3. PRIJEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

D1:US3546226 publicada el 8 de diciembre de 1970.

4. FUNDAMENTO DE DERECJ-lO

Fundamento esta observaciOn en las normas legates siguientes:

4.1. Numeral I del articulo 586 del Codigo de Comercio.

4.2. Articulo 42 de la Decision 486 de La Comision del Acuerdo de Cartagena.

4.3. En las dermis normas concordantes,

5. ANEXOS

Para los efectos correspondientes anew al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de PROCAPS S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

D1:US3546226 publicada el 8 de d kicuibre de 1970.

Carrera 13 No 119-95, Oficina 104 TI - (571)2 13 12 13 - Fax. (571)6 12 19 79 / E-mail: riegocios@optii co.corn - www.opthnum-co.com
Be Colombia

6. NOTIFICACIONES

Para efectos de notificaciones que pot disposición del articulo 50 del Decreto
01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretarla de su Despacho o en mis oficinas situadas en la Carrera 13 No 119-95, Of. 104 de esta ciudad de Bogota.

Seæor Superintendente,

- kp
LAURA CATALINA SILVA BARRERA

C.C. 52’455.803 de Bogota
T.P.A. 147399 del C.S. de la J.

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United 31,546s226 States Patent Office Patented Dec. 8, 1970

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11..BASIC- D1BBNZOXAZP1NES.
lean Schnzntr, Marl, near Bern, and Fritz thuizlker and
Franz Marlin Klinzln, Bern, Switzerland, assignors to

Dr. A. Wander, S.A., Bern, Switzerland1 a corporation of Switzerland
No Drawing. ConfInuallon4npart of applications 8cr. No. 371,123, May 28, 1964, and 8cr. No. 712,956, Mar, 14,

1968. This application. Feb. 6, 1969, 8cr. No. 797,281 Claims priority, application Switzerland, May 30, 1963,

6.762/63; Sept. 27, 1963, 11,907/63; Mar. 13, 1967, 3,582/61; Mar. 22, 1961, 4,103/67; May’ 1967 6,557/67; July 14, 1967,.10,115/67; Nov.. 4 1967: 15,453/67
Int. CL C074 51/70
U.S. CL, 260-268 9 ClaIms

ABSTRACT OF THE JMSCLOSVRE

(A) 11-basic substituted dibenzoxazepines having the general Formula A:

wherein R. is a member of the class consisting of hydro-gen, lower alkyl, lower bydroxyalkyl, acetylated lower hydroxyalkyl, and alkoxyalkyl having not more than S carbon atoms; and

(B) Derivatives of A substituted in the beuzene nu- clei by at least one member of the class consisting of

halogen, iriftuoromethyl, lower alkyl, lower alkozy, and lower alkyitbia; and
(C) 11-baste substituted dibeuzoxazepiucs having the general Formula C:

wherein R, represents a member of the group consisting of hydrogen, allyl, alkyl containing not more than 3 car-

bon atoms, hydroxyalkyl containing not more than 3 car- bon atoms, alkoxyalkyl containing not more than 6 carbon
atoms and aikoylozyalkyl containing not more than 6 carbon atoms; and k5 Is a member of the group consist. lag of nitro, amino, amlnosuiphonyl of the formula -802NR4R5 wherein R4 and R5 are the same or differ-ent members of the group consisting of hydrogen and methyl, alkyt-suiphinyl of the formula -SOR0 wherein R0 denotes alkyl with not more than 3 carbon atoms, and alkylsulpbonyl of the formula r.-S02R. wherein R6 de-notes alkyl with not more than. 3 carbon atoms; and

(D) The non-toxic pharmaceutically acceptable acid- addition salts of A, B and C.
These compounds have a pronounced therapeutic effect on the central nervous system and are particularly active as neuroplegics, neuroleptics, neuroleptic antidepressants, antimetics, analgesics and sedatives.

This Is a continuation-in-part application of our co.

pending patent application Soy. No. 371,123, filed May 28, 1964, and 8cr. No. 712,956, filed Mar. 14, 1968 both now abandoned.

The object of the present invention is to provide 11- basic substituted dibenz[b,f] (1,4]oxazepinea having a pronounced therapeutic effect on the central nervous system.

A further object of the invention Is to provide Il-basic

o substituted dibenztb,fl (1,4joxazepines having the above- mentioned action of the general formula:
RI

15

(N)

20

ao,1?06!?O (I)

25 wherein RX denotes hydrogen, lower alkyl, lower by-dyozyalkyl, acetylated lower bydroxyalkyi, or alkoxyal-kyl having not more than 5 carbon atoms, and which

compounds are nnsubstituted in the benzene nuclei or substituted by halogen, trifluoromethyl, lower alkyl, lower

so alkoxy or lower alkylthlo; as well as acid addition salts of these basic compounds. Substituents In the benzene nuclei are preferably in the 2-, 4-, or 8-positions. The

term "lower" alkyl em is intended to mean alkyl etc. hay- Ingfrom Ito3 carbon atoms.
A further object of the invention is to provide 11-basic

substituted dibenz[b,f:I 11,41oxnzepines having the above- mentioned action of the general formula:

40

45

(U)
60

and acid addition salts thereof. In Formula TI R2 repre-sents hydrogen, ailyl, alkyl containing not more than 3 carbon atoms, hydroxy-alkyl containing not more than 3

carbon atoms, alkoxyalkyl containing not more than 6 s5 carbon atoms or alkoyloxyalkyl containing not more than 6 carbon, atoms. R3 denotes ultra; amino; amino-

suiphonyl of the formula -SOeNRB4, wherein B4 and

R5 are the same or different and represent hydrogen or methyl; alkylsuiphinyl of the formula -’-SOB6, wherein oo R5 denotes ethyl with not more than.3 carbon atoms; or alkylsuiphonyl of the formula -SOB4, in which R4
represents alkyl with not more than 3 carbon atoms.
The compounds of Formula I are obtained by reacting

a reaction mixture containing nitrillum or Imonluni Ca- 65 dons of the formulae: (yN-O70o

(W)

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3
which are unsubstituted In the benzene nuclei or substi-tuted by halogen, trifluoromethyl, lower alkyl, lower alkoxy or lower alkylthio with piperazine or a piperazine derivative, respectively, of the formula:

(IV)

wherein R1 has the indicated meaning.
Nitrilium or imonium cations of Formulae m can be

regarded as dissociation products of corresponding com- pounds of the formula:

a?o

10

4
Compounds of Formula I are also obtained by dehy-dration of urea derivatives of the formula:

(Vii)

wherein R1 has the meaning indicated above, and which are unsubstituted in the benzene nuclei or substituted by is halogen, tzifluoromethyl, lower alkyl, lower alkoxy or lower alkylthio, for instance through several hours’ action
by dehydrating agents like zinc dichloride, aluminum chloride, tin tetrachloride, phosphoric acid and the like, but preferably phosphoroxychioride, if required in the 20 presence of an inert solvent with a suitable boiling point, such as benzene, toluene, etc.
Compounds of Formula I are also obtained by ring closure, through intramolecular condensation, of acid amities or thloamldes of the formula:
25

wherein A represents a halogen atom, the sulfhydryl group, or an alkoxy or alkylthio, group which is activated

if required, e.g., the p-nitrobenzyithio group. Such com- pounds V are obtained, for instance, by conversion of

lactams of the formula: 30

0:70-10-0-0 (Vi)
into the th.iolactams, if required with subsequent alkyla-

tion of the latter, or by reacting the lactams (VI) with a halogenating agent like phosphoroxychioride or phos-

phorus pentachioride, preferably in the presence of cata-

lytic amounts of dimethylaniline or diinethyiforinamide. The lactams (VI) can be obtained, for example, by ring closure of suitable o-isocyanato-diphenyl ethers with

aluminum chloride. Depending upon the chemical nature

of the residue A and also of eventual nuclear substituents, the V compounds in the reaction mixtures obtained are dissociated to a higher or lower degree into the nitrilium or imoniurn cations, so that the reaction mixtures can be

used directly for reacting with piperazine or the pipera-zine derivative of Formula IV. In part the compounds

of Formula V produced in this or in another manner can be isolated in undissociated form and then yield the de-
sired nitrilium or imonium cations (Iii) upon dissolution

in a suitable, preferably polar solvent, if required by heating and in the presence of piperazine or the pipera- zine derivative of Formula IV, which can also serve as a solvent. Reaction mixtures containing cations of Formula

III can also be produced, for example, by intramolecular

Ritter’s reaction (action of a nitrile group on a phenyl cation) in o-cyanodiphenyloxldes, by Beckmann’s trans-

formation of (if desired suitably substituted) zantho-

noximes, or by Schmidt’s reaction of (if desired suitably substituted) xanthones with hydrazoic acid. Both the

last-named reactions may lead, If the starting material consists of unsymmetrically substituted oxlmes or ke-tones, to isomeric products which, if necessary, must be subsequently separated. In the said reaction mixtures the anionoid components which may appear arebesides those derived from the substituent A of Formula Vde-pending upon the mode of preparation of the cations (III), for example also anions of sulphuric, toluene-suipho, phosphoric, bydrofluoric, or hydrofluoboric acids,
etc.

(VIII)

tj wherein R1 has the above-mentioned meaning, and Y

represents an oxygen or sulphur atom, and which are unsubstituted in the benzene nuclei or substituted by halogen, trifluoromethyl, lower alkyl, lower alkoxy or lower alkylthio. A purely thermal condensation cannot
40 usually be successfully carried out with the acid amities, which, in turn, are produced, for example, by reduction

of suitable nitro compounds, but it can rather in the case of the thiogmides, which are obtained, for example, by treating the acid amides with phosphorus pentasuiphide and do not require to be isolated prior to the subsequent 45 condensation. Especially in the case of the acid amities

it is useful to work in the presence of condensing agents, such as phosphorus pentachioride, phoaphoroxychioride,

phosgene, polyphosphoric acid, and the like. It is to be

supposed that the ring closure involved goes partly 50 through intermediate stages, like imide chlorides, amide
chlorides, iinidophosphates, ainidophosphates or salt-like derivatives thereof, which can not generally be isolated. Condensation of the thioamides may be aided by the 55 presence of mercury salts or by intermediate formation’

of (if desired activated) imido thio ethers. Heating and, if required, the use of an inert diluent are useful when working with pliosphoroxychioride and phosphorus pen- tachioride, as also the addition of catalytic amounts of

dimethylformanmide or dimethylanifino. UO Finally, compounds of Formula I can be prepared by reacting primary amines of the formula:
05

0-0 (IX)

or derivatives thereof substituted in the benzene nuclei, with reactive esters of alcohols having the formula:

70

(X)

wherein R1 has the meaning identified above. The re. 75 action Is carried out following or by simultaneous treat-

0

ment with a basic catalyst or metallization agent such as sodamide,lithium amide, sodium hydride, butyl lithium, phenyl sodium, sodium ethylate or potasslum4-butoxtde. The primary amines of Formula IV are obtained by treating a reaction mixture containing nitrilium or boo-nium cations of Formula mwith ammonia.
Compounds of Formula I, obtained according to one of the above methods, wherein R1 represents hydrogen, can be converted to such compounds, wherein R1 does not represent hydrogen, e.g., by treatment with reactive esters of alcohols of formula R1OH. Hydrohalic acid or toluene suiphonic acid esters are suitable for this pur-pose.

Compounds of Formula II are obtained when a com-pound of the formula:

wherein R3 has the meaning defined above and X denotes a residue capable of being split off with the hydrogen of amines, Is reacted with piperazine or a plperazlne deriva-tive, respectively, of the formula:
112

(NJ (Xfl)
wherein R2 has the above-mentioned meaning.
A residue capable of being split off with the hydrogen of amines, which can be bound Lonically or covalently to the carbon atom, can most conveniently be represented by halogen, sulpbydiyl, or alkoxy and alkylthlo which may be activated, e.g. methoxy, thiomethyl or p-nitro beuzylthio, or. by tosyl.
Starting materials of the Formula XI are obtained by converting lactams of the formula:

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6
The lactam of Formula XIII in which R3 represents amino
is most suitably obtained by reduction of the correspond-
ing nitrolactam
Compounds of Formula II may further be obtained
by ring closure through intramolecular condensation of acid amides or acid thioamides of the formula:

10

15

wherein R2 and Its have the above-mentioned meaning and Y represents oxygen or sulphur. A purely thermal condensation rarely succeeds with the acid amities but 20 rather with the thioamides which are, for example, ob-tained from the acid amities by treatment with phos-phorus pentasulpbide and need.not be isolated before the following condensation. Especially In the case of the acid amities It is desirable to perform the ring closure In the 25 presence of condensing agents, such as phosphorus penta-chloride, phosphorus oxycbloride, phosgene, polyphos-phone acid, and the like. It is assumed that the ring closure proceeds by way of intermediate steps such as imidochlo-.

rides,.amidocblorides, imidophosphates, amidophosphates 80 or salt-like derivatives thereof, which, in general, are not

Isolatable. The condensation of the thioamides is favoured by the presence of mercury (II) salts or by intermediate formation of imidothioethers which may be activated.
- Heating and, if required, the use of a suitable inert eel-vent are desirable, and when using phosphorus oxychlo-ride and phosphorus pentachioride addition of catalytic amounts of dimethylforseamide or dimethylaniline. Compounds of Formula II can also be obtained by de-.

40 hydration of urea derivatives of the formula:

a7o? Or (Xtfl)45

wherein R3 has the meaning given above, into the thin-lanterns which may be followed by alkylatlon, or by reaction of the lactams with a halogenating agent such as phosphorus oxychioride or phosphorus pentacliloride, most suitable in a. presence of a catalytic amount of dimethylanhine or. dimethylformaznide. Lactanis of Formula XLII are themselves obtained by ring closure of compounds of the formula:
OR?

HS

07 R’
(XIV)

wherein R3 has the above-mentioned meaning and R., denotes hydrogen or lower alkyl. Lactams of Formula XIII may also be obtained by ring closure of compounds of the formula:

1,,Lon

on.
ins) (XV)
wherein Hal stands for halogen, or of Isocyanates of the formula:

(:ro_i(:r (XVI)

60 (XvJTh

wherein Its has the above-mentioned meaning and R3 means R2 or denotes a removable group, especially a hydrolyticaily removable group. The ring closure Is pref-
erably carried out by heating in the presence of dehydrat- 55 ing agents such as zinc chloride, aiwninuni chloride,
stannic chloride, phosphoric acid, polyphosphoric acid and the like, especially phosphorus oxychioride or phos-phorus oxychioride and phosphorus pentoxide, if desired

In an inert solvent of suitable boiling point such as hen- "F zene or toluene etc. According to the chosen reaction con- ditions the starting materials of Formula XVIII with a bydrolytically removable group R8, e.g. carbaikoxy,

especially carbethoxy, are cycicized directly to the lj(l-

piperazinyl) compounds by hydrolysis of the removable 65 group. Other removable groups can be split off after ring closure in away known per se, e.g. by bydrogenolysis.

As long as R3 does not denote amino, the compounds
of Formula. U can also be obtained when amldinea of the

TO formula:

0?_OT

RIB

(Xix)

11

4A

7
wherein R’. represents Its with exclusion of amino, are treated with a reactive ester of an alcohol of the formula:

(XX)

wherein R2 has the above-mentioned meaning. The re-action is carried out following or by simultaneous treat-ment with a basic catalyst or metallization agent such as sodarnide, lithium amble, sodium hydride, butyl lithium, phenyl sodium, sodium ethylene or potassium-t-butoxlde. Suitable esters are those of inorganic or organic acids, e.g. hydrohalic acid, suiphonic acid or carbonic acid esters. The required amidines XIX are in turn obtained by treat-ing compounds or Formula XX with ammonia.
On the other hand, compounds of Formula It, wherein R3 is amino, may be obtained by reduction of the cor-responding nitro compounds. The reduction Is most suit-ably carried out by treatment with hydrogen In the pres-ence of a catalyst such as palladium charcoal or Raney nickel or by treatment with stannous chloride and hydro-
chloric acid.

Compounds of Formula U, wherein R3 represents alkyl-suiphinyl or alkylsuiphonyl, respectively, can also be ob-tained by mild (e.g. with periodates) or strong (e.g. with hydrogen peroxide or peracetic acid) oxidation of the corresponding alkylthio compounds. Products wherein R3 represents alkylsuiphonyl are also obtainable by strong oxidation of the corresponding alkylsulphlnyl compounds. Finally, compounds of Formula II, wherein R3 denotes aminosniphonyl of the formula SO5NR4R, are ob-tained when the corresponding compounds containing the group SO2X instead of aminosuiphonyl, wherein X de-notes a residue which is removable with the hydrogen of amines, especially halogen, are reacted with ammonia or an amine of the formula EINR4R5, wherein E4 and R5 have the above defined meaning. Starting materials con-taining a suiphochloride group (SO5CI) are obtained by diazotization of the corresponding amino compounds followed by the Meerwein reaction.
Compounds of Formula II, obtained according to one of the above methods, wherein R2 represents hydrogen can be converted to such compounds wherein R2 does not represent hydrogen, e.g. by treatment with reactive esters of alcohols of the formula R2-011 Rydrobalic acid or toluenesuiplionic acid esters are suitable for this purpose. An alkyl group R2 can also be introduced by the method of reductive allcylation, i.e. by reaction with corresponding aldehydes either with hydrogen in the pres-ence of a catalyst with a reducing agent such as formic acid. The introduction of a hydrozyalkyl group R2 can also be carried out by treating with a corresponding alkyl-ene oxide.

Compounds of Formula II in which R2 denotes a by-droxy-alkyl group can be subsequently treated with an acylating agent to obtain products wherein R2 represents an alkoyloxyalkyl group. Acid chlorides and acid anhy-drides are especially suitable as acylating agents. Subsequent introduction of a group R2, other than hy-drogen, and also subsequent acylation of a hydroxyalkyl group R2 can lead to additional substitution in products in which R3 denotes an amino group; this amino group being additionally substituted.
The bases 1 or U obtained in this manner are In most cases crystallizable or can otherwise be distilled in high vacuum without decomposition and react with inorganic and organic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid, acetic aid, maleic acid, succinic acid, tartaric acid, toluene sal-phonic acid and the like to form addition salts which
are stable in water, in which form the products may also
be used.
The bases I and II as well as their acid addition salts are new compounds which can be used as active sub-stances in pharmaceuticals. They produce a favourable

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effect on the central nervous system and may therefore be used, for example, as neuroplegics, neuroleptics, neuro-
leptic antidepressants, antlemetics, analgesics and seda-
tives.

The compounds of Formula I and their acid-addition salts are particularly of interest as neuroplegics, neurolep-tics and analgesics. Some of them are suitable for the treatment of psychotic conditions.
Preferred specific compounds are:

10 1 I-(4.methyl-1-pipera2inyl)-dlbenz[b,f]) 1,4]oxazepinc, 2-chloro-1 1-(4-methyl-1-piperazinyl)-dibenz(b,fj [1,4] ozazepine,
2-brozno-1 l-(4-methyl-1-piperazinyl)-dibenz(’b,f] [1,4]

oxazepine, 15 4-chloro-1 1-(4-methyl-1-piperazinyl)).cllbenz[b,f] (1,4]
oxazepine,
2-fluoro-1 1-(4-methyl-1-piperazinyl)-dibenz[b,f] [1,4] oxazepine and

8-ohloro-1 l-(4-methyl-1-piperazinyl)-dibenz(b,f] [1,4] 20 as well as their acid-addition salts.
oxazepine

The utility as neuroplegic or neuroleptic, respectively, manifests pharmacologically e.g. in a supression of lace-25 motor activity, a cataleptic and/or an apomorphine an-tagonising effect in mice or rats, respectively. The motility depressing action can be shown by measuring the loco-motor activity in accordance with the method of Caviezel and Baillod [Pharm. Acta Helv. 33, 469 (1958)]. In the 30 following Table I, the locomotor activity obtained with some compounds of Formula I, as well as their toxicity, are compared with the corresponding data of chioro-promazine. From Table I it can be seen that the 2-sub-stituted products are the most active.

35 TABLE

40 ActIve substance

Toxicityactivity
(mouse)
LDSO

mg./kg. p.o.

Loemnotor

(mouse)
EDSO

mg./kg. p.o.
135 5.5
230 2.7

47 0.05

05 0.05

120 0.13

800 5.4

410 10.5

50

Compounds of Formula U in which R3 denotes nitro show also the typical behaviour pattern for neuroleptics. The most effective compounds in this respect are 2-ultra-
I 1-(4-niethyl-1-piperazinyl) - dibenz(b,fJ [1,4]oxazepine, 55 obtained according to Example 5, as well as its acid ad-dition salts.
Other compounds, especially those with 11-(1-piper-azinyl) residue show simultaneously the behaviour pattern for neuroleptics and antidepressants whereby the antide-60 pressant action is shown pharmacologically by a tetra-benazine antagonism observed in rats. Especially active In this respect are the compounds 2-uitro-1 l-(1-piper-aziny1)dibenz[b,f] [1,4]oxazepine obtained according to Example 41 and its acid addition salts.
a5 Compounds of Formula U in which R3 represents ami-nosulphonyl or alkylsulphonyl exhibit a marked antiemetic activity. This is shown pharmacologically by a strong apomorphine antagonising effect In dogs and rats as well as a comparatively weak cataleptic and locomotor activity 70 suppressing effect. -Pronounced antiemetic activity is shown by 2-dimethylaminosulpbonyl. 11 - (4 - methyl-i-piper-azinyl)-dibenz[b,f] [1,4]oxazepine and 2-methylsuiphon-yl-1 1-(3-methyl - 1 - piperazinyl)-dibenz[b,f] 11,41oxaze-pine obtained according to Examples 6 or 7, respectively, 75 and their acid addition salts.

S.
The compounds of this Invention can be administered in the form of pharmaceutical preparations containing, besides the active substance, organic Or inorganic solid or liquid carriers suitable for euteral or paronteral admin-istration. The pharmaceutical preparations may be, for example, In the form of tablets, dragees, or solutions for injection, one dosage unit containing from 1 to 100 mg. of active substance, depending on its nature, on the route of administration and.on the physician’s prescription, the etiective daily dose’ amounting to from S to 500 mg. of active substance.

EXAMPLE 1

3 nil, of NN-diniethylanfllne are poured. over 10 gin, of 2-cbloro-10,11-dlhydro-11-oxo-dibenz[b,1] 11,43 oxazepine and, after adding 80 ml. of phosphoroxychlo-

ride, heated for 3 hours under reflux. The reaction mix- tin’s is evaporated in vacua. The residue Is suspended

In absolute xylol. The residue obtained by re-evaporating the suspension In vacua, is taken up In 300 ml. of ether and poured over Ice/water. The ethereal phase is sepa.. rated and washed 3 times with dilute hydrochloric acid, the hydrochloric washing water being rewasbed with

ether. The combined ether phases are successively washed with water, sodium bicarbonate solution, water
and saturated sodium chloride solution, dried over sodium

sulphate, treated with active charcoal, filtered through alumina and largely concentrated by evaporation. Upon

adding petroleum ether there are obtained 9.3 gin. (86.5% of the theory) of2,11-dichloro.dibenz[b,f] [1,4]oxaze- pine in the form of yellow needles of melting point 131-

134° C.

9.3 gin. of the 2,11-dicbloro-dibenz[b,f] (l,4]oxazepine thus obtained are heated In 100 ml. of absolute xylol with

10 ml. of N-methylpiperazlne for 4 hours under reilux.

The reaction mixture Is mixed with water and concen- trated soda lye. The aqueous phase is separated and washed with ether, and the ether used for washing is com- bined with the xylol phase. The organic phase is exhaus-

tively extracted with dilute acetic acid and then with dilute hydrochloric acid. The combined acid extracts are washed with ether, made alkaline with concentrated soda lye and then, extracted with ether. The ethereal extract is washed

with water and saturated sodium chloride solution, dried over sodium sulphate, treated with active charcoal and
evaporated. The residue is taken up in petroleum ether.

The solution is filtered through alumina and largely con- centrated by evaporation. When the concentrated solu-
tion cools down pale yellowish, grainy crystals are formed. There are obtained 8.9 gin. of 2-chloro-1l-(4-methyl-l. piperazinyl)-dibenz[b,f] (1,4]oxazepine of. melting point 109110° C;
EXAMPLE 2

8 gin, of &chloro-14),11.dlhydro.11-oxo.dl7enzb,f]

t1,41oxazepine are mixed with 8 gin, of phosphorus pentachioride and, after adding 50 ml. of phosphoroxy-
chloride, heated for 4 hours under reflux. Excess phos-phoroxychioride Is removed from the reaction mixture by distillation, in vacuo. The residue is mixed with xylol, which Is removed by evaporation, once again taken up In

xylol and poured over ice water. The xylol phase is sepa- rated, dried over sodium sulphate, treated with active

charcoal, evaporated in vacua to 100 niL and, after add-

ing 10 ml. of N-methylpiperazine, heated for 4 hours un- der reftux. The reaction mixture Is mixed with water and
concentrated soda lye. The xylol phase Is,separated and exhaustively extracted with dilute hydrochloric acid. The hydrochloric extract is washed with ether, made alkaline with concentrated soda lye and then extracted with ether.

The ethereal extract Is washed with water, dried over sodium sulphate, treated with active charcoal, filtered
through alumina and evaporated. The residue is crystal-
lized from methanol, yielding 5.9 gm, of 8-cbloro-l1-(4.

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10
mcthyl-1-piperazinyl).dibcnz[b,f](1,4loxazepine in the form of yellow prisms of melting point 165-166° C; EXAMPLE 3

13.4 gin. of 2-(4"-metbyl-l"-piperazinyl-earbouyl-amino) diphenyloxlde are heated with 150 ml. of phos-phoroxychioride for 30 bows under rethix. The reaction mixture is evaporated in vacua to dryness. While being cooled the residue Is mixed with water and made alkaline

10 with concentrated soda lye. The ethereal extract obtained by shaking twice with ether Is washed twice with water and then exhaustively, extracted with dilute hydrochloric acid. The combined hydrochloric extracts are washed with ether, made alkaline with concentrated soda lye and 15 extracted twice with ether. The ethereal extract is washed with water and saturated sodium chloride solution, dried over sodium sulphate, filtered through alumina and evapo-rated. The residue is crystallized from petroleum ether. 6.2 gin. of Z1-(4-methyl-1-piperazi.uyl)-dibenz(b,f](1,43, 20 oxazepine of melting point 102-104° C. are obtained. EXAMPLE 4

8.3 gin. of 2-amIno-2’-(4"-methyl4’-piperazinyl.car-bonyl)diphenyloxlde are boiled under reflux with 8.5 gin. 26.offluelypowderedmercuriacetate In 100 ml. xy]ene during 24 hours, The reaction mixture is filtered and the filtrate
is extracted with dilute acetic acid. The acid solution is treated with ammonia and extracted with ether. The ethereal solution Is washed with water, dried over sodium 80 sulphate, filtered through alumina and evaporated. The residue is crystallized from petroleum ether. 4.5 gin. of

11-(4-methyl- 1 - piperazinyl).dibenz[b,f] [1,4]oxuzepine of melting point 97-98° C. are obtained; the product Is

identical to that of Example 3.

36 EXAMPLE S

4.9 S. of 2-nitro-10,11-d1hydro-1 l-oxo-dibenztb,fJ[1,4] oxazepine (M.P. 263° C.) and 2 niL of N,N-dimethyl-

aniline are heated in 60 nil. of phosphorus oxychioride 40 at influx for 4 hours. The reaction mixture is then evapo- rated in vacuo to remove the excess phosphorus oxychlo- ride and the residue is decomposed with Ice/water and

shaken out Immediately with chloroform. The chloroform extracts are washed with dilute hydrochloric acid and

45 water, dried over sodium sulphate and evaporated to dry- ness In vacua. The crystalline residue consisting of crude
2-nitro-11-chloro.dibenz[b,f][1,4]oxazepine is heated at reflux for 6 hours with 6 ml. of N-methylplperazlne In 200 ml. of nylons. The organic phase is then shaken out

with water and dilute hydrochloric acid. The acid extracts are made alkaline with concentrated soda lye and the bass

which separates is extracted with chloroform. The chloro-form. extracts are washed with water, dried over sodium

sulphate and evaporated to dryness. The residue Is an crystallized from chloroform/acetone/petroleum ether and gives 4.7 g. of 2-nitro-l1-(4-methyl-1-pfpernzinyj).. dibenz[b,t!] (1,4]ozazepine In the form of yellow needles

Of melting point 192-193° C.

go EXAMPLE 6
18 g. of 2-dimethylaminosulphonyl1O,j1..iJihydr0.1 1-oxo.dibenz[b,fj [1,4]oxazep1ne (M.P. 243-245° C.) and 0.6 ml. of NN-dimethyhanfline are refluxed. in 20 in!. of phosphorus oxychlorlde for 4 hours. The excess phos. as phorus oxycliloride in removed completely In vacua and the residue dissolved in xylone and poured onto ice/water.

The xylene solution is shaken out twice with dilute hydro- chloric acid and once with water, then dried over sodium
sulphate and concentrated to 50 nil. in vacuo. 3 ml. of
o N-methylpiperazine are added and the reaction mixture Is

refiuxed for 4 hours and then treated with dilute soda lye and water. The zylene phase is separated and shaken out

with dilute hydrochloric acid. The acid extracts are made alkaline with concentrated ammonia solution and the base 75 which separates is extracted with chloroform. The chioro-

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form extracts are dried over sodium sulphate and evapo-rated in vacuo. The residue is crystallized from ether/petroleum ether whereby 1.8 g. of 2-dimethylaminosul. phonyl-1 l-(4-methyl-1-piperazinyl) - dibenzyl[b,f] (1,4] oxazepine of melting point 149-150° C. are obtained.
EXAMPLE 7

5 S. of 2-methylsulphonyl-l0,1 1-dihydro-1 1-oxo-dibeuz-[b,f] [1,4]oxazepine (M.P. 242-244° C.) and 1.8 ml. of N,N-dimethylanhline are refiuxed In 50 ml, of phosphorus oxychloride for 5 hours after which the reaction mixture is evaporated to dryness in vacuo. The residue is treated with zylene, once again evaporated and then dissolved in xylene and poured onto ice. The aqueous phase is shaken out three times with xylene. The combined xylene extracts are washed with dilute hydrochloric acid, water and aque-ous sodium chloride solution, dried over sodium sulphate, treated with active charcoal and filtered through a small amount of aluminum oxide. The filtrate is concentrated and then refluzed with 12 ml. of N.methylpiperazine for 6 hours. The reaction mixture is treated with water and concentrated soda lye and shaken out twice with ether. The ether extracts are washed several times with water and then shaken out with dilute hydrochloric acid. The acid extracts are made alkaline and extracted twice with ether. The ether phase is washed with water and aqueous sodium chloride solution, dried over sodium sulphate, treated with active charcoal and filtered through a small amount of aluminum oxide. The filtrate is concentrated and treated with petroleum ether. The crystals which pre-cipitate are dissolved in acetone and, after concentrating, recrystallized by addition of ether/petroleum ether. 5.8 g. of 2 - methylsulphonyl-1 l-(4methyl-1-piperazinyl)-di-beuz[b,f] (1,4joxazepine in the form of slightly yellow needles of melting point 178-179° C. are obtained.
EXAMPLE 8

3 g. of 2-(4"-methyl-I "-piperazinyi-carbonylantino)-4’- methylsulphonyl-diphenyloxide (M.P. 145-146° C.) and a mixture of 2 g, of phosphorus pentoxide and 10 ml. of phosphorus oxychioride are refiuxed for 24 hours. The ex-cess phosphorus oxychioride is then distilled off in vacuo and the residue decomposed with ice/water. The solution obtained is made alkaline with concentrated soda lye and shaken out with ether. The ether extracts are washed with water and shaken out thoroughly with dilute hydro-chloric acid. The acid extracts are made alkaline with concentrated soda lye and shaken out with chloroform. The chloroform extracts are washed with water, dried over sodium sulphate and evaporated to dryness in vacuo. The residue is crystallized from acetone/petroleum ether and gives 1.5 S. of 2methylsu1phonyl-ll-(4-methYl-1-piPer-azinyl)-dibenz[b,f] [1,4]oxazepine of melting point 178-179° C. identical to the product obtained according to Example 7.
EXAMPLE 9

15.2 g. of 2-nitro-1 1-(4-methyl-1-piperazlnyl)-dlbenz-[b,f] {l,4]oxazepine obtained according to Example S are hydrogenated with hydrogen in the presence of I g. of 5% palladium-charcoal in 450 ml. of methanol at normal pressure. After take-up of 3.05 1. of hydrogen the hy-drogenation is discontinued and the reaction mixture fil-tered to remove the catalyst. The filtrate is evaporated in vacuo and the residue taken up In chloroform, filtered through aluminum oxide and concentrated. On addition of petroleum ether crystals are formed which are separated
and recrystallized from chloroform/ether/petroleum
ether. 14.1 g. of.2-amino-I l-(4-methyl-1-piperazinyl)-di-benz[b,f] (1,4]oxazepine of melting point 153-156° C. are obtained.
EXAMPLE 10

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and 10 sal. of glacial acetic acid. This solution is treated dropwise while stirring at 0’ C. with a solution of 3.42 g.
of sodium metaperiodate in 10 ml. of water. After the addition is complete the reaction mixture is left to stand at room temperature for 24 hours then made alkaline with concentrated soda lye and shaken out with ether. The ether extracts are -washed with water and then ex-haustively shaken out with dilute hydrochloric acid. The acid extracts are made alkaline with concentrated soda lye

10 and shaken out with chloroform. The chloroform ex-tracts are washed with water, dried over sodium sulphate and evaporated to dryness in vacuo. The residue is dis-solved in acetone and treated with 1.8 g. of maleic acid. After concentration and addition of ether crystals pre-15 cipitate which are recrystallized from methanol/acetone/ether to give 6.0 g. of 2-methylsulphinyl-1 1-(4-methyl-1-piperazinyl)-dibenz[b,f] (1,4]oxazepine.maleate of melt-ing point 206-20.7° C.
EXAMPLE 11
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A solution of 5.2 g. of crude 2.chlorosulphonyl-1 1-(4-methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine, ob-tained as described below, in. 80 ml. of chloroform is treated dropwiso at room temperature with 50 ml. of a 25 10% dimethylarnine solution in. toluene. The reaction mix-ture is stirred for a further 2 hours at room tempera-ture, then for 1 hour at 40° C. and finally evaporated to dryness in vacuo. The residue is taken up in dilute acetic acid, treated with active charcoal and made alkaline with 30 concentrated ammonia solution. The base which separates is taken up in benzene, the benzene solution washed three times with water, dried over sodium sulphate and evapo-rated. The residue Is taken up in benzene and filtered through basic aluminium oxide. The residue obtained after 35 evaporation of the solvent is crystallized from acetone/petroleum ether to give 3.2 g. of 2-diniethylaxninosul-phonyl-1 1-(4 - methyl-1-piperazinyl) - dibenztb,f] [1,4] ozazepine of melting point 148-150° C. which is identi-cal to the product obtained according to Example 6.
40 2-cblorosulphonyl-1 1-(4 - methyl-1-piperazinyl)-dibenz-[b,f] [1,4]oxazepine used as starting material is obtained
as follows:
15.4 g. of 2-amino-i l-(4-methyl-1-piperazinyl)-di-benz-[b,f] [i,4]oxazepine (M.P 153-156° C.) are dis-solved in SO ml. of glacial acetic acid and 15 ml. of 38% hydrochloric acid and diazotized in the usual manner at 0°-50 C. with a solution of 3.6 g. of sodium nitrite in 6 ml, of water. The diazonium solution obtained is added within a few minutes while stirring at 10° C. to 40 ml. of a 30% solution of sulphur dioxide in glacial acetic acid containing 2 g. of cuprous chloride. After the development of nitrogen subsides at room temperature the reaction mixture is warmed for 15 minutes at 40° C. The reaction mixture is then diluted to 1:1 with water and treated with active charcoal. While stirring and cooling carefully, the basic fraction Is precipitated with concentrated soda lye and taken up in chloroform. The chloroform extracts are washed once with dilute soda lye and once with water, dried over sodium sulphate and evaporated. Crude 2-00 chlorosulphonyl - 11 - (4 - friethyl-1-piperazinyi)-dibenz [b,f] [l,4]-oxazepfne is obtained as residue.
EXAMPLE 12

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The free base obtained from 6.83 g. of 2-tbiomethyl-1 1-(4methy1-1-piperazlnyl)-dibeflZ[b,f) (1,4]oxazepine male-ate (M.P. 198-201° C.) is dissolved in 40 ml. of water 75

5.4 g. of 2-dimethylamlnosnlphonyl-1 l-(1-piperazinyl)- dibenz[b,f] (l,4]oxazepine obtained according to Ex-ample 50 are dissolved in 50 ml. of acetone and treated with I g. of anhydrous potassium carbonate and 2.24g. of ethyl iodide in 20 ml. of acetone and refiuxed for 3 hours while stirring. The reaction mixture is then evaporated in vacuo and the residue distributed between dilute soda lye and ether. The other extracts are washed with water and exhaustively shaken out with dilute aqueous hydrochloric acid, The acid extracts are made alkaline with concen-trated soda lye and shaken out with chloroform. The chloroform extracts are washed with water, dried over

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Substitneits

in the boo- nxampla B or Ri respectively sine nuclei Physical constants

 CWi---OB,---OORi 2-NO2 M.P.of the base 102-ifl4 C (from rip). 48. CE,--OR 2SOW(C, ILP. f the base: l84-168 C.

(from a/ep).
40. O-OR=CEs 2.SON(Ca) M.P. of the base: 150-lW C.

(from alp) 80. R 2SOiN(OEi)i M.P. ci the

C.

(from c/p).

Production of tablets (B)

ventionmethyl

For the manufacture of tablets, the products of thisIn- can be mixed with lactose and granulated with, e Y m19?sU

Y,; - Iii I’

10 water, 05% sodium alginate or 1% gelatlne solution The g

UIYIJ UIUCflZEU, IL,rjoxazepme ---------70

dried granulate is compressed into tablets in the presence
of about 5% of talcum, 5% of corn starch and 0.1% of C----------------------------------- magnesium stearate In this way, there are obtained g 4CUUI -------------------------------------
tablets of the following composition Magnesium stearate --------------------------- 01

(A) 20 These 90 mg. tablets, which are provided with a crack- Mg line, can be administered orally in a dosage of one half

2. chioro - 11 - (4-methyl-1-piperazmyl)-dibenz to two tablets one to three times per day in the treatment

(b,f] [1,4]oxazcpme -----------------------2 of subjects suffering from nausea and vomiting follow- Lactose ------------------------------------34 ing operations or ray treatment or due to stomach or Corn starch ----------------------------------2 25 metabolism disorders, intoxications, drug incompatability, Talcum ------------------------------------ 2pressure on the brain or pregnancy. These tablets may Magnesium stearate ------------------------005 also bc used prophylactically against post operative vomit-
These 40 rug tablets possess neuroleptic action They are Weclaim administered orally in a dosage of 3 to 6 tablets per, day SO 1 A compound selected from the class consisting of for the treatment of agitated conditions In psychotic (A): It - basic substituted dlbenz(b,f] [1,4]oxazepines patients. (fl) having the general Formula A:

Mg. Ri
11 - (4 methyl - I - pzperamnyl)-dzbenz-fb,f] t 1,4] 35 I
oxazepine ---------------------------------30
Lactose -------------------------------------160
Cornstarch ----------------------------------10
Talcum -------------------------------------10 N

Magnesium stearate -------------------------02 40
ion

These 210 mg. tablets possess neuroleptic action. They are administered orally in a dosage of S to 10 tablets per C)05

day for the treatment of agitated conditions in psychotic
patients. wherein R Is a member of the class consisting of hydro-
(C) 45 gen, lower alkyl, lower hydroxyalkyl, acetylated lower
Mg hydroxyalkyl, and alkoxyalkyl having not more than 5
2 - intro - 11 - (4 methyl - 1 - piperazinyl) dibenz carbon atoms, and (B) derivatives of (A) substituted in
[b,f] (1,4]oxazepine -------------------------25 a benzene nucleus at the 2-position by a member of the
Lactose --------------------------------------115 class consisting of halogen, triuoroxnethyl, lower alkyl,
Corn starch ---------------------------------- 1.5 lOwer a1kox3r and lower alkytbio; and (C) the non-tonic
Talcum -------------------------------------75 pharmaceutically acceptable acid addition salts of (A)
Magnesium stearate --------------------------0.15 and (B),

2. A compound selected from the consisting of (A): These 155 mg tablets, which are provided with a crack- 11 - basic substituted dsbenz[b,f] [l,4]oxazepmes having line, can be administered orally in a dosage of one half 55 the general Formula A

to two tablets two to four times per day in the treatment
of subjects suffering from any form of scblzcipbrenia, any,
form of mania, severe psychotic and non-psychotic states /M\

of excitement, chorea, atbetosis, and extrapyramidal move- ment disorders. 00
(1)) N
Mg. nil
2 - ultra - 11 - (1 - piperazinyl) - dibenz[b,f][1,4]
oxazep:ne --------------------------------20
Lactose ------------------------------------120 05 Cr_0*
Cornstarch ---------------------------------75

Talcum -------------------------------------75 wherein R? Is a member of the class consisting of alkyl
Magnesium stearate -------------------------015 having not more than 3 carbon atoms, hydroxyalkyl hay-
ing not more than 3 carbon atoms, alkoxyalkyl having not
These 155 jug tablets, which are provided with a cinch- 70 more than 6 carbon atoms and alkoyloxyalkyl having not
line can be administered orally In the dosage of one- more than 6 carbon atoms, and R.2 is a member of the
half to two tablets two to five times, in some cases up group consisting of halogen, lower alkyl, lower alkoxy,
to 5 times 4 tablets per day an the treatment of inbjectslower alkylthzo, and trafluoromethyl and (B) the non-
suffering from states of mental depression and especially toxic pharmaceutically acceptable acid addition salts of
agitated forms of depression. 75 (A).

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3. A compound selected from the class consisting of 6. 2- bronze

11

(4- methyl

I.. piperazinyl).-dlbenz (A)z 11-basic substituted dibenz[b,f] U,4]oxazepines of [b,f] LI,4]oxazepine. and its non-toxin pharmaceutically the Formula A: acceptable acid addition salts.

7. 4- chloro

11

(4 -methyl

I

piperazlnyl)-dlbenz

tb,f] [1,4]oxazepine and its non-toxic pharmaceutically acceptable acid addition salts.
I I

S. 8

chioro

11

(4

methyl

1

plperaz!nyl)-dibenz
I J (b,1) [j,4]oxazepine
and its. non-toxic pharmaceutically acceptable acid addition salts.
10 9. 2- fluoro

11.- (4 -methyl.- I
piperazinyl)-dibenz (b,f] [l,4joxazepine
and its non-toxic pharmaceutically LJ o__l,,J acceptable acid addition salts.
R!’I Is a member of the class consisting of alkyl References Cited
having not more than 3 carbon atoms and hydroxyalkyl ig UNITED STATES PATENTS

having not more than 3 carbon atoms, and R"5 is a mem- her of the group consisting of halogen, and methyl; 3,107,261 10/1963 Gerber et at --------260-153
and (B) the non-toxic pharmaceutically acceptable acid 3,347,849 10/1967 ShaUtu ------------260-239
3,412,193 11/1968 Coppola ----------- 26o-26aX addition salts of (A).
4. 11

(4 methyl

1

pxperazmyl)

clibenz[b,f](l,41

3,444,169 $/1969 Howell -------------260-268

oxazepine and its non-toxic pharmaceutically acceptable DONALD G. DAVIS, Primary Examiner
acid addition salts.
5. 2- chioro

11 r (4- methyl

1

piperazlnyl)-dibenz U.S. Cl. X.R.

tb,fJ E1,4]ozazepinc and its non-toxic pharmaceutically ac- 260-140, 333, 335,.453, 465.6, 558, 687, 689, 691, 694; ceptable acid addition salts. 25 424-258

1. INTERS PARA ATUAR

Conforme a to dispuesto en el articulo 42 de La DecisiOn 486 de 2000 de la. CAN, estando dentro del tØrmino estipulado por La ley, manifiesto el legitimo interØs de nuestra representada para oponerse at registro de la patente de Ia referencia, atendiendo a que La solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizarÆ mÆs adelante y de set concedida afectaria directamente la comercializaciOn de algunos productos de ml representada, que contienen, en particular quetiapina. Por to tanto, solicito respetuosamente a ese Despacho se sirva tenet en cuenta la presente oposiciOn deritro del trÆmite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.11a. solicitud objeto de Ia presente fue presentada el 12 de enero de 2006, reivindicando prioridad bajo la solicitud US60/484,365 del 2 de julio de 2003 y fue publicada en Colombia, en la Gaceta de la. Propiedad Industrial No 577 del 29 de junio de 2007, pÆgina481, No publicacion 25, cuya publicacion internacional corresponde a la W02005002586 del 13 de enero de 2005

2.2,La solicitud colombiana 06 002.323 objeto de la presente oposiciOn, se refiere a una composiciOn oral que comprende 11-piperazin-1-ildibenzo[b,fl[1,4]tiazepina o una sal farmacØuticamente aceptable de la misma junto con por to menos un portador o diluyente farmacØuticamente aceptable, en don& dicho compuesto de la fOrmula I estÆ presente en dichacomposiciOn) eLi una caritidad efectiva para el tratamiento de por to menos un sintoma o condicion asociada con esquizofrenia,

Carrera 13 No 11995, Oficina 104 Tel. (571)2 13 12 13 - Fax (571)6 12 19 79 E-mail: negocios@optimurn-cocom www.opthnum-co.com Bogota Colombia

3. PRUEBAS

De conformidad con to dispuesto pot las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

D1:US3546226 publicada el 8 de diciembre de 1970.

4. FU1DAMENTO DE DERECHO

Fundamento esta observaciOn en las normas legales siguientes:

4.1. Numeral 1 del articulo 586 del COdigo de Comercio.

4.2. Articulo 42 de la DecisiOn 486 de La ComisiOn del Acuerdo de Cartagena.

4.3, En las demÆs normas concordantes.

5. ANIEXOS

Para los efectos correspondierites anexo at presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita at representante legal de PROCAPS S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

D1:US3546226 publicada el 8 de diciembre de 1970.

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Bogota Colombia