any of claims 1 to 10 and a pharmaceutically acceptable carrier.

15. A method of treatment of CNS disorders in mammals including man which method comprises administering as effective amount a compound of formula (I), or a pharmaceutically accepable salt thereof to the sufferer.

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