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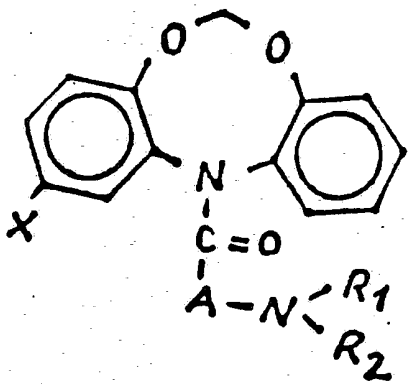
(54) 12-aminoalkanoyl-dibenzo [d,g] [1,3,6] dioxazocines and a process for the preparation thereof

(57) Aminoalkanoyl-dibenzo-[d,g] [1,3,6] dioxazocines of the formula



(I)

wherein
X is hydrogen or halo;
A is a valence bond or a C_{1-10} straight or branched chained alkylene;
R_1 and R_2 are independently hydrogen, C_{1-4} alkyl or C_{3-6} cycloalkyl; or
R_1 and R_2 together with the nitrogen they are attached to and optionally with one or more further nitrogen, oxygen and/or sulfur atoms (s) form a 5- to 6- membered heterocyclic group optionally substituted with C_{1-4} alkyl and pharmaceutically acceptable acid addition salts thereof, *have local anaesthetic, tranquillo-sedative, antiparkinsonic antiarhythmic and antianginous activity.*

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NOVEL AMINOALKANOYL-DIBENZO[d,g][1,3,6]DIOXAZOCINES AND A PROCESS FOR THE PREPARATION THEREOF

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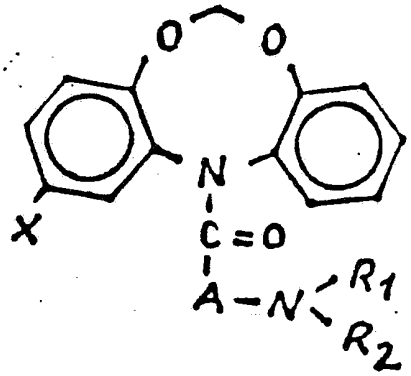
The invention relates to novel aminoalkanoyl-dibenzo[d,g][1,3,6]dioxazocines, a process for the preparation thereof and pharmaceutical compositions comprising such active substances.

The novel compounds possess valuable pharmaceutical properties such as local anaesthetic, tranquillo-sedative and/or antidepressant, antiparkinsonic, furthermore anti-arrhytmic and antianginous activities.

12-Aminoalkyl-12H-dibenzo[d,g][1,3,6]dioxazocines having local anaesthetic and antiparkinsonic activities are described in the US-Pat. No. 4,208,410.

It was found that the pharmaceutical activity of the known compounds can be favourably modified by substituting the ring nitrogen by an aminoalkanoyl group instead of an aminoalkyl group.

Thus, the invention provides for the novel compounds of the formula



(I)

wherein

X represents hydrogen or halo,

A stands for a valence bond or a straight or branched chained alkylene having 1 to 10 carbon atoms,

R_1 and R_2 independently represent hydrogen, an alkyl having 1 to 4 carbon atoms or a cycloalkyl having 3 to 6 carbon atoms, or

R_1 and R_2 together with the nitrogen atom they are attached to and optionally with one or more further nitrogen, oxygen and/or sulfur atom(s) form a 5- to 6-membered heterocyclic group optionally substituted with an alkyl having 1 to 4 carbon atoms,

and pharmaceutically acceptable acid addition salts thereof.

In the specification and Claims, halo means fluoro, chloro, bromo or iodo.

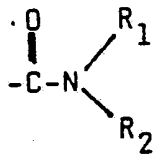
The straight or branched chained alkylene having 1 to 10 carbon atoms is for example methylene, ethylene, isopropylene, n-propylene, n-butylene, isobutylene, pentylene, hexylene, heptylene, octylene, nonylene or decylene group.

The alkyl having 1 to 4 carbon atoms can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl or tert.-butyl.

The cycloalkyl having 3 to 6 carbon atoms can be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The 5- to 6-membered heterocyclic group is preferably piperazine, piperidine, pyrrolidine or morpholine. The heterocyclic group can be substituted with an alkyl group having 1 to 4 carbon atoms, preferably a methyl group.

If A stands for a valence bond, the group of the formula



is attached directly to the ring nitrogen.

The compounds of the formula (I) may form pharmaceutically acceptable acid addition salts. For the salt formation, suitable inorganic or organic acids are for example hydrogen chloride, hydrogen bromide, sulphuric acid, acetic acid, fumaric acid, lactic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, citric acid etc.

The compounds of the formula (I) may comprise one or more chiral carbon atom(s), depending on the meaning of A. In such cases, optically active isomers may exist. The invention relates to the optically active antipodes and any mixtures thereof.

Preferred compounds of the invention are compounds of the formula (I) wherein

X represents hydrogen or halo,

A stands for a valence bond or an alkylene having 1 to 3 carbon atoms,

R_1 and R_2 independently represent hydrogen, an alkyl having 1 to 3 carbon atoms or a cycloalkyl having 3 to 6 carbon atoms, or

R_1 and R_2 together with the nitrogen they are attached to and optionally with an oxygen atom form a 4-methylpiperazinyl, 2-methylpiperidinyl, pyrrolidinyl or

morpholinyl group,

and pharmaceutically acceptable acid addition salts thereof.

Especially preferred compounds of the formula (I) are as follows:

12H-12-/(4-methylpiperazinyl)-acetyl/-dibenzo/d,g/1,3,6/-dioxazocine,

12H-2-chloro-12-/(4-methylpiperazinyl)-acetyl/-dibenzo-/d,g/1,3,6/dioxazocine,

(±)-12H-2-chloro-12-/(2-methylpiperidinyl)-acetyl/-dibenzo-/d,g/1,3,6/dioxazocine,

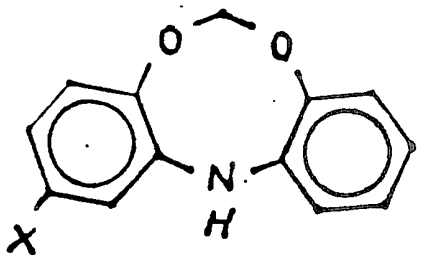
12H-12-diethylcarbamoyl-2-chloro-dibenzo/d,g/1,3,6/-dioxazocine,

12H-2-chloro-12-/3-(diethylamino)propionyl/-dibenzo/d,g/-/1,3,6/dioxazocine,

and pharmaceutically acceptable acid addition salts thereof.

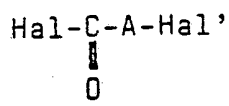
The compounds of the formula (I) are prepared as follows:

a) a dibenzo/d,g/1,3,6/dioxazocine of the formula



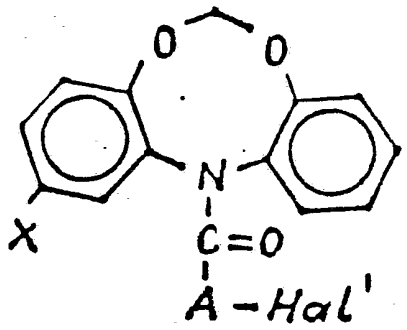
(II)

wherein X is as defined above, is acylated with a compound of the formula



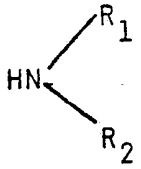
(III)

wherein A is as defined above, Hal and Hal' independently represent a halo, and the obtained alkanoyl-dibenzo[d,g][1,3,6]dioxazocine of the formula



(IV)

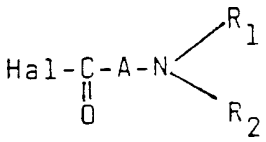
wherein X, A and Hal' are as defined above, is reacted with an amine of the formula



(VIII)

wherein R_1 and R_2 are as defined above; or

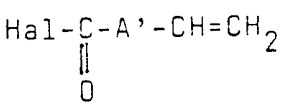
b) a dibenzo[d,g][1,3,6]dioxazocine of the formula (II) is acylated with a compound of the formula



(V)

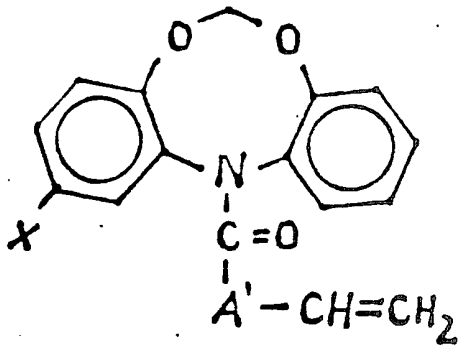
wherein A, R_1 and R_2 are as defined above, Hal stands for a halo; or

c) a dibenzo[d,g][1,3,6]dioxazocine of the formula (II) is acylated with a compound of the formula



(VI)

wherein Hal stands for halo, A' represents a valence bond or a straight or branched chained alkylene having 1 to 8 carbon atoms, and the obtained compound of the formula



(VII)

wherein X and A' are as defined above, is reacted with an amine of the formula (VIII);

and, if desired, a compound of the formula (I) is converted into an acid addition salt with a pharmaceutically acceptable inorganic or organic acid, or from an acid addition salt the compound of the formula (I) is deliberated with a base.

In the compounds of the formulae (III), (IV), (V) and (VI) halo is preferably chloro or bromo.

The dibenzo/-d,g7/-1,3,6/dioxazocines of the formula (II) which are used as starting compounds for the preparation of the compounds of the invention are prepared as described in US-Pat. No. 4,208,410.

The compounds of the formulae (III), (V), (VI) and (VIII) are known reagents being commercially available or they can be prepared by known methods.

In process a) of the invention, the compound of the formula (II) is acylated in apolar or dipolar aprotic solvents, preferably benzene, toluene, xylene or dimethylformamide, in the presence or absence of an acid binding agent. The acylating agent of the formula (III) is employed in an equivalent amount or in excess relative to the amount of the dibenzo/-d,g7/-1,3,6/dioxazocine of the formula (II).

It is preferred to acylate the compound of the formula (II) in toluene, generally at a temperature of 60 to 110 °C with the compound of the formula (III) which is used in an excess of 200 to 300 per cent.

The omega-halo-alkanoyl-dibenzo/-d,g7/-1,3,6/dioxazocine of the formula (IV) which is formed in the acylation reaction is reacted in a polar, apolar or dipolar solvent with the amine of the formula (VIII). Preferably benzene, toluene, xylene, isopropanol or dimethylformamide is employed as the solvent. The amine of the formula (VIII) can be employed in an equimolar amount or in excess. The excess of the amine of the formula (VIII) can bind the hydrogen halide formed in the

reaction. However, other usual acid binding agents can be used for this purpose, too.

The acid binding agent used both in the acylation and amination can be a suitable inorganic base e.g. sodium carbonate, potassium carbonate etc., or a suitable organic base such as a tertiary amine e.g. triethylamine, N,N-diisopropyl-N-ethylamine, pyridine etc.

It is preferred to react the compound of the formula (IV) in benzene with an excess of the amine of the formula (VIII).

Process a) of the invention can be performed starting from a metal salt of the compound of the formula (II). In this case, the compound of the formula (II) is reacted with e.g. sodium hydride or sodium amide in a dipolar aprotic solvent, suitably dimethylformamide, to give the corresponding sodium salt thereof which is acylated, in general, at 0 to 40 °C. Of course, in the acylation, no further acid binding agent is necessary.

In process b) of the invention, the compound of the formula (II) is acylated with the compound of the formula (V) in a similar way, generally at 0 to 140 °C.

It is preferred to prepare the alkali metal salt of the compound of the formula (II) at first, then to react it with an excess of the compound of the formula (V) at a temperature of 0 to 50 °C.

In process c) of the invention, the reaction of the compounds of the formulae (II) and (VI) is performed in an apolar organic solvent such as benzene, toluene or xylene,

in general, at 50 to 140 °C. The obtained compound of the formula (VII) is reacted with the amine of the formula (VIII) at atmospheric pressure or under higher pressure. For the reaction, the solvent is an apolar organic solvent or an excess of the amine of the formula (VIII).

In case of compounds of the formula (I) comprising one or more chiral carbon atom(s), the enantiomers can be separated by resolving the racemic compound. To effect this, the racemic compound comprising a basic nitrogen is reacted with an optically active carboxylic acid to give pairs of diastereomeric salts which are separated and the enantiomers are deliberated. As an optically active organic acid practically any carboxylic acid used for resolutions can be employed such as optically active tartaric acid, dibenzoyltartaric acid, lactic acid, atrolactic acid, mandelic acid etc., furthermore optically active sulfonic acids such as 10-camphorsulfonic acid etc.

The enantiomers of the novel aminoalkanoyl-dibenzo-/⁻d,g7/⁻1,3,67dioxazocines comprising a chiral carbon atoms can be also prepared by acylating the compound of the formula (II) with an optically active agent of the formula (III), (V) or (VI).

The compounds of the formula (I) have valuable pharmacological activities as indicated by the following screening tests.

Acute toxicity on white mice

Acute toxicity of the compounds was tested on white mice of both sexes from the strain CFLP in groups consisting of 10 animals weighing 18 to 22 g. The compounds to be tested were administered percrally in a volume of 20 ml/kg. After the administration, the mice were observed for 7 days while keeping them in plastic mouse boxes over a litter made of scrapings at room temperature. The animals could consume tap water and standard mouse feed ad libitum. The LD_{50}-values were determined according to Litchfield and Wilcoxon [J. Pharmacol. Exp. Ther., 96, 99 (1949)]. The results obtained are shown in Table. I.

Table I

Compound (Example No.)	LD_{50} p.o. in mg/kg
1	2000
2	700
3	280
4	2000
5	2000
6	250
7	1000
8	450
9	900
10	900
11	2000

continuation of Table I

Compound (Example No.)	LD_{50} p.o. in mg/kg
12	260
13	300
14	160
15	250
16	250
17	650
18	250
19	370
20	220
21	300

Local anaesthetic activity

The tests were performed according to Truant d'Amato [Acta Chir. Scand., 116, 351 (1958)]. 0.2 ml of a 0.25 or 0.50 per cent solution of the test compound were injected around the nervus ischiadicus, into the centre of the femur. The absence of the motor control of the leg muscles was looked upon as the criterium of anaesthesia. The test animals were mice. The duration of the effect was recorded, and from the dose versus action plot, the concentration at which the activity amounted to 50 per cent (EC_{50}) was determined. In the test, lidocaine [2-diethylamino-2',6'-acetoxy-xylidide] was used for comparison. The results obtained are given in

Table II.

Table II

Compound (Example No.)	EC_{50} in percentage	Duration of the effect at a concentration of 0.25 %	0.50 %
4	0.21	55.8	97.7
8	0.25	51.1	98.8
12	0.15	54.1	107.3
13	0.14	122.1	217.3
14	0.19	83.2	160.0
15	0.16	52.4	113.8
16	0.25	80.0	114.6
18	0.10	85.7	146.4
19	0.22	43.7	73.8
20	0.11	53.5	67.8
21	0.08	93.1	93.1
lidocaine	0.17	23.9	40.1

From Table II it can be seen that most compounds tested are effective in a lower concentration than lidocaine. The duration of effect of all the compounds of the invention is much longer than that of lidocaine in both concentration.

Sleep induced with hexobarbital on mice

Groups consisting of 6 mice each were treated with the compound to be examined, perorally. After one hour,

hexobarbital [5-(1-cyclohexenyl)-1,5-dimethylbarbituric acid] was injected, intravenously, at a dosage of 40 mg/kg. The control group was treated only with hexobarbital to provoke sleep. The duration of sleep was recorded. If the duration of sleep of an animal exceeded that of the mean value of the control group by a factor of 2.5, it was considered as a positive reaction. From the data referring to the animals indicating a positive reaction, the ED_{50}-value was calculated. From the values of LD_{50} and ED_{50}, the therapeutical index was determined for each compound tested. In the test, meprobamate [2-methyl-2-propylpropandiol-1,3-dicarbamate] and chlordiazepoxide [7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide] were used for comparison. The results obtained are summarized in Table III.

Table III

Compound (Example No.)	ED_{50} in mg/kg	Therapeutical index LD_{50}/ED_{50}
1	21.0	95.2
3	25.0	31.2
4	8.5	235.0
6	15.0	16.7
12	30.0	8.7
15	9.8	25.5
19	15.0	24.7

continuation of Table III

Compound (Example No.)	ED_{50} in mg/kg	Therapeutical index LD_{50}/ED_{50}
meprobamate (LD_{50} = 1100 mg/kg)	260.0	4.2
chlordiazepoxide (LD_{50} = 620 mg/kg)	10.0	62.0

From the data given in Table III it can be seen that the therapeutical index of the most effective novel compound (i.e. the compound prepared in Example 4) is higher by one order of magnitude than that of chlordiazepoxide. At the same time, the compounds of the invention are more effective than the meprobamate used as the reference.

Antagonism of tetrabenazine ptosis on mice

The tests were performed according to the method of Hoffmeister et al. which was adapted to mice /-Arzneim.--Forschung, 19, 846-858 (1969)7. Groups consisting of 10 mice each were treated, perorally, with different doses of the compounds to be tested. The control group was treated only with the corresponding carrier. After 30 minutes, tetrabenazine /-3-isobutyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydrobenzo/-a7quinolizine-2-one7 was administered intraperitoneally at a dosage of 50 mg/kg. The number of animals having closed palpebral fissure was determined in each group after

30, 60, 90 and 120 minutes. Then, the mean value of ptosis was calculated in each group, and the deviation from that of the control group (i.e. the inhibition) was expressed in percentage. From the data obtained, the ED_{50}-value and the therapeutical index were determined for each novel compound tested as well as for amitryptiline /5-(3-dimethylaminopropylidine)-10,11-dihydro-5H-dibenzo/a,d/cycloheptene hydrochloride/ employed for comparison. The results obtained are shown in Table IV.

Table IV

Compound (Example No.)	ED_{50} in mg/kg	Therapeutical index LD_{50}/ED_{50}
2	13.0	53.9
11	23.0	86.9
20	13.5	13.6
amitryptiline	12.0	18.7

The therapeutical index of the compounds of the invention is, in general, higher than that of the amitryptiline used for comparison.

Inhibition of nicotine lethality on mice

The tests were performed on white mice using the method of Stone /Arch. Int. Pharmacodyn., 177, 419 (1958)/. The

animals were treated with the compounds to be tested, perorally, then, after 1 hour, nicotine was injected, intravenously, at a dosage of 1.4 mg/kg. The spasms as well as the lethality observed within one hour were recorded, the ED_{50}-value and the therapeutical index were calculated for each novel compound tested and for trihexyphenidyl /-alpha--cyclohexyl-alpha-phenyl-piperidinepropanol hydrochloride/ used for comparison. The results obtained are given in Table V.

Table V

Compound (Example No.)	ED_{50} in mg/kg	Therapeutical index LD_{50}/ED_{50}
1	72	27.8
3	7	111.0
4	35	57.0
5	13	154.0
6	5	50.0
7	15	66.7
8	15	30.0
9	17	52.9
10	21	42.9
trihexyphenidyl	20	18.25

Inhibition of tremor induced by tremorine on mice

The tests were carried out according to Everett /Science, 124, 79 (1956)/. Tremor was induced by tremorine /1,1'-(2-butynylene)-dipyrollidine/ administered intraperitoneally at a dosage of 20 mg/kg. The compounds to be examined were given perorally to the animals one hour prior to the administration of tremorine, and the tremor developed was evaluated 45 minutes after the administration of tremorine. The results are set forth in Table VI.

Table VI

Compound (Example No.)	ED_{50} in mg/kg	Therapeutical index LD_{50}/ED_{50}
1	16.0	125.0
3	15.0	52.0
4	42.0	47.6
7	37.5	26.7
13	4.0	75.0
14	8.1	19.8
trihexyphenidyl	15.0	24.3

Since the inhibition of nicotine lethality and of tremor is characteristic of the antiparkinsonic activity of a substance, from Tables V and VI it can be concluded that the antiparkinsonic activity of the compounds of the invention surpasses that of the known compound used for

comparison, considering either the absolute dosage or the therapeutical index.

Antiarrhythmic activity on rats

The antiarrhythmic activity of the novel compounds was examined by influencing the arrhythmia provoked by aconitine on rats weighing 160 to 200 g according to a modified method of Marmo et al. [Arzneim.-Forsch., 20, 12 (1970)]. The animals were anaesthetized by the administration of 1.2 g/kg of ethyl urethane, intraperitoneally. Aconitine was given at a dosage of 75 µg/kg, intravenously. The compounds to be tested were administered perorally, 30 minutes prior to the treatment with aconitine. The inhibition observed is shown in Table VII in percentage. In the test, lidocaine and quinidine was employed for comparison.

Table VII

Compound (Example No.)	Dose in mg/kg	Inhibition in percentage
3	4	45.5
15	4	54.2
21	4	62.9
lidocaine	4	23.4
quinidine	4	27.3

From Table VII it appears that the antiarrhythmic activity of the compounds of the invention surpasses that of the known compounds used for comparison.

Antianginous activity on rats

The antianginous activity of the compounds was determined on anaesthetized (for this purpose chloralose urethane was used) male rats weighing 180 to 220 g according to Nischultz [Arzneim.-Forsch., 5, 680 (1955)]. An experimental coronary insufficience was developed by the administration of glanduitrine - an extract of the posterior lobe of pituitary - at an intravenous dosage of 4 IU/kg. The height of wave T in ECG was measured before and after the administration of glanduitrine in both the control and treated groups, and the inhibition provided by the compounds tested was calculated. In the test, prenylamine [3,3-diphenylpropyl-1--methylphenetylamine lactate] was used for comparison.

Table VIII

Compound (Example No.)	Dose in mg/kg	Inhibition in percentage
15	2	55.4
21	3	83.6
prenylamine	2	41.3

From the above pharmacological test results it can be concluded that the novel compounds of the formula (I) or the pharmaceutically acceptable acid addition salts thereof can be used as the active substance in pharmaceutical compositions. The pharmaceutical composition of the invention comprises a therapeutically active amount of a compound of the formula (I) or a pharmaceutically acceptable acid addition salt thereof and one or more usual additive(s).

The pharmaceutical composition of the invention, which has especially local anaesthetic, tranquillo-sedative or antiparkinsonic activity, is prepared by admixing a compound of the formula (I) or a pharmaceutically acceptable acid addition salt thereof to one or more pharmaceutically acceptable additive(s) e.g. carrier(s), and converting the mixture obtained to a pharmaceutical composition in a manner known per se. As to the additives and methods see e.g. Remington's Pharmaceutical Sciences, 16th Edition, Mack Publishing Company, Easton, USA, 1980.

In general, the pharmaceutical compositions of the invention are suitable for peroral or parenteral administration or for local treatment, and can be solid or liquid.

The solid pharmaceutical compositions may be powders, capsules, tablets, dragées etc., and can comprise binding agents such as gelatine, sorbitol, polyvinylpyrrolidone etc.; filling agents such as lactose, glucose, starch, calcium phosphate etc.; auxiliary substances for tabletting such as magnesium stearate, talc, polyethyleneglycol, silica etc.; wetting agents such as sodium laurylsulfate etc. as the

additive.

The additives of the liquid pharmaceutical compositions used for oral treatment are preferably suspending agents such as sorbitol, sugar solution, gelatine, carboxymethylcellulose etc.; emulsifiers such as sorbitane monooleate etc.; solvents such as oils, oil esters glycerol, propyleneglycol, ethanol etc.; preservatives such as methyl p-hydroxybenzoate etc.

Pharmaceutical compositions suitable for parenteral administration consist of sterile solutions, in general.

The pharmaceutical composition of the invention contains, in general, 0.1 to 95.0 per cent of the active substance. A typical dose for adult patients amounts to 0.1 to 20 mg of the compound of the formula (I) or a pharmaceutically acceptable acid addition salt thereof, daily. The actual dosage is determined depending on many factors such as the state and person to be treated, the method of treatment etc.

The invention is further elucidated by means of the following Examples.

Example 1

12H-12-/(4-Methylpiperazinyl)-acetyl/-dibenzo/d,g/-/1,3,6/dioxazocine dimaleate

A) A mixture of 30.0 g (0.141 mole) of 12H-12-dibenzo-/d,g/1,3,6/dioxazocine (m. p.: 189 to 191 °C), 150 cm^3 of anhydrous toluene and 19.5 g (0.173 moles) of chloroacetyl chloride is heated to boiling point and refluxed for 2 hours. Then, further 19.5 g (0.173 moles) of chloroacetyl

chloride are added to the reaction mixture that is refluxed for further 4 hours. The mixture is cooled to 25 °C and poured into crushed ice under stirring. After one hour stirring, the solids are filtered, washed with water and recrystallized from isopropanol.

Thus, 35.6 g (87.3 %) of 12H-12-(2-chloroacetyl)-dibenzo/⁻d,g7/⁻1,3,6/7dioxazocine are obtained. M. p.: 151 to 153 °C.

Analysis for $C_{15}H_{12}ClNO_3$ (289.7):

calculated: C 62.19 %, H 4.18 %, Cl 12.24 %, N 4.83 %;

found: C 62.57 %, H 4.12 %, Cl 12.23 %, N 4.77 %.

B) A mixture of 12.0 g (0.041 moles) of 12H-12-(2-chloroacetyl)-dibenzo/⁻d,g7/⁻1,3,6/7dioxazocine, 130 cm^3 of anhydrous benzene and 27.6 g (0.276 moles) of 4-methylpiperazine is refluxed for 6 hours, then cooled to 25 °C, and the salt precipitated is filtered. The organic filtrate is washed with water, dried over anhydrous magnesium sulfate, the solvent is distilled off and the residue is crystallized from isopropanol. The product is recrystallized from isopropanol.

Thus, 9.7 g (66.4 %) of 12H-12-/⁻(4-methylpiperazinyl)-acetyl7-dibenzo/⁻d,g7/⁻1,3,6/7dioxazocine are obtained. M. p.: 160 to 162 °C.

Analysis for $C_{20}H_{23}N_3O_3$ (353.425):

calculated: C 67.97 %, H 6.56 %, N 11.89 %;

found: C 68.14 %, H 7.02 %, N 11.78 %.

C) To a stirred solution of 8.4 g (0.024 moles) of 12H-12-/(4-methylpiperazinyl)-acetyl/7-dibenzo/d,g/7-/1,3,6/dioxazocine in 100 cm^3 isopropanol, a solution of 5.6 g (0.048 moles) of maleic acid in 30 cm^3 of isopropanol is added at 20 °C. The reaction mixture is stirred for 2 hours, then cooled to 0 °C, stirred for a further hour, the product is filtered, washed with isopropanol and recrystallized from methanol.

10.5 g (74.7 %) of the title compound are obtained.

M. p.: 179 to 183 °C.

Analysis for $C_{28}H_{31}N_3O_{11}$ (585.572):

calculated: C 57.43 %, H 5.34 %, N 7.18 %;

found: C 57.38 %, H 5.31 %, N 7.06 %.

Example 2

12H-12-/(N-Cyclohexyl-N-methylamino)-acetyl/7-dibenzo-/d,g/7/1,3,6/dioxazocine maleate

A) A mixture of 13.0 g (0.045 moles) of 12H-12-chloroacetyl-dibenzo/d,g/7/1,3,6/dioxazocine, 150 cm^3 of anhydrous benzene and 32.2 g (0.28 moles) of N-cyclohexyl-N-methylamine is heated under reflux for 8 hours. The product is isolated as described in Example 1, section B) and recrystallized from isopropanol to give 13.9 g (84.2 %) of 12H-12-/(N--cyclohexyl-N-methylamino)-acetyl/7dibenzo/d,g/7/1,3,6/dioxazocine. M. p.: 103 to 105 °C.

Analysis for $C_{22}H_{26}N_2O_3$ (366.463):

calculated: C 72.11 %, H 7.15 %, N 7.64 %;

found: C 72.17 %, H 7.18 %, N 7.60 %.

B) 12.8 g (0.035 moles) of 12H-12-/(N-cyclohexyl-N--methylamino)-acetyl/-dibenzo/d,g/1,3,6/dioxazocine are reacted with 4.2 g (0.036 moles) of maleic acid as described in Example 1, section C). After recrystallization from isopropanol, 14.9 g (88.2 %) of the title compound are obtained. M. p.: 148 to 150 °C.

Analysis for $C_{26}H_{30}N_2O_7$ (482.536):

calculated: C 64.72 %, H 6.27 %, N 5.81 %;

found: C 64.58 %, H 6.34 %, N 5.67 %.

Example 3

12H-12-/2-(Isopropylamino)-acetyl/-2-chloro-dibenzo-/d,g/1,3,6/dioxazocine hydrochloride

A) A mixture of 24.8 g (0.10 moles) of 12H-2-chloro--dibenzo/d,g/1,3,6/dioxazocine (m. p.: 182 to 184 °C), 300 cm^3 of anhydrous toluene and 23.0 g (0.20 moles) of 2-chloroacetyl chloride is heated under reflux for 4 hours. The mixture is cooled to 25 °C, the solvent is removed under reduced pressure, and the residue is rubbed with benzene to induce crystallization. The product is recrystallized from isopropanol to give 23.1 g (71.3 %) of 12H-12-chloroacetyl--2-chloro-dibenzo/d,g/1,3,6/dioxazocine. M. p.: 149 to 151 °C.

Analysis for $C_{15}H_{11}Cl_2NO_3$ (324.2):

calculated: C 55.57 %, H 3.42 %, Cl 21.87 %, N 4.32 %;

found: C 55.48 %, H 3.63 %, Cl 21.95 %, N 4.28 %.

B) A mixture of 15.0 g (0.046 moles) of chloroacetyl derivative prepared in Example 3, section A), 180 cm^3 anhydrous benzene and 17.7 g (0.30 moles) of isopropylamine is heated under reflux for 4 hours. The organic solvent is removed under reduced pressure, the residue is mixed with 100 cm^3 of diethyl ether and 80 cm^3 of water for 30 minutes. The organic phase is separated, dried over anhydrous magnesium sulfate, cooled to 0 °C and treated with diethyl ether saturated with hydrogen chloride under stirring until a pH value of 4 is reached. The crystals are filtered, suspended in diethyl ether and filtered again. The process is repeated twice, and the product is recrystallized from ethanol to give 13.0 g (74.0 %) of the title compound as white crystals. M.p.: 235 to 240 °C.

Analysis for $C_{18}H_{20}Cl_2N_2O_3$ (383.282):
calculated: C 56.41 %, H 5.26 %, Cl 18.50 %, N 7.31 %, Cl^- 9.25 %;
found: C 56.15 %, H 5.60 %, Cl 17.96 %, N 7.16 %, Cl^- 9.08 %.

Example 4

12H-12-/(4-Methylpiperazinyl)acetyl/-2-chloro-dibenzo/d,g/-/1,3,6/dioxazocine dimaleate

A) A mixture of 49.0 g (0.129 moles) of 12H-12-chloro-acetyl-2-chloro-dibenzo/d,g/1,3,6/dioxazocine, 80.0 g (0.80 moles) of 4-methylpiperazine and 410 cm^3 of anhydrous benzene is heated under reflux for 4 hours. Then, the organic solvent and the excess of 4-methylpiperazine are removed under reduced pressure. To the residue, 150 cm^3 of benzene and 10 cm^3 of water are added, the mixture is stirred for

30 minutes, the organic phase is separated and washed with water three times using 80 cm^3 of water each time. 45.0 g (0.30 moles) of tartaric acid in 150 cm^3 of water are added to the organic solution, the mixture is stirred for an hour and the phases are separated. To the aqueous phase, 150 cm^3 of benzene are added, the mixture is stirred and treated with 25 per cent aqueous ammonia until a pH value of 9 to 10 is obtained. Stirring is continued for an hour, then the organic phase is separated, dried over anhydrous magnesium sulfate and the solvent is removed under reduced pressure. The residue is stirred with benzene to induce crystallization, the crystals are filtered, suspended is benzene and filtered again. The product is recrystallized from isopropanol to obtain 38.0 g (76.0 %) of 12H-12-[(4-methylpiperazino)-acetyl]-2-chloro-dibenzo[d,g][1,3,6]-dioxazocine. M. p.: 124 to 127 °C.

Analysis for $C_{20}H_{22}ClN_3O_3$ (387.870):

calculated: C 61.93 %, H 5.72 %, Cl 9.14 %, N 10.83 %;

found: C 62.18 %, H 5.93 %, Cl 9.18 %, N 10.61 %.

B) 34.1 g (0.088 moles) of 12H-12-[(4-methylpiperazinyl)-acetyl]-2-chloro-dibenzo[d,g][1,3,6]dioxazocine are reacted with 20.4 g (0.176 moles) of maleic acid as described in Example 1, section C) to give the acid addition salt. After recrystallization from methanol, 44.2 g (81 %) of the title compound are obtained. M. p.: 188 to 190 °C.

Analysis for $C_{28}H_{30}ClN_3O_{11}$ (620.014):

calculated: C 54.24 %, H 4.88 %, Cl 5.72 %, N 6.78 %;
found: C 54.18 %, H 5.12 %, Cl 5.70 %, N 6.62 %.

Example 5

12H-12-/(N-Cyclohexyl-N-methylamino)-acetyl/-2-chloro-dibenzo/d,g/1,3,6/dioxazocine maleate

A) A mixture of 35.0 g (0.108 moles) of 12H-12-chloroacetyl-2-chloro-dibenzo/d,g/1,3,6/dioxazocine, 350 cm^3 of anhydrous benzene and 2 x 76.9 g (2 x 0.678 moles) of N-cyclohexyl-N-methylamine is heated under reflux for a total of 12 hours. The product is isolated as described in Example 4, section A). The crude product is crystallized, then recrystallized from petroleum ether to obtain 32.1 g (79.8 %) of 12H-12-/(N-cyclohexyl-N-methylamine)-acetyl/-2-chloro-dibenzo/d,g/1,3,6/dioxazocine. M. p.: 93 to 95 °C.
Analysis for $C_{22}H_{25}ClN_2O_3$ (400.909):
calculated: C 65.91 %, H 6.29 %, Cl 8.84 %, N 6.99 %;
found: C 65.60 %, H 7.00 %, Cl 8.89 %, N 6.61 %.

B) 30.0 g (0.075 moles) of 12H-12-/(N-cyclohexyl-N-methylamino)-acetyl/-2-chloro-dibenzo/d,g/1,3,6/dioxazocine are reacted with 8.7 g (0.075 moles) of maleic acid as described in Example 1, section C). The product is recrystallized from methanol to obtain 34.8 g (89.7 %) of the title compound. M.p.: 191 to 193 °C.
Analysis for $C_{26}H_{29}ClN_2O_7$ (516.980):
calculated: C 60.41 %, H 5.65 %, Cl 6.86 %, N 5.42 %;
found: C 61.23 %, H 5.92 %, Cl 6.79 %, N 5.30 %.

Example 6

12H-12-(Diethylamino-acetyl)-2-chloro-dibenzo/d,g7-/1,3,67dioxazocine hydrochloride

A) A mixture of 32.4 g (0.10 moles) of 12H-12-chloro-acetyl-2-chloro-dibenzo/d,g7/1,3,67dioxazocine, 2 x 36.5 g (2 x 0.50 moles) of diethylamine and 250 cm^3 of anhydrous benzene is heated under reflux for 6 hour, altogether. The product is isolated as described in Example 4, section A). The yellowish-brown, viscous liquid obtained as the crude product is crystallized, then recrystallized from n-hexane. Thus, 28.5 g (78.9 %) of 12H-12-(diethylamino-acetyl)-2--chloro-dibenzo/d,g7/1,3,67dioxazocine are obtained.

M.p.: 75 to 80 °C.

Analysis for $C_{19}H_{21}ClN_2O_3$ (360.844):

calculated: C 63.24 %, H 5.87 %, Cl 9.83 %, N 7.76 %;

found: C 63.96 %, H 5.32 %, Cl 9.85 %, N 7.50 %.

B) 19.0 g (0.053 moles) of dioxazocine prepared in Example 6, section A) is treated with isopropanol containing 20 per cent hydrogen chloride to give the corresponding acid addition salt. After crystallization from isopropanol, 17.5 g (82.9 %) of the title compound are obtained. M. p.: 198 to 201 °C.

Analysis for $C_{19}H_{22}Cl_2N_2O_3$ (397.302):

calculated: C 57.44 %, H 5.58 %, Cl 17.85 %, N 7.05 %, Cl^- 8.92 %;

found: C 57.56 %, H 5.84 %, Cl 17.50 %, N 7.06 %, Cl^- 8.88 %.

Example 7

(±)-12H-12-/(2-Methylpiperidinyl)-acetyl/-2-chloro--dibenzo/d,g/1,3,6/dioxazocine hydrochloride

A) A mixture of 32.4 g (0.10 moles) of 12H-12-chloroacetyl-2-chloro-dibenzo/d,g/1,3,6/dioxazocine, 39.7 g (0.40 moles) of 2-methylpiperidine and 250 cm^3 of anhydrous benzene is heated under reflux for 4 hours. The reaction product is isolated as described in Example 4, section A). The crude product is crystallized, then recrystallized from isopropanol to obtain 30.8 g (79.6 %) of (±)-12H-12-/(2--methylpiperidinyl)-acetyl/-2-chloro-dibenzo/d,g/1,3,6/-dioxazocine. M. p.: 90 to 92 °C.

Analysis for $C_{21}H_{23}ClN_2O_3$ (386.882):

calculated: C 65.20 %, H 5.99 %, Cl 9.16 %, N 7.24 %;

found: C 65.01 %, H 6.33 %, Cl 9.15 %, N 7.08 %.

B) 9.6 g (0.0248 moles) of the base prepared in section A) is treated with diethyl ether saturated with hydrogen chloride as described in Example 3, section B) to give 10.3 g (98.1 %) of the title compound. M.p.: 146 to 154 °C (decomposition).

Analysis for $C_{21}H_{24}Cl_2N_2O_3$ (423.342):

calculated: C 59.58 %, H 5.71 %, Cl 16.75 %, N 6.62 %, Cl^- 8.38 %;

found: C 58.45 %, H 6.11 %, Cl 16.92 %, N 6.65 %, Cl^- 8.47 %.

Example 8

12H-12-Pyrrolidinylacetyl-2-chloro-dibenzo/d,g7-/1,3,67dioxazocine maleate

A) A mixture of 22.0 g (0.068 moles) of 12H-12-chloro-acetyl-2-chloro-dibenzo/d,g7/1,3,67dioxazocine, 24.2 g of pyrrolidine and 250 cm^3 of benzene is heated under reflux for 3 hours. The reaction product is isolated as described in Example 4, section A). The crude product is crystallized, then recrystallized from petroleum ether to obtain 19.8 g (81.1 %) of 12H-12-pyrrolidinylacetyl-2-chloro-dibenzo/d,g7-/1,3,67dioxazocine. M. p.: 80 to 83 °C.

Analysis for $C_{19}H_{19}ClN_2O_3$ (358.827):

calculated: C 63.60 %, H 5.34 %, Cl 9.88 %, N 7.81 %;

found: C 63.11 %, H 4.82 %, Cl 9.80 %, N 7.71 %.

B) 14.0 g (0.039 moles) of 12H-12-pyrrolidinylacetyl-2--chloro-dibenzo/d,g7/1,3,67dioxazocine is reacted with 4.6 g (0.04 moles) of maleic acid as described in Example 1, section C). The acid addition salt formed is recrystallized from ethanol to obtain 15.8 g (85.5 %) of the title compound. M.p.: 187 to 192 °C.

Analysis for $C_{23}H_{23}ClN_2O_7$ (474.899):

calculated: C 58.17 %, H 4.88 %, Cl 7.47 %, N 5.90 %;

found: C 58.48 %, H 4.50 %, Cl 7.47 %, N 5.93 %.

Example 9

12H-12-Morpholinylacetyl-2-chloro-dibenzo/d,g/-/1,3,6/dioxazocine maleate

A) A mixture of 25.0 g (0.077 moles) of 12H-12-chloroacetyl-2-chloro-dibenzo/d,g/1,3,6/dioxazocine, 30.4 g (0.35 moles) of morpholine and 250 cm^3 anhydrous benzene is heated under reflux for 3 hours. The reaction product is isolated as described in Example 4, section A). The crude product is crystallized from hexane and recrystallized from isopropanol. 24.9 g (86.2 %) of 12H-12-morpholinylacetyl-2-chloro-dibenzo/d,g/1,3,6/dioxazocine are obtained. M.p.: 123 to 125 °C.

Analysis for $C_{19}H_{19}ClN_2O_4$ (374.827):

calculated: C 60.88 %, H 5.11 %, Cl 9.46 %, N 7.47 %;

found: C 59.70 %, H 5.70 %, Cl 9.52 %, N 7.21 %.

B) 20.0 g (0.053 moles) of 12H-12-morpholinylacetyl-2-chloro-dibenzo/d,g/1,3,6/dioxazocine are treated with 6.2 g (0.053 moles) of maleic acid as described in Example 1, section C) to give the corresponding maleate that is recrystallized from ethanol. Thus, 20.2 g (77.7 %) of the title compound are obtained. M. p.: 197 to 199 °C.

Analysis for $C_{23}H_{23}ClN_2O_8$ (490.898):

calculated: C 56.28 %, H 4.72 %, Cl 7.22 %, N 5.71 %;

found: C 56.71 %, H 4.88 %, Cl 7.23 %, N 5.72 %.

Example 10

12H-12-/2-(Cyclopropylamino)-acetyl/-2-chloro--dibenzo/d,g/1,3,6/dioxazocine maleate

A) A mixture of 25.0 g (0.077 moles) of 12H-12-chloroacetyl-2-chloro-dibenzo/d,g/1,3,6/dioxazocine, 2 x 8.6 g (2 x 0.15 moles) of cyclopropylamine and 200 cm^3 of anhydrous benzene is heated under reflux for 11 hours. The reaction product is isolated as described in Example 4, section A). The crude product is crystallized, then recrystallized from petroleum ether to obtain 18.3 g (69.1 %) of 12H-12-/2-(cyclopropylamino)-acetyl/-2-chloro-dibenzo/d,g/1,3,6/-dioxazocine. M.p.: 80 to 85 °C.

Analysis for $C_{18}H_{17}ClN_2O_3$ (344.800):

calculated: C 62.70 %, H 4.97 %, Cl 10.28 %, N 8.12 %;

found: C 63.02 %, H 4.60 %, Cl 10.35 %, N 8.01 %.

B) 11.4 g (0.033 moles) of base prepared in section A) above are treated with 3.9 g (0.034 moles) of maleic acid as described in Example 1, section C) to give the corresponding maleate that is recrystallized from ethanol to obtain 11.9 g (78.3 %) of the title compound. M.p.: 176 to 181 °C.

Analysis for $C_{22}H_{21}ClN_2O_7$ (460.872):

calculated: C 57.34 %, H 4.59 %, Cl 7.69 %, N 6.08 %;

found: C 57.70 %, H 5.00 %, Cl 7.91 %, N 6.15 %.

Example 11

12H-12-Diethylcarbamoyl-2-chloro-dibenzo/d,g7-/1,3,67dioxazocine

An 50 per cent dispersion of 4.8 g (0.10 moles) of sodium hydride in mineral oil is added to 100 cm^3 of dimethylformamide at 25 °C under stirring. Then, 24.8 g (0.10 moles) of 12H-2-chloro-dibenzo/d,g7/1,3,67dioxazocine are added to the mixture at a constant temperature of 25 °C. The reaction mixture is heated to 40 °C and stirred for an hour at this temperature, then cooled to 20 °C. 20.3 g (0.15 moles) of N,N-diethylcarbamoyl chloride are added to the mixture, then the reaction mixture is stirred for 16 hours at 40 °C. 120 cm^3 of water are added to the mixture cooled to 0 °C. The viscous oil formed is separated, dissolved in 150 cm^3 of benzene, washed with water 3 times using 80 cm^3 of water each time. The organic solution is dried over anhydrous magnesium sulfate, the solvent is removed under reduced pressure, the residue is treated with petroleum ether to induce crystallization. The crude product is recrystallized from isopropanol. Thus, 22.9 g (66.0 %) of the title compound are obtained. M.p.: 93 to 95 °C.

Analysis for $C_{18}H_{19}ClN_2O_3$ (346.823):

calculated: C 62.34 %, H 5.52 %, Cl 10.22 %, N 8.08 %;

found: C 62.83 %, H 5.45 %, Cl 10.48 %, N 8.00 %.

Example 12

12H-12-/3-(4-Methylpiperazinyl)-propionyl/7-2-chloro--dibenzo/d,g/1,3,6/dioxazocine dimaleate

A) A mixture of 24.8 g (0.10 moles) of 12H-2-chloro--dibenzo/d,g/1,3,6/dioxazocine, 150 cm^3 of anhydrous benzene and 25.4 g (0.20 moles) of 3-chloropropionyl chloride is heated under reflux for 5 hours. The solvent is removed under reduced pressure, the residue is dissolved in 150 cm^3 benzene, and the solution obtained is poured into crushed ice. The mixture is stirred for an hour, the organic phase is separated, washed with 4 x 100 cm^3 of 5 percent aqueous sodium bicarbonate solution, then with 100 cm^3 of water. The organic solution is dried over anhydrous magnesium sulfate, the solvent is removed under reduced pressure, and the residue is crystallized with isopropanol. The crude product is recrystallized from isopropanol to give 26.7 g (79.0 %) of 12H-12-(3-chloropropionyl)-2-chloro-dibenzo/d,g/1,3,6/-dioxazocine. M. p.: 76 to 81 °C.

Analysis for $C_{16}H_{13}Cl_2NO_3$ (338.193):

calculated: C 56.82 %, H 3.87 %, Cl 20.97 %, N 4.14 %;

found: C 56.41 %, H 3.30 %, Cl 21.35 %, N 4.04 %.

B) A mixture of 33.8 g (0.10 moles) of 12H-12-(3-chloropropionyl)-2-chloro-dibenzo/d,g/1,3,6/dioxazocine, 60.0 g (0.60 moles) of 4-methylpiperazine and 250 cm^3 of anhydrous benzene is heated under reflux for 5 hours. The reaction product is isolated as described in Example 4, section A). 30.0 g of crude 12H-12-/3-(4-methylpiperazino)-propionyl/7-

-2-chloro-dibenzo/d,g/1,3,6/dioxazocine are obtained as a brown, viscous liquid.

C) 30.0 g of the crude base prepared in section B) above is reacted with 18.6 g (0.16 moles) of maleic acid as described in Example 1, section C) to give the corresponding salt that is recrystallized from methanol. Thus, 24.6 g (67.0 %) of the title compound are obtained. M.p.: 185 to 187 °C.

Analysis for $C_{29}H_{32}ClN_3O_{11}$ (634.041):
calculated: C 54.94 %, H 5.09 %, Cl 5.59 %, N 6.63 %;
found: C 54.74 %, H 5.46 %, Cl 5.56 %, N 6.52 %.

Example 13

12H-12-/3-(Diethylamino)-propionyl/-2-chloro-dibenzo-/d,g/1,3,6/dioxazocine hydrochloride

A) A mixture of 33.8 g (0.10 moles) of 12H-12-(3-chloro-propionyl)-2-chloro-dibenzo/d,g/1,3,6/dioxazocine, 2 x 29.2 g (2 x 0.40 moles) of diethylamine and 250 cm^3 of anhydrous benzene is heated under reflux for 6 hours, altogether. The reaction is performed and the reaction product is isolated as described in Example 4, section A). The crude product is crystallized, then recrystallized from n-hexane to obtain 30.9 g (82.5 %) of 12H-12-/3-(diethylamino)-propionyl/-2--chloro-dibenzo/d,g/1,3,6/dioxazocine. M. p.: 68 to 72 °C.

Analysis for $C_{20}H_{23}ClN_2O_3$ (374.870):
calculated: C 64.08 %, H 6.18 %, Cl 9.46 %, N 7.47 %;
found: C 63.52 %, H 6.61 %, Cl 9.59 %, N 7.25 %.

B) 18.7 g (0.05 moles) of 12H-12-/3-(diethylamino)-propionyl/-2-chloro-dibenzo/d,g/1,3,6/dioxazocine are dissolved in 70 cm^3 of isopropanol. To the stirred solution cooled to 0 °C, isopropanol comprising 20 per cent gaseous hydrogen chloride in dissolved form is added until a pH value of 3. The mixture is stirred for an hour, the crystals are filtered and recrystallized from isopropanol. Thus, 17.9 g (81.0 %) of the title compound are obtained. M. p.: 176 to 182 °C.

Analysis for $C_{20}H_{24}Cl_2N_2O_3$ (441.329):

calculated: C 58.40 %, H 5.88 %, Cl 17.24 %, N 6.81 %, Cl^- 8.62 %;

found: C 58.12 %, H 6.07 %, Cl 17.12 %, N 6.68 %, Cl^- 8.66 %.

Example 14

12H-12-/3-(Isopropylamino)-propionyl/-2-chloro-dibenzo/d,g/1,3,6/dioxazocine hydrochloride

A mixture of 30.0 g (0.089 moles) of 12H-12-(3-chloropropionyl)-2-chloro-dibenzo/d,g/1,3,6/dioxazocine, 2 x 21.0 g (2 x 0.356 moles) of isopropylamine and 250 cm^3 of anhydrous benzene is heated under reflux for 6 hours, altogether. The reaction is performed and the reaction product is isolated as described in Example 4, section A) to obtain 28.5 g 12H-12-/3-(isopropylamino)-propionyl/-2-chloro-dibenzo/d,g/1,3,6/dioxazocine as a viscous liquid.

The dioxazocine base is converted to the hydrochloride as described in Example 3, section B). After recrystalliza-

tion from ethanol, 25.8 g (73.0 %) of the title compound are obtained. M. p.: 240 to 243 °C.

Analysis for $C_{19}H_{22}Cl_2N_2O_3$ (397.301):

calculated: C 57.44 %, H 5.58 %, Cl 17.86 %, N 7.05 %, Cl^- 8.93 %;

found: C 57.66 %, H 5.45 %, Cl 17.86 %, N 6.98 %, Cl^- 8.92 %.

Example 15

12H-12-(3-Pyrrolidinyl-propionyl)-2-chloro-dibenzo-/⁻d,g7/⁻1,3,67dioxazocine maleate

A) A mixture of 25.0 g (0.074 moles) of 12H-12-(3-chloro-propionyl)-2-chloro-dibenzo/⁻d,g7/⁻1,3,67dioxazocine, 21.3 g (0.30 moles) of pyrrolidine and 250 cm^3 of anhydrous benzene is heated under reflux for 3 hours. The reaction product is isolated as described in Example 4, section A), the crude product is crystallized from petroleum ether and recrystallized from the same solvent to obtain 21.8 g (79.0 %) of 12H--12-(3-pyrrolidinyl-propionyl)-2-chloro-dibenzo/⁻d,g7/1,3,67-dioxazocine. M. p.: 115 to 118 °C.

Analysis for $C_{20}H_{21}ClN_2O_3$ (372.854):

calculated: C 64.43 %, H 5.68 %, Cl 9.51 %, N 7.51 %;

found: C 64.00 %, H 5.12 %, Cl 9.61 %, N 7.40 %.

B) 20.0 g (0.054 moles) of the base prepared in section A) above is reacted with 6.4 g (0.055 moles) of maleic acid as described in Example 1, section C) to give the corresponding salt that is recrystallized from ethanol. Thus, 22.7 g

(85.9 %) of the title compound are obtained. M. p.: 161 to 164 °C.

Analysis for $C_{24}H_{25}ClN_2O_7$ (488.926):

calculated: C 58.96 %, H 5.15 %, Cl 7.25 %, N 5.73 %;

found: C 59.52 %, H 5.28 %, Cl 7.35 %, N 5.79 %.

Example 16

12H-12-/3-(Cyclopropylamino)-propionyl/-2-chloro--dibenzo/d,g/1,3,6/dioxazocine hydrochloride

A mixture of 25.0 g (0.074 moles) of 12H-12-(3-chloropropionyl)-2-chloro-dibenzo/d,g/1,3,6/dioxazocine, 2 x 8.7 g (2 x 0.16 moles) of cyclopropylamine and 250 cm^3 of anhydrous benzene is heated under reflux for 15 hours, altogether. The reaction is performed and the reaction product is isolated as described in Example 4, section A) to obtain 21.7 g of 12H-12-/3-(cyclopropylamino)-propionyl/-2-chloro-dibenzo/d,g/1,3,6/dioxazocine as a viscous liquid.

The dioxazocine base obtained above is converted to the hydrochloride as described in Example 3, section B). After recrystallization from ethanol, 18.7 g (64.0 %) of the title compound are obtained. M. p.: 196 to 204 °C.

Analysis for $C_{19}H_{20}Cl_2N_2O_3$ (395.288):

calculated: C 57.73 %, H 5.10 %, Cl 17.94 %, N 7.09 %, Cl^- 8.97 %;

found: C 58.34 %, H 5.38 %, Cl 18.18 %, N 7.10 %, Cl^- 8.89 %.

Example 17

12H-12-(3-Morpholinylpropionyl)-2-chloro-dibenzo-/-d,g7/-1,3,6/dioxazocine hydrochloride

A) A mixture of 25.0 g (0.074 moles) of 12H-12-(3-chloro-propionyl)-2-chloro-dibenzo/-d,g7/-1,3,6/dioxazocine, 30.4 g (0.35 moles) of morpholine and 250 cm^3 of anhydrous benzene is heated under reflux for 5 hours. The reaction product is isolated as described in Example 4, section A) and crystallized in n-hexane. The crude product is recrystallized from isopropanol to obtain 23.9 g (83.0 %) of 12H-12-(3-morpholinyl-propionyl)-2-chloro-dibenzo/-d,g7/-1,3,6/dioxazocine. M. p.: 122 to 125 °C.

Analysis for $C_{20}H_{21}ClN_2O_4$ (388.854):

caculated: C 61.78 %, H 5.44 %, Cl 9.12 %, N 7.20 %;

found: C 60.98 %, H 5.93 %, Cl 9.21 %, N 7.03 %.

B) 15.0 g (0.0386 moles) of 12H-12-(3-morpholinylpropionyl)--2-chloro-dibenzo/-d,g7/-1,3,6/dioxazocine is converted to the hydrochloride as described in Example 3, section B). After recrystallization from ethanol, 13.5 g (82.3 %) of the title compound are obtained. M. p.: 225 to 229 °C.

Analysis for $C_{20}H_{22}Cl_2N_2O_4$ (425.315):

calculated: C 56.48 %, H 5.21 %, Cl 16.67 %, N 6.59 %, Cl^- 8.34 %;

found: C 56.92 %, H 5.35 %, Cl 16.77 %, N 6.55 %, Cl^- 8.36 %.

Example 18

(±)-12H-12-[2-(4-methylpiperazinyl)-propionyl]-2-chloro-dibenzo[d,g][1,3,6]dioxazocine maleate

A) A mixture of 123.9 g (0.50 moles) of 12H-2-chloro-dibenzo[d,g][1,3,6]dioxazocine, 750 cm^3 of anhydrous toluene and 127.0 g (1.00 mole) of 2-chloropropionyl chloride is heated under reflux for 3 hours. The reaction product is isolated as described in Example 3, section A). After recrystallization from isopropanol, 131.1 g (77.5 %) of (±)-12H-12-(2-chloropropionyl)-2 chloro-dibenzo [d,g] [1,3,6]dioxazocine are obtained. M. p.: 152 to 155 °C.

Analysis for $C_{16}H_{13}Cl_2NO_3$ (338.201):

calculated: C 56.82 %, H 3.87 %, Cl 20.97 %, H 4.14 %;

found: C 56.32 %, H 3.99 %, Cl 21.20 %, H 4.10 %.

B) A mixture of 20.0 g (0.059 moles) of chloropropionyl-dioxazocine prepared in section A) above, 2 x 25.1 g (2 x 0.25 moles) of 4-methylpiperazine and 200 cm^3 of anhydrous benzene is heated under reflux for 11 hours, altogether. The reaction is performed and the reaction product is isolated as described in Example 4, section A). The crude product is treated with petroleum ether to induce crystallization, and the crystals are recrystallized from isopropanol. Thus, 18.8 g (79.2 %) of (±)-12H-12-[2-(4-methylpiperazinyl)-propionyl]-2-chloro-dibenzo[d,g][1,3,6]dioxazocine are obtained. M. p.: 133 to 136 °C.

Analysis for $C_{21}H_{24}ClN_3O_3$ (401.896):

calculated: C 62.76 %, H 6.02 %, Cl 8.82 %. N 10.46 %;

found: C 61.98 %, H 6.60 %, Cl 8.93 %, N 10.20 %.

C) 13.0 g (0.032 moles) of the dioxazocine base prepared in section B) above is reacted with 7.6 g (0.066 moles) of maleic acid as described in Example 1, section C) to give the acid addition salt. After recrystallization from ethanol, 17.1 g (84.2 %) of the title compound are obtained. M. p.: 177 to 182 °C.

Analysis for $C_{29}H_{32}ClN_3O_{11}$ (634.041):

calculated: C 54.94 %, H 5.09 %, Cl 5.59 %, N 6.63 %;

found: C 55.27 %, H 4.89 %, Cl 5.63 %, N 6.61 %.

Example 19

(±)-12H-12-(2-Pyrrolidinylpropionyl)-2-chloro-dibenzo-/⁻d,g7/⁻1,3,6/7dioxazocine hydrochloride

A) A mixture of 28.0 g (0.083 moles) of (±)-12H-12-(2--chloropropionyl)-2-chloro-dibenzo/⁻d,g7/⁻1,3,6/7dioxazocine, 21.3 g (0.30 moles) of pyrrolidine and 250 cm^3 of anhydrous benzene is heated under reflux for 10 hours. The reaction product is isolated as described in Example 4, section A). The crude product is treated with petroleum ether to induce crystallization, and the crystals are recrystallized from the same solvent. Thus, 24.9 g (80.3 %) of (±)-12H-12-(2-pyrrolidinylpropionyl)-2-chloro-dibenzo/⁻d,g7/⁻1,3,6/7dioxazocine are obtained. M.p.: 98 to 102 °C.

Analysis for $C_{20}H_{21}ClN_2O_3$ (372.854):

calculated: C 64.43 %, H 5.68 %, Cl 9.51 %, N 7.51 %;

found: C 63.89 %, H 6.03 %, Cl 9.60 %, N 7.43 %.

B) 16.0 g (0.043 moles) of the dioxazocine base prepared in section A) above is converted to the hydrochloride as described in Example 3, section B). After recrystallization from isopropanol, 14.2 g (80.7 %) of the title compound are obtained. M.p.: 223 to 225 °C.

Analysis for $C_{20}H_{22}Cl_2N_2O_3$ (409.315):

calculated: C 58.69 %, H 5.42 %, Cl 17.32 %, N 6.84 %, Cl^- 8.66 %;

found: C 59.03 %, H 5.88 %, Cl 16.93 %, N 6.91 %, Cl^- 8.47 %.

Example 20

(±)-12H-12-(2-Isopropylaminopropionyl)-2-chloro--dibenzo[d,g][1,3,6]dioxazocine hydrochloride

A) A mixture of 23.7 g (0.070 moles) of (±)-12H-12-(2--chloropropionyl)-2-chloro-dibenzo[d,g][1,3,6]dioxazocine, 17.7 g (0.21 moles) of isopropylamine and 250 cm^3 of anhydrous benzene is heated under reflux for 6 hours. The reaction product is isolated as described in Example 4, section A). The crude product is treated with petrol to induce crystallization, and the crystals are recrystallized from the same solvent. Thus, 18.2 g (72.1 %) of (±)-12H-12-(2--isopropylaminopropionyl)-2-chloro-dibenzo[d,g][1,3,6]-dioxazocine are obtained. M. p.: 102 to 105 °C.

Analysis for $C_{19}H_{21}ClN_2O_3$ (360.843):

calculated: C 63.24 %, H 5.87 %, Cl 9.83 %, N 7.76 %;

found: C 62.85 %, H 6.13 %, Cl 9.98 %, N 7.61 %.

B) 10.0 g (0.0277 moles) of dioxazocine base prepared in section A) above is converted to the hydrochloride as described in Example 3, section B). After recrystallization from isopropanol, 9.6 g (87.3 %) of the title compound are obtained. M. p.: 224 to 227 °C.

Analysis for $C_{19}H_{22}Cl_2N_2O_3$ (397.304):

calculated: C 57.44 %, H 5.58 %, Cl 17.85 %, N 7.05 %, Cl^- 8.92 %;

found: C 57.44 %, H 5.70 %, Cl 17.63 %, N 6.94 %, Cl^- 8.90 %.

Example 21

(±)-12H-12-/2-Methyl-3-(4-methylpiperazinyl)-propionyl/-2-chloro-dibenzo/d,g/1,3,6/dioxazocine dimaleate

A) A mixture of 26.1 g (0.11 moles) of 12H-2-chloro-dibenzo/d,g/1,3,6/dioxazocine, 300 cm^3 of anhydrous toluene and 39.0 g (0.21 moles) of 3-bromo-2-methylpropionyl chloride is heated under reflux for 8 hours, then cooled to 25 °C, and poured into 300 g of crushed ice under stirring. The mixture is stirred for 2 hours, the organic phase is separated, washed with 3 x 100 cm^3 of 5 per cent aqueous sodium bicarbonate and 100 cm^3 of water, and dried over anhydrous magnesium sulfate. The solvent is removed under reduced pressure, the residue is treated with isopropanol to induce crystallization, and the crystals are recrystallized from the same solvent. Thus, 33.2 g (76.1 %) of (±)-12H-12-(3-bromo-2-methylpropionyl)-2-chloro-dibenzo/d,g/1,3,6/-

dioxazocine are obtained. M.p.: 115 to 119 °C.

Analysis for $C_{17}H_{15}BrClNO_3$ (396.688):

calculated: C 51.47 %, H 3.81 %, Br 20.15 %, Cl 8.94 %, N 3.53 %;

found: C 51.35 %, H 3.98 %, Br 20.20 %, Cl 8.90 %, N 3.52 %.

B) A mixture of 28.6 g (0.072 moles) of the bromomethyl-propionyl-dioxazocine prepared in section A) above, 2 x 30.0 g (2 x 0.295 moles) of 4-methylpiperazine and 250 cm^3 of anhydrous benzene is heated under reflux for 7 hours, altogether. The reaction is performed and the reaction product is isolated as described in Example 4, section A). The crude product is treated with petroleum ether to induce crystallization, and the crystals are recrystallized from n-hexane to obtain 25.3 g (84.6 %) of (±)-12H-12-/-2-methyl-3-(4-methylpiperazinyl)-propionyl7-2-chloro-dibenzo/-d,g7/-1,3,67-dioxazocine. M. p.: 128 to 131 °C.

Analysis for $C_{22}H_{26}ClN_3O_3$ (415.921):

calculated: C 63.53 %, H 6.30 %, Cl 8.52 %, N 10.10 %;

found: C 62.80 %, H 6.75 %, Cl 8.63 %, N 9.87 %.

C) 9.0 g (0.022 moles) of the dioxazocine base prepared in section B) above is reacted with 5.2 g (0.045 moles) of maleic acid as described in Example 1, section C) to give the acid addition salt. After recrystallization from acetonitrile, 11.8 g (82.5 %) of the title compound are obtained. M.p.: 152 to 157 °C.

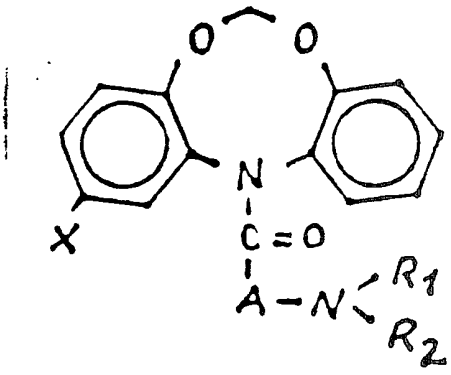
Analysis for $C_{30}H_{34}ClN_3O_{11}$ (648.068):

calculated: C 55.60 %, H 5.29 %, Cl 5.47 %, N 6.48 %;

found: C 55.78 %, H 5.52 %, Cl 5.42 %, N 6.42 %.

CLAIMS

1. Novel aminoalkanoyl-dibenzo/-d,g7/-1,3,67di-oxazocines of the formula



(I)

wherein

X represents hydrogen or halo,

A stands for a valence bond or straight or branched chained alkylene having 1 to 10 carbon atoms,

R_1 and R_2 independently represent hydrogen, an alkyl having 1 to 4 carbon atoms or a cycloalkyl having 3 to 6 carbon atoms, or

R_1 and R_2 together with the nitrogen they are attached to and optionally with one or more further nitrogen, oxygen and/or sulfur atom(s) form a 5- to 6-membered heterocyclic group optionally substituted with an alkyl having 1 to 4 carbon atoms,

and pharmaceutically acceptable acid addition salts thereof.

2. Compounds of the formula (I) as claimed in Claim 1, wherein

X represents hydrogen or halo,

A stands for a valence bond or an alkylene having 1 to 3 carbon atoms,

R_1 and R_2 independently represent hydrogen, an alkyl having 1 to 3 carbon atoms or a cycloalkyl having 3 to 6 carbon atoms, or

R_1 and R_2 together with the nitrogen they are attached to and optionally with an oxygen form a 4-methyl-piperazinyl, 2-methyl-piperidinyl, pyrrolidinyl or morpholinyl group.

3. 12H-12-/(4-methylpiperazinyl)-acetyl/-dibenzo-/d,g/-1,3,6/dioxazocine and pharmaceutically acceptable acid addition salts thereof.

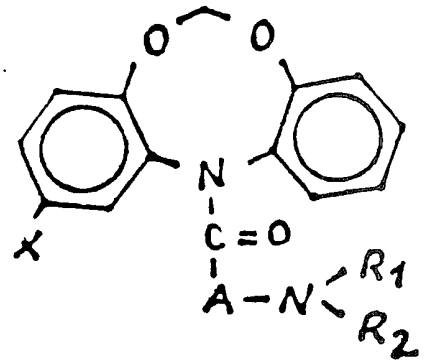
4. 12H-2-Chloro-12-/(4-methylpiperazinyl)-acetyl/--dibenzo/d,g/-1,3,6/dioxazocine and pharmaceutically acceptable acid addition salts thereof.

5. (±)-12H-2-Chloro-12-/(2-methylpiperidinyl)-acetyl/--dibenzo/d,g/-1,3,6/dioxazocine and pharmaceutically acceptable acid addition salts thereof.

6. 12H-12-Diethylcarbamoyl-2-chloro--dibenzo/d,g/-1,3,6/dioxazocine and pharmaceutically acceptable acid addition salts thereof.

7. 12H-2-Chloro-12-/3-(diethylamino)propionyl/--dibenzo/d,g/-1,3,6/dioxazocine and pharmaceutically acceptable acid addition salts thereof.

8. A process for the preparation of novel aminoalkanoyl--dibenzo/d,g/-1,3,6/dioxazocines of the formula



(I)

wherein

X represents hydrogen or halo,

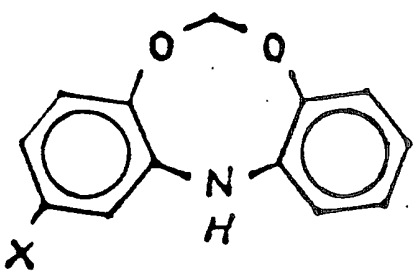
A stands for a valence bond or a straight or branched chained alkylene having 1 to 10 carbon atoms,

R_1 and R_2 independently represent hydrogen, an alkyl having 1 to 4 carbon atoms or a cycloalkyl having 3 to 6 carbon atoms, or

R_1 and R_2 together with the nitrogen they are attached to and optionally with one or more further nitrogen, oxygen and/or sulfur atom(s) form a 5 to 6 membered heterocyclic group optionally substituted with an alkyl having 1 to 4 carbon atoms,

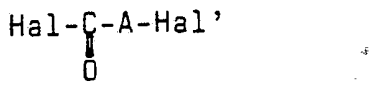
and pharmaceutically acceptable acid addition salts thereof, in which

a) a dibenzo/d,g/1,3,6/dioxazocine of the formula



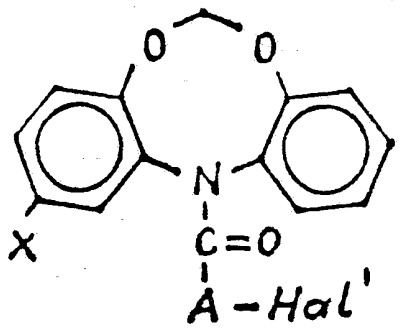
(II)

wherein X is as defined above, is acylated with a compound of the formula



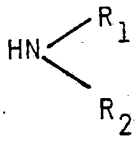
(III)

wherein A is as defined above, Hal and Hal' independently represent a halo, and the obtained alkanoyl-dibenzo/⁻d,g7-/⁻1,3,67dioxazocine of the formula



(IV)

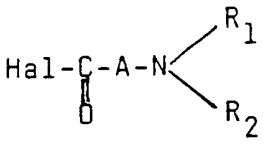
wherein X, A and Hal' are as defined above, is reacted with an amine of the formula



(VIII)

wherein R_1 and R_2 are as defined above; or

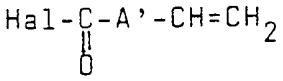
b) a dibenzo/⁻d,g7/⁻1,3,67dioxazocine of the formula (II) is acylated with a compound of the formula



(V)

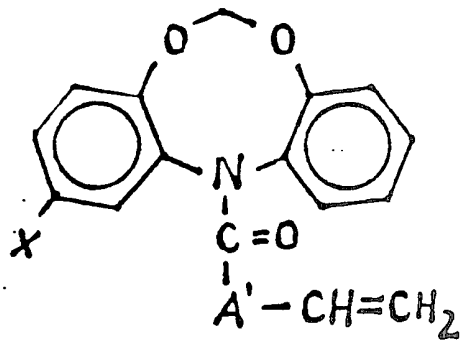
wherein A, R_1 and R_2 are as defined above, Hal stands for halo; or

c) a dibenzo/d,g/1,3,6/dioxazocine of the formula (II) is acylated with a compound of the formula



(VI)

wherein Hal stands for halo, A' represents a valence bond or a straight or branched chained alkylene having 1 to 8 carbon atoms, and the obtained compound of the formula



(VII)

wherein X and A' are as defined above, is reacted with an amine of the formula (VIII);

and, if desired, a compound of the formula (I) is converted into an acid addition salt with a pharmaceutically acceptable inorganic or organic acid, or from an acid addition salt the compound of the formula (I) is deliberated with a base.

9. Compounds as claimed in claim 1 which are substantially as hereinbefore described in any one of Examples 1 to 21.

10. A pharmaceutical composition having local anaesthetic, tranquillo-sedative or antiparkinsonic activity, comprising a therapeutically effective amount of a compound or salt as claimed in any one of claims 1 to 7 or 9 in admixture with one or more pharmaceutically acceptable carrier(s).

11. Compounds as claimed in any one of claims 1 to 7 or 9 for use in treating the human or animal body by way of therapy.

12. Use of the compounds as claimed in any one of claims 1 to 7 or 9 in the preparation of a medicament having local anaesthetic, tranquillo-sedative or antiparkinsonic activity.

13. A process as claimed in claim 8 substantially as hereinbefore described in any one of Examples 1 to 21.

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