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PATENT SPECIFICATION

(11) 1 561 072

- (21) Application No. 30155/76 (22) Filed 20 July 1976
 (31) Convention Application No. 597697
 (32) Filed 21 July 1975 in
 (33) United States of America (US)
 (44) Complete Specification published 13 Feb. 1980
 (51) INT CL³ C07C 149/42 C07D 211/20 295/08
 (52) Index at acceptance

C2C 1341 1532 1626 215 220 225 227 22Y 246 251 252 25Y 26Y
 280 29X 29Y 30Y 321 322 323 32X 32Y 342 34Y 360 361
 366 367 368 36Y 373 37Y 552 573 583 613 620 623 625
 638 650 652 65Y 665 668 675 699 775 801 80Y AA QN
 QT RE RN

- (72) Inventors NARIMAN BOMANSHAW MEHTA and
 LAWRENCE EDWARD BRIEADDY

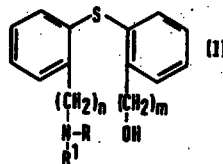


(54) SUBSTITUTED DIPHENYL SULPHIDES

(71) We, THE WELLCOME FOUNDATION LIMITED, of 183—193 Euston Road, London, N.W.1., a Company incorporated in England, 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:—

The present invention relates to substituted diphenyl sulfides, processes for their preparation, pharmaceutical formulations containing them, and their use in medicine.

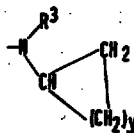
In particular the present invention is directed to compounds represented by the formula I



or an acid addition salt thereof where R and R' are the same or different and are each hydrogen or straight or branched alkyl of 1 to 6 carbon atoms preferably of 1 to 4 carbon atoms or R and R' taken together are (CH₂)_x where X is 4 or 5 or NRR' is



where R² is hydrogen or lower alkyl or NRR' is



where y is 3 or 4 and R³ is hydrogen or lower alkyl, in the above, unless stated otherwise, lower alkyl has 1 to 4 carbon atoms and may be straight or branched and n and m are the same or different and are each 1, 2 or 3.

According to certain aspects of the invention, for the free bases and/or the acid addition salts of the compounds of formula (I), when m and n are each 1, especially when m and n are 1, 2 or 3, there is the proviso that

- (i) when one of R and R' is methyl the other is not hydrogen and
 (ii) when R and R' together are —(CH₂)_x— then x is 4;

or, further, for the free bases and/or the acid addition salts of the compounds of formula (I), when m and n are each 1, more especially when m and n are 1, 2 or 3 there may be the proviso that

- (i) when one of R and R' is methyl the other is not hydrogen or methyl and
 (ii) R and R' together are not $-(CH_2)_n-$.

The salts of a compound of formula (I) should be pharmaceutically acceptable acid addition salts when used in medicine but toxic salts may conveniently be used to prepare the bases or pharmaceutically acceptable salts and are within the scope of this invention.

Such pharmaceutically acceptable salts include those prepared from hydrochloric, sulphuric, phosphoric, toluenesulphonic, maleic, fumaric, tartaric, citric, pamoic, succinic and nitric acids.

The Applicants have shown that the compounds of formula (I) and acid addition salts thereof are useful in the treatment of depression in mammals. The compounds of formula (I) possess valuable properties as antidepressants in mammals when tested by standard techniques used in the art for determining antidepressant activity, for example the tetrabenzene-induced sedation test in the rat. The compounds of this invention are also notable for their low toxicity.

Of the compounds of formula (I) the following is especially preferred for its high antidepressant activity.

2-*N,N*-Dimethylaminomethyl-2'-hydroxymethyldiphenyl sulphide

Other compounds of notable activity are as follows:—

2-*N*-Methylaminomethyl-2'-hydroxymethyldiphenyl sulphide.

2-Aminomethyl-2'-hydroxymethyldiphenyl sulphide.

2-*N,N*-Diethylaminomethyl-2'-hydroxymethyldiphenyl sulphide.

2-*N*-Ethylaminomethyl-2'-hydroxymethyldiphenyl sulphide.

Other compounds of particular interest include those of formula (I) which are as follows:—

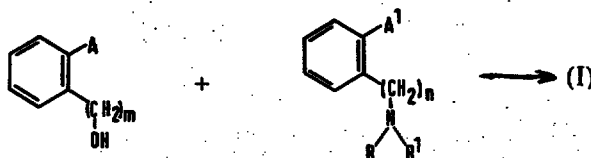
2-Pyrrolidinomethyl-2'-hydroxymethyldiphenyl sulphide.

2-Piperidinomethyl-2'-hydroxymethyldiphenyl sulphide.

2-*N*-Methylpiperazinomethyl-2'-hydroxymethyldiphenyl sulphide.

The compounds of formula (I) may be synthesised by any method known in the art for making compounds of an analogous structure.

In particular the compounds of formula (I) may be prepared by the formation of the sulphide bridge, as indicated in the following reaction scheme:—



wherein R, R', n and m are as defined hereinabove and one of A and A' is a mercapto group and the other is halo such as bromo or chloro. the reaction may be carried out under anhydrous conditions in the presence of an alkali metal lower alkoxide, for example, sodium methoxide and a suitable polar, aprotic solvent such as dimethylformamide, dimethylacetamide or dimethyl sulfoxide and at a temperature in the range of 20°C to 200°C.

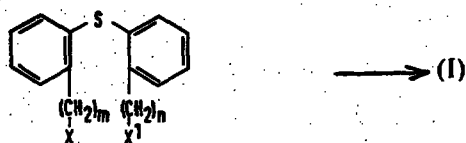
The compounds of formula (I) may also be prepared by the reduction of a compound of formula (II):



wherein Q¹ is $-(CH_2)_m.OH$ or $-(CH_2)_m.CO_2R''$, and Q² is $-(CH_2)_n.NRR'$ or $-(CH_2)_n.CO.NRR'$, where R'' is alkyl of 1 to 4 carbon atoms and R, R', n and m are as defined hereinabove, provided that at least one of Q¹ and Q² is other than $-(CH_2)_m.OH$ and $-(CH_2)_n.NRR'$, respectively. The reaction may be carried out in the presence of a suitable reducing agent such as lithium aluminium hydride in a solvent such as diethyl ether or tetrahydrofuran and at room temperature or at a slightly elevated temperature.

The compounds of formula (I) may further be prepared by replacement of a leaving group on one of the methylene substituents of formula (III):

(III)



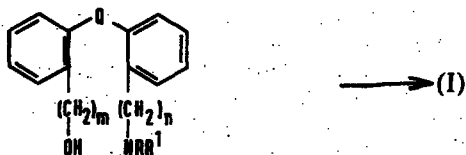
wherein m and n are as defined hereinabove, X is hydroxy or a leaving group and X' is —NRR' or a leaving group, provided one of X' and X is a leaving group. Suitable leaving groups are halo (for example, bromo or chloro), *p*-toluenesulphonyl, lower alkane sulphonyl (for example mesylate), or azido.

When X is hydroxy, the compound of formula (III) is reacted with the secondary amine RR'NH, in the presence of an inert solvent such as toluene, dioxane or acetonitrile and at a temperature in the range of 20°C to the reflux temperature of the reaction mixture.

When X' is —NRR', and X is a leaving group as defined hereinabove, or is a carboxylate ester group, the compound of formula (III) may be reacted with an alkali metal hydroxide, preferably in a solvent such as water, acetonitrile, or dimethylformamide and at an elevated temperature.

Another method of preparing the compounds of formula (I) is by reducing the compounds of formula (IV):

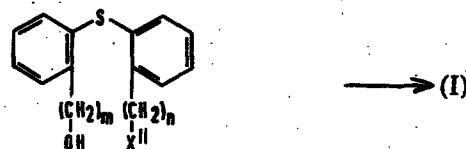
(IV)



wherein R, R', n and m are as defined hereinabove and Q represents a sulphone or a sulphoxide group. Reducing agents such as triphenylphosphine or metal hydride derivatives such as lithium aluminium hydride may be used in non-reactive organic solvents such as ethers.

Certain compounds of formula (I), may be conveniently prepared by reducing a compound of formula (V):

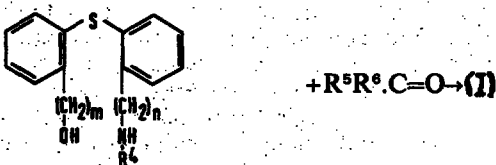
(V)



wherein n and m are as defined hereinabove and X'' represents —(R'R)N→O or —NR', CO. R³ in which R and R' are as defined in formula (I), other than hydrogen, R⁷ is hydrogen or alkyl of 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, and R³ is alkyl of 1 to 5 carbon atoms. The reaction may be conveniently carried out in the presence of a reducing agent such as triphenylphosphine or metal hydride derivatives such as lithium aluminium hydride in non-reactive organic solvents such as ethers.

The compounds of formula (I), wherein R and R' are alkyl may be prepared from a compound of formula (VI) by reductive alkylation (including a Leukart reaction) illustrated by the following reaction scheme:—

(VI)



wherein m and n are as defined hereinabove, R₄ is hydrogen or alkyl of 1 to 6 carbon atoms, R⁵ and R⁶ are the same or different and are hydrogen or alkyl of 1 to 5 carbon atoms provided that when both R⁵ and R⁶ are both alkyl their combined total number of carbon atoms does not exceed 5. The reaction may be carried out in the presence of hydrogen and Adam's catalyst formic acid, or formic acid derivatives such as ammonium formate, or metal hydride derivatives such as sodium cyanoborohydride. See for example, "Org. Reactions", 1948, 4, 174 and

"Org. Reactions", 1949, 5, 301. The reaction may be carried out in any suitable inert organic solvent for example polar solvents such as ethanol, acetonitrile, dimethylformamide, or dimethylsulphoxide, and at an elevated temperature.

The compounds of formula (I) and pharmaceutically acceptable acid addition salts thereof may be used in treating the three main types of depression: neurotic or reactive depression with anxiety, somatic concern and tension; psychotic or endogenous depression with emotional withdrawal, motor retardation, blunted affect, guilt feelings and conceptual disorganisation; and a group showing features of both neurotic and psychotic depression with hostility and suspiciousness.

The compounds of this invention may be administered orally, parenterally or rectally.

The preferred antidepressant dosage for parenteral administration of a compound of formula (I) (estimated as the base) is 0.3 mg/kg to 75 mg/kg of mammal body weight, and the most preferred dosage being 2 mg/kg to 35 mg/kg of mammal body weight.

For the oral or rectal mode of administration, the preferred antidepressant dosage of a compound of formula (I) (estimated as the base) is 0.6 mg/kg to 150 mg/kg of mammal body weight while the most preferred dosage (estimated as the base) is about 3 mg/kg to 70 mg/kg of mammal body weight. A compound of formula (I), or an acid addition salt thereof, is preferably administered four times daily although the number of daily administrations of the medication and the total dose will vary according to the mammal being treated, according to the exercise of the physician's discretion.

For example, for the treatment of depression in humans, the preferred unit dosage of a compound of formula (I) or an acid addition salt thereof (as the base) for oral administration, or administration as a suppository, is about 15 milligrams to 1500 milligrams with the more preferred unit dosage being about 100 milligrams to 500 milligrams, and the most preferred unit dosage being about 125 milligrams to 360 milligrams. All the above doses are given in terms of the weight of a compound of formula (I) in the form of its base, but as will be appreciated from the foregoing information, it is preferably administered in the form of a pharmaceutically acceptable acid addition salt thereof.

The compounds of formula (I) or pharmaceutically acceptable salts thereof (the active ingredients) are preferably administered in unit dosage form to the mammal being treated.

A pharmaceutical composition containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, may be presented in discrete units such as tablets, capsules, ampoules or suppositories, each containing an effective antidepressant non-toxic amount of the compound and one or more pharmaceutically acceptable carriers.

The pharmaceutical compositions may be in the form of an oral unit preparation for example a cachet, tablet or capsule. Suitable pharmaceutically acceptable carriers for such compositions include solid diluents such as lactose, cornstarch, micronized silica gel, or merely the capsule shell as well as other excipients well known in the art for this purpose.

The pharmaceutical compositions may further take the form of those suitable for rectal use as a suppository with the usual pharmaceutically acceptable carriers such as cocoa butter. Those for parenteral use include an ampoule of a sterile solution or suspension with water or other pharmaceutically acceptable liquid as the carrier therefor, or an ampoule of a sterile powder for dilution with a pharmaceutically acceptable liquid.

It should be understood that in addition to the aforementioned ingredients, the pharmaceutical compositions of this invention may include one or more of additional ingredients such as diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives, and the like. The compositions may be prepared by admixture of the ingredients, and, if necessary, shaping the resulting mass, and filling into suitable containers.

According to the present invention there is provided a compound of the formula (I) and a pharmaceutically acceptable salt thereof.

According to the present invention in yet another aspect there are provided methods of synthesizing compounds of formula (I) comprising the application of known methods and those specified for the preparation of compounds of formula (I) or acid addition salts thereof.

According to the present invention, in yet another aspect, there is provided a pharmaceutical composition (preferably in unit dosage form) comprising a

compound of formula (I) (or a pharmaceutically acceptable salt thereof) together with a pharmaceutically acceptable carrier.

According to still a further aspect of the present invention, there is provided a method of treating a depressed state in mammals (excluding man), for example, mice, rats, dogs, etc., which comprises the administration of an antidepressant effective non-toxic amount (dose), preferably in a unit dosage form, of a compound of formula (I) or a pharmaceutically acceptable salt thereof. Conveniently the compound of formula (I) or its acid addition salt comprises from 5 to 95% by weight of the composition.

The following Examples are provided by way of an illustration of the present invention and should in no way constitute a limitation thereof.

All temperatures are in degrees Celsius.

EXAMPLE 1

2-carboxy-2'-carbethoxydiphenyl Sulfide

2,2'-Dicarbethoxydiphenyl sulfide (120 g) was added to a solution of potassium hydroxide (22 g) in one liter of ethanol and stirred at room temperature for 4 days. It was acidified with concentrated hydrochloric acid and filtered. The product obtained on concentration of the filtrate to dryness was partitioned between ether and five percent sodium bicarbonate. The mixture of diacid and half ester-acid obtained on acidification was triturated with warm benzene to separate the insoluble diacid. The product was precipitated by the addition of n-hexane to the benzene extract. Recrystallization from acetone/n-hexane mixture gave 2-carboxy-2'-carbethoxydiphenyl sulfide (43.0 g, 37%), m.p.=122—123°C.

EXAMPLE 2

2-Carbethoxy-2'-dimethylaminocarbonyldiphenyl Sulfide

The half ester-acid chloride (32.0 g) obtained by the reaction of 2-carbethoxy-2'-carboxydiphenyl sulfide (30.2 g) with excess thionyl chloride was dissolved in 150 ml. of dry dioxane and added to an excess of ice-cold solution of dimethylamine in dry dioxane. The solution was stirred at room temperature for one hour, acidified and filtered. The residue obtained by concentrating the filtrate *in vacuo* was dissolved in 250 ml. of chloroform and washed successively with 10% acid, 5% bicarbonate and water. On drying and subsequent removal of the solvent, 32.0 g (97%) of the amido-ester was obtained as an orange colored oil.

EXAMPLES 3 and 4

The following were prepared by the procedure of Example 2.

2-Carbethoxy-2'-aminocarbonyldiphenyl Sulfide
m.p.=126—129°C (80% yield)

2-Carbethoxy-2'-methylaminocarbonyldiphenyl Sulfide
m.p.=92—94°C (96% yield).

EXAMPLE 5

2-Hydroxymethyl-2'-dimethylaminomethyldiphenyl Sulfide . HCl

To a slurry of lithium aluminium hydride (15.2 g) in 800 ml. of tetrahydrofuran, at room temperature, was added a solution of 2-carbethoxy-2'-dimethylaminocarbonyldiphenyl sulfide 32.9 g in 150 ml. of tetrahydrofuran and the mixture was stirred at room temperature for 18 hours. The reaction was worked up in the usual manner and the free base was obtained as a yellow oil. The hydrochloride salt was crystallized from ethanol/ether mixtures to give 19.0 g of 2-hydroxymethyl-2'-dimethylaminomethyldiphenyl sulfide, m.p. 162—164°C.

EXAMPLES 6 and 7

The following were prepared by the procedures of Examples 2 and 5.

2-Hydroxymethyl-2'-aminomethyldiphenyl Sulfide . HCl
m.p.=188—189°C.

2-Hydroxymethyl-2'-methylaminomethyldiphenyl Sulfide . HCl
m.p.=218—220°C.

EXAMPLE 8

2,2'-Dicarboxy Diphenyl Sulfide

2-Bromobenzoic acid (40.0 g) and 2-mercaptobenzoic acid (32.0 g) were dissolved in 140 ml. of water, containing 56 g. of potassium carbonate. Upon dissolution, 13.0 g of powdered Cu was added. This homogeneous solution was transferred to a stainless steel bomb and heated at 130—140° for 3 hours. Bomb was cooled; contents were filtered and the filtrate acidified with concentrated HCl. Filtration yielded 52.8 g (97%) of 2,2'-dicarboxydiphenyl sulfide, m.p. 225—230°C [Lit. m.p. 233°, C. A. 54, 9815d (1960)].

EXAMPLE 9

2,2'-Dicarbethoxydiphenyl Sulfide

2,2'-Dicarboxydiphenyl sulfide (54.8 g., 0.20 mol.) was treated with excess thionyl chloride (100 ml.) at 60°C until a clear solution was obtained. The excess thionyl chloride was removed under reduced pressure. The resulting solid was then treated with 200 ml. of EtOH at reflux for 30 minutes. The ethanol solution was added to 1 litre of ice water. The diester was filtered and dried, yielding 62.0 g (90%), m.p. 56—57° [Lit. m.p. 58—59°, C. A. 54, 9815d (1960)].

EXAMPLE 10

2-Carbethoxy-2'-N-methylpiperazinocarbonyldiphenyl Sulfide

To the solution of 3.6 g. of 2-carbethoxy-2'-chlorocarbonyldiphenyl sulfide in 100 ml. of acetonitrile, at room temperature, was added a solution of 11.6 g. of N-methylpiperzine in 50 ml. of triethylamine. After 3 hours of stirring the solvent was removed and the residue was taken up in 250 ml. chloroform. It was washed successively with 10% hydrochloric acid, sodium bicarbonate and water. On concentration 13.0 g. (94% yield) of an orange oil was obtained.

EXAMPLE 11

2-Hydroxymethyl-2'-N-methylpiperazinomethyldiphenyl Sulfide . HCl

To a slurry of 4.0 g. of lithium aluminium hydride in 500 ml. of tetrahydrofuran, at room temperature, was added a solution of 12.6 g of 2-carbethoxy-2'-N-methylpiperazinocarbonyldiphenyl sulfide in 100 ml. of tetrahydrofuran. The mixture was stirred at room temperature for 18 hours. The reaction was worked up in the usual manner to afford 9.2 g. (85%) of the free base as a yellow oil. The hydrochloride salt was crystallized from 50% aqueous EtOH to afford 9.0 g. of the product as a dihydrate, m.p. 243—244°C.

EXAMPLE 12

2-Carbethoxy-2'-pyrrolidinocarbonyldiphenyl Sulfide

To the stirred solution, at room temperature, of 4.8 g. of pyrrolidine in 50 ml. of triethylamine was added 20 g. of 2-carbethoxy-2'-chlorocarbonyl diphenyl sulfide in 150 ml. of dry acetonitrile. After stirring for 3 hours the solvents were removed *in vacuo* and the residue taken up in 250 ml. of chloroform. It was successively treated with 10% hydrochloric acid, 5% bicarbonate and water. After drying, concentration and recrystallization from acetone-hexane mixtures 17.0 g. (72% yield) of pure product, m.p. 117—119°C, was obtained.

EXAMPLE 13

2-Carbethoxy-2'-piperidinocarbonyldiphenyl Sulfide

Following the procedure of Example 12, 2-carbethoxy-2'-piperidinocarbonyldiphenyl sulfide, m.p. 111—113°C, was prepared in 75% yield.

EXAMPLE 14

To the slurry of 13.3 g. of lithium aluminium hydride in 800 ml. of tetrahydrofuran was added a solution of 25 g. of 2-carbethoxy-2'-pyrrolidinocarbonyldiphenyl sulfide in 150 ml. of tetrahydrofuran under nitrogen atmosphere at room temperature. It was stirred for 18 hours. The reaction mixture was decomposed by the usual procedure and the hydrochloride salt of the base, m.p. 190—192°C, 17.0 g. was obtained. The compound obtained was 2-hydroxymethyl-2'-pyrrolidinomethyldiphenyl sulfide . HCl.

EXAMPLE 15

2-Hydroxymethyl-2'-piperidinomethyldiphenyl Sulfide . HCl

m.p. 172—173°C.

Following the procedure of Example 14, 2-hydroxymethyl-2'-piperidinomethyldiphenyl sulfide was prepared as the hydrochloride salt, m.p. 172—173°C.

EXAMPLE 16

2-Hydroxymethyl-2'-neopentylaminomethyldiphenyl Sulphide

A solution of pivaloyl chloride (5.1 g.) in triethylamine (50 ml.) was added with stirring to a solution of 2-hydroxymethyl-2'-aminomethyldiphenyl sulphide (5.0 g.) in acetonitrile (100 ml.) at room temperature. The reaction mixture was stirred for 2.5 hours, and the solvent was then removed under reduced pressure. Chloroform (250 ml.) was added to the residue and the resulting mixture washed successively with 10% hydrochloric acid (250 ml.), 5% sodium bicarbonate (250 ml.), and water (250 ml.). The solvent was removed under reduced pressure, giving a dark red oil which was reduced, following the general procedure of Example 14 and to give 2-hydroxymethyl-2'-neopentylaminomethyldiphenyl sulphide. This was isolated as its hydrochloride salt and recrystallized from methanol ethyl acetate, m.p. 196—198°C.

The compounds of the following Examples 17—24 were prepared following the procedures of Examples 12 and 14.

EXAMPLE 17

2-Hydroxymethyl-2'-butylaminomethyldiphenyl sulphide hydrochloride

m.p. 138—140°C

EXAMPLE 18

2-Hydroxymethyl-2'-N-(*n*-butyl)-N-methylaminomethyldiphenyl sulphide hydrochloride

m.p. 154—155°C

EXAMPLE 19

2-Hydroxymethyl-2'-*n*-propylaminomethyldiphenyl sulphide hydrochloride

m.p. 156—157°C

EXAMPLE 20

2-Hydroxymethyl-2'-N-ethyl-N-methylaminomethyldiphenyl sulphide hydrochloride

m.p. 135—138°C

EXAMPLE 21

2-Hydroxymethyl-2'-isopropylaminomethyldiphenyl sulphide hydrochloride

m.p. 171—172°C

EXAMPLE 22

2-Hydroxymethyl-2'-cyclohexylaminomethyldiphenyl sulphide hydrochloride

m.p. 203—205°C

EXAMPLE 23

2-Hydroxymethyl-2'-N,N-diethylaminomethyldiphenyl sulphide hydrochloride

m.p. 148—150°C

EXAMPLE 24

2-Hydroxymethyl-2'-N-ethylaminomethyldiphenyl sulphide hydrochloride

m.p. 186—187°C

EXAMPLE 25

Tablet Formulation

150 mg. of 2-N,N-Dimethylaminomethyl-2'-hydroxymethyldiphenyl sulfide hydrochloride
85 mg. Lactose
50 mg. Cornstarch
10 mg. Micronized Silica Gel
5 mg. Polyvinyl pyrrolidone

Procedure

The lactose, cornstarch and salt is mixed together and granulated with a binder, polyvinyl pyrrolidone in alcoholic solution, to form granules. The granules were passed through a 16—20 mesh screen, then air dried, lubricated with micronized silica gel and compressed into tablets. A film coating could then have been applied if desired.

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EXAMPLE 26

Capsule Formulation

150 mg. of 2-N-methylaminomethyl-2'-hydroxymethyl diphenyl sulfide hydrochloride is mixed with 125 mg. of lactose and 125 mg. of cornstarch. The mixture is filled into a two piece hard gelatin capsule.

EXAMPLE 27

Parenteral Solution

150 mg. of 2-N,N-diethylaminomethyl-2'-hydroxymethyldiphenyl sulfide hydrochloride is dissolved in sterile water U.S.P. to make 1 ml. A multi-dose preparation may include bacteriostats such as 0.2 to 0.5% w/v of phenol.

EXAMPLE 28

Suppository

150 mg. of 2-aminomethyl-2'-hydroxymethyldiphenyl sulfide hydrochloride is mixed with 205 mg. of softened or melted cocoa butter, and suppositories were formed by chilling and shaping in moulds.

EXAMPLE 29

Capsule

200 mg. of 2-N-ethylaminomethyl-2'-hydroxymethyldiphenyl sulfide hydrochloride is placed in a two piece hard gelatin capsule.

EXAMPLE 30

Anti-Tetrabenazine Test

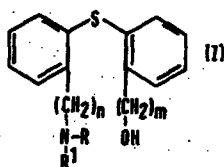
Sprague-Dawley male rats weighing approximately 130 g. were grouped six per cage. Compounds of formula I as the hydrochloride salt in saline are injected i.p. thirty minutes prior to the administration of tetrabenazine, 20 mg/kg, i.p. Animals were scored according to the method of Sulser and Soroko, *Psycho-pharmacology* 8, 191 (1965).

Results

Compound of Example No.	Dose (mg/kg i.p.)	Effective Anti-Tetrabenazine activity in the Rat
5	9	50%
6	14	50%
7	12	50%
11	25	37%
14	25	50%
15	25	60%
16	25	51%
17	25	78%
18	25	71%
19	25	57%
23	50	50%
24	25	57%

WHAT WE CLAIM IS:—

1. A compound of the formula (I)



or an acid addition salt thereof, wherein

R and R' are the same or different and are each hydrogen or straight or branched alkyl of 1 to 6 carbon atoms or R and R' taken together are (CH₂)_x where x is 4 or 5, or NRR' is



wherein R² is hydrogen or alkyl of 1 to 4 carbon atoms or NRR' is

(17)



EXAMPLE 26

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150 mg. of 2-N-methylaminomethyl-2'-hydroxymethyl diphenyl sulfide hydrochloride is mixed with 125 mg. of lactose and 125 mg. of cornstarch. The mixture is filled into a two piece hard gelatin capsule.

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Parenteral Solution

150 mg. of 2-N,N-diethylaminomethyl-2'-hydroxymethyldiphenyl sulfide hydrochloride is dissolved in sterile water U.S.P. to make 1 ml. A multi-dose preparation may include bacteriostats such as 0.2 to 0.5% w/v of phenol.

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EXAMPLE 30

Anti-Tetrabenazine Test

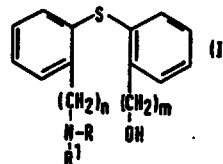
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Results

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5	9	50%
6	14	50%
7	12	50%
11	25	37%
14	25	50%
15	25	60%
16	25	51%
17	25	78%
18	25	71%
19	25	57%
23	50	50%
24	25	57%

WHAT WE CLAIM IS:—

1. A compound of the formula (I)



or an acid addition salt thereof, wherein

R and R' are the same or different and are each hydrogen or straight or branched alkyl of 1 to 6 carbon atoms or R and R' taken together are (CH₂)_x where x is 4 or 5, or NRR' is



wherein R² is hydrogen or alkyl of 1 to 4 carbon atoms or NRR¹ is

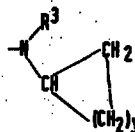


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wherein y is 3 or 4 and R³ is hydrogen or alkyl of 1 to 4 carbon atoms; and n and m are the same or different and each 1, 2 or 3.

2. A compound or salt according to Claim 1 with the proviso that, for free bases of formula (I), when m and n are each 1 and

- (i) when one of R and R' is methyl the other is not hydrogen, and
- (ii) when R and R' together are $-(CH_2)_x-$ then x is 4.

3. A compound or salt according to Claim 2 with the further proviso that, for an acid addition salt, when m and n are each 1, and

- (i) when one of R and R' is methyl the other is not hydrogen and
- (ii) when R and R' together are $-(CH_2)_x-$ then x is 4.

4. A compound or salt according to Claim 1 with the proviso that, for the free bases of formula (I), when m and n are each 1 and

- (i) when one of R and R' is methyl the other is not hydrogen or methyl and
- (ii) R and R' together are not $-(CH_2)_x-$.

5. A compound or salt according to Claim 4 with the further proviso that, for an acid addition salt, when m and n are each 1, and

- (i) when one of R and R' is methyl the other is not hydrogen or methyl, and
- (ii) R and R' together are not $-(CH_2)_x-$.

6. A compound or an acid addition salt thereof according to Claim 1 with the proviso that

- (i) when one of R and R' is methyl the other is not hydrogen, and
- (ii) when R and R' together are $-(CH_2)_x-$ then x is 4.

7. A compound or acid addition salt thereof according to Claim 1 with the proviso that

- (i) when one of R and R' is methyl the other is not hydrogen or methyl, and
- (ii) R and R' together are not $-(CH_2)_x-$.

8. A compound or an acid addition salt thereof according to Claim 1, with the proviso that when one or both of R and R' is an alkyl group, it has 1 to 4 carbon atoms.

9. 2-N,N-Dimethylaminomethyl-2'-hydroxymethyldiphenyl sulphide or an acid addition salt thereof.

10. 2-N-Methylaminomethyl-2'-hydroxymethyldiphenyl sulphide or an acid addition salt thereof.

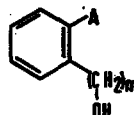
11. 2-Aminomethyl-2'-hydroxymethyldiphenyl sulphide or an acid addition salt thereof.

12. A pharmaceutically acceptable acid addition salt of a compound defined in any of Claims 1 to 11.

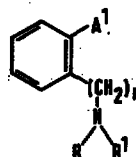
13. An hydrochloric acid addition salt of a compound defined in any of Claims 1 to 11.

14. A process for the preparation of a compound or an acid addition salt thereof as defined in any of Claims 1 to 13 which comprises

- (a) reacting a compound of the formula



with a compound of the formula



wherein R, R', n and m are as defined in any of Claims 1 to 11, one of A and A' is a mercapto group and the other is halo; or

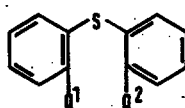
- (b) the reduction of a compound of formula (II)



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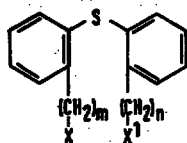
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(II)

wherein Q^1 is $-(CH_2)_m$, OH or $-(CH_2)_{m-1}$, CO_2R'' and Q^2 is $-(CH_2)_n$, NRR^1 or $-(CH_2)_{n-1}$, CO , NRR^1 , where R'' is alkyl of 1 to 4 carbon atoms and R , R^1 , n and m are as defined in any of Claims 1 to 11, and provided that at least one of Q^1 and Q^2 is other than $-(CH_2)_m$, OH and $-(CH_2)_n$, NRR^1 respectively; or

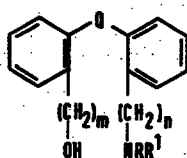
(c) the replacement of a leaving group by an hydroxy group or a group $-NRR^1$, as appropriate, in a compound of the formula (III).



(III)

wherein m and n are as defined in any of Claims 1 to 11, X is hydroxy or a leaving group and X' is $-NRR^1$ or a leaving group, provided that only one of X and X' is a leaving group; or

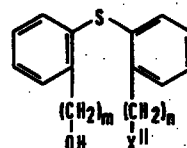
(d) the reduction of a compound of the formula (IV)



(IV)

wherein R , R^1 , n and m are as defined in any of Claims 1 to 11 and Q represents a sulphone or a sulfoxide group; or

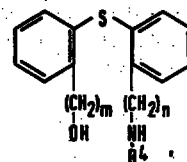
(e) when R and R^1 are both other than hydrogen, the reduction of a compound of the formula (V)



(V)

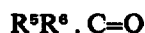
wherein n and m are as defined in any of Claims 1 to 11 and X'' represents $-(R^1R)N=O$ or $-NR^7$, CO , R^8 , in which R^8 is alkyl of 1 to 5 carbon atoms and R^7 is hydrogen or alkyl of 1 to 6 carbon atoms;

(f) when R and R^1 are both alkyl, the reductive alkylation of a compound of the formula (VI).



(VI)

with a compound of the formula



wherein n and m are as defined in any of Claims 1 to 11, R^4 is hydrogen or alkyl of 1 to 6 carbon atoms, and R^5 and R^6 are the same or different and are each hydrogen or alkyl of 1 to 5 carbon atoms provided that their combined number of carbon atoms does not exceed 5;

followed by the optional conversion of the product to the base or an acid addition salt thereof, as appropriate.

15. A process as defined in Claim 14(a) wherein the reaction is effected under anhydrous conditions in the presence of an alkali metal lower alkoxide and a suitable polar, aprotic solvent.



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16. A process as defined in Claim 15, wherein the solvent is selected from dimethylformamide, dimethylacetamide and dimethylsulphoxide.
17. A process as defined in Claim 14(b), wherein the reduction is effected in the presence of lithium aluminium hydride.
- 5 18. A process as defined in either of Claims 14(b) and 17, wherein the reduction is effected in the presence of an inert solvent.
19. A process as defined in Claim 18, wherein the inert solvent is diethylether or tetrahydrofuran.
- 10 20. A process as defined in Claim 14(c), wherein X is hydroxy, X' is a leaving group and the compound of formula (III) is reacted with a secondary amine RR'NH, R and R' being as defined in any of Claims 1 to 8.
21. A process as defined in Claim 20, wherein the reaction is effected in the presence of an inert solvent.
- 15 22. A process as defined in Claim 14(c) wherein X is a leaving group and X' is —NRR', the compound of formula (III) is reacted with an alkali metal hydroxide.
23. A process as defined in Claim 22, wherein the reaction is effected in the presence of a solvent.
24. A process as defined in any of Claims 14(c) and 20 to 23, wherein the leaving group is selected from halo, *p*-toluenesulphonyl, lower alkanesulphonyl and azido.
- 20 25. A process as defined in Claim 14(d), wherein the reduction is effected in the presence of a reducing agent selected from triphenylphosphine and a metal hydride.
- 25 26. A process as defined in either of Claims 14(d) and 25, wherein the reduction is effected in the presence of a non-reactive organic solvent.
27. A process as defined in Claim 14(e), wherein the reduction is effected in the presence of a reducing agent selected from triphenylphosphine and a metal hydride.
- 30 28. A process as defined in either of Claims 14(e) and 27, wherein the reduction is effected in the presence of a non-reactive organic solvent.
29. A process as defined in Claim 14(f), wherein the reductive alkylation is effected in the presence of a reducing agent selected from formic acid or a derivative thereof, a metal hydride, and hydrogen and Adam's catalyst.
- 35 30. A process as defined in either of Claims 14(f) and 29, wherein the reductive alkylation is effected in a solvent.
31. A compound as defined in any of Claims 1 to 13, prepared by a process defined in any of Claims 14 to 30.
- 40 32. A pharmaceutical formulation which comprises a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof, according to any of Claims 1 to 11 and 13, in association with a pharmaceutically acceptable carrier therefor.
33. A formulation according to Claim 32, wherein the carrier is a liquid.
34. A formulation according to Claim 32, wherein the carrier is a solid.
- 45 35. A formulation according to any of Claims 32 to 34 in unit dosage form.
36. A formulation according to any of Claims 32 to 35 which is suitable for administration by a route selected from oral, parenteral and rectal.
37. A formulation according to Claim 36, which comprises the compound of formula (I) or acid addition salt thereof in an amount in the range of from 15 to 1500 mg. calculated as the base.
- 50 38. A formulation according to Claim 37 which is a tablet.
39. A formulation according to Claim 37 which is a sterile solution or suspension.
40. A formulation according to Claim 37 which is a suppository.
- 55 41. A method for the preparation of a pharmaceutical formulation according to any of Claims 32 to 40 which comprises admixture of the compound of formula (I) or acid addition salt thereof with the acceptable carrier therefor.
42. A pharmaceutical formulation according to any of Claims 32 to 40, prepared by the method of Claim 41.
- 60 43. A method for the treatment of depression in a mammal (excluding man) which comprises the administration to the mammal of a non-toxic, effective-antidepressant dose of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof as defined in any of Claims 1 to 11 and 13.
44. A method according to Claim 43, wherein the compounds of formula (I) or acid addition salt thereof is administered by a parenteral route in an amount in the range of from 0.3 to 75 mg/kg of mammal body weight, calculated as the base.
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45. A method according to Claim 43, wherein the compound of formula (I) or acid addition salt thereof is administered by an oral or rectal route in an amount in the range of from 0.6 to 150 mg/kg of mammal body weight, calculated as the base.

46. A method according to any of Claims 43 to 45 which comprises administration to the mammal of a compound selected from

- (a) 2-*N,N*-dimethylaminomethyl-2'-hydroxymethyldiphenyl sulphide;
- (b) 2-*N*-methylaminomethyl-2'-hydroxymethyldiphenyl sulphide; and
- (c) 2-aminomethyl-2'-hydroxymethyldiphenyl sulphide;

and pharmaceutically acceptable acid addition salts thereof.

47. A compound of formula (I) or acid addition salt thereof, substantially as hereinbefore described with particular reference to any one of Examples 5, 6, 7, 11 and 14 to 24.

48. A process for the preparation of a compound or an acid addition salt thereof of formula (I), substantially as hereinbefore described with particular reference to any one of Examples 5, 6, 7, 11 and 14 to 24.

49. A pharmaceutical formulation which comprises a compound of formula (I) or pharmaceutically acceptable acid addition salt thereof in association with an acceptable carrier therefor, substantially as hereinbefore described with particular reference to any one of Examples 25 to 29.

50. 2-Aminomethyl-2'-hydroxymethyldiphenyl sulphide hydrochloride.

51. A formulation according to any of Claims 32 to 40 and 42, wherein the compound of formula (I) is 2-aminomethyl-2'-hydroxymethyldiphenyl sulphide.

52. A formulation according to any of Claims 32 to 40 and 42, wherein the acid addition salt of a compound of formula (I) is 2-aminomethyl-2'-hydroxymethyldiphenyl sulphide hydrochloride.

53. A tablet which comprises 2-aminomethyl-2'-hydroxymethyldiphenyl sulphide or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutically acceptable carrier therefor.

54. A tablet which comprises 2-aminomethyl-2'-hydroxymethyldiphenyl sulphide hydrochloride in association with a pharmaceutically acceptable carrier thereof.

55. A tablet according to either of Claims 53 and 54 which comprises 2-aminomethyl-2'-hydroxymethyldiphenyl sulphide or the hydrochloride salt thereof in an amount in the range of from 15 to 1500 mg calculated as the base.

L. D. JENKINS,
Agent for the Applicants,
Chartered Patent Agent.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1980
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.

