United States Patent [19]

van der Burg

[11] **3,892,695**

[45] **July 1, 1975**

[54] **PYRIMIDINO-DIBENZO-AZEPINE,-OXAZEPINE,-THIAZEPINE AND DIAZEPINE DERIVATIVES**

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[52] **U.S. Cl.**.. **260/251 A**; 260/239 D; 260/239 DD; 260/256.4 F; 424/251

[51] **Int. Cl.**[2] **C07D 471/04**

[58] **Field of Search** ..... 260/251 A, 256.4 F

[56] **References Cited**

UNITED STATES PATENTS

3,470,181 9/1969 Wei et al. 260/251

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[57] **ABSTRACT**

Compounds of the formula:

in which

X represents oxygen, sulphur, the group NR_4 or the group $-CR_5R_6-$,

r and *s* stand for an integer from 0–4,

R_1 and R_2 represent halogen, hydroxy, an alkyl or alkoxy group with 1–6 carbon atoms, a trifluoromethyl group or an acyloxy group with 1–8 carbon atoms,

R_3 means hydrogen, an alkyl group with 1–6 carbon atoms, an aralkyl group with 7–10 carbon atoms or an aryl group, and

R_4, R_5 and R_6 stand for hydrogen or an alkyl group with 1–6 carbon atoms,

as well as the acid addition salts and quaternary ammonium compounds thereof. These compounds exert a potent antidepressive and anxiolytic activity.

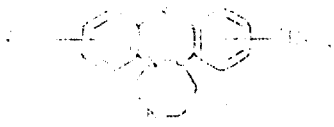
3 Claims, No Drawings

PYRIMIDINO-DIBENZO-AZEPINE,-OXAZEPINE,-THIAZEPINE AND DIAZEPINE DERIVATIVES

The present invention relates to novel biologically active pyrimidino derivatives. More particularly it relates to hexahydro-pyrimidino-dibenzo-azepines and tetrahydro-pyrimidino-dibenzo-oxazepines, -thiazepines and -diazepines.

From the British Pat. No. 1,229,252 compounds are known differing from the present compounds in that they contain a piperazine instead of a pyrimidino ring. These known piperazine derivatives possess potent antihistamine and antiserotonine activity.

Surprisingly it has now been found that the present pyrimidino derivatives of the general formula:



3

in which

r and s stand for an integer from 0–4,

R_1 and R_2 represent hydroxy, halogen, alkyl or alkoxy with 1–6 carbon atoms, acyloxy with 1–8 carbon atoms, or a trifluoromethyl group,

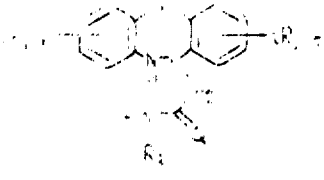
R_3: hydrogen, an alkyl group with 1–6 carbon atoms, an aralkyl group with 7–10 carbon atoms or an aryl group,

X: oxygen, sulphur, the guoup N—R_4 or the group —CR_5R_6—, and

R_4, R_5, R_6: hydrogen or a lower alkyl group with 1–6 carbon atoms,

as well as the pharmaceutically acceptable acid addition salts and pharmaceutically acceptable quaternary ammonium compounds thereof, have a completely different pharmacological profile. The compounds according to this invention snow, fully contrary to the compounds described in the said British patent, a positive effect in the reserpine antagonism test, which means that they possess anti-depressant activity, whereas the antihistamine and anti-serotonine activity of the present compounds is considerably lowered in comparison with the strong antihistamine and/or antiserotonine activity of the compounds described in the British patent.

The compounds according to the invention can be prepared by any method commonly used for this type of compounds. They are, however, prepared most conveniently starting from a substance with the general formula:

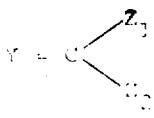


or an acid addition salt thereof, in which

X, R_1, R_2, R_3, r and s have the meanings indicated previously, and

Q means hydrogen (H_2) or oxygen.

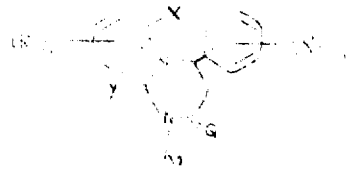
The starting substance II is cyclisized by means of a condensation with a reagent of the formula:



III

in which

Y represents hydrogen (H_2), oxygen or sulphur and Z_1 and Z_2 represents the same or different, reactive or leaving groups, or may be together a bivalent reactive group, that can be eliminated together with the hydrogen atoms attached to both nitrogen atoms of the diamine II, so forming a compound of the formula:



in which X, Y, Q, R_1, R_2, R_3, r and s have the aforesaid meanings.

In general, the groups Z_1 and Z_2 may represent halogen, a substituted or unsubstituted amino group, a free, etherified or esterified hydroxy or mercapto group or Z_1 and Z_2 together may represent sulphur or oxygen.

If Y represents hydrogen (= H_2), Z_1 and Z_2 stand preferably for halogen or hydroxy groups. Reagents III belonging to this type of compounds are, for example, methylenechloride, methylenebromide or methylene diol (= formaldehyde solution in water or a water containing solvent).

If Y represents oxygen or sulphur the most suitable moieties for Z_1 and Z_2 are halogen, substituted or unsubstituted amino groups, an etherified or sulphonylated hydroxy or mercapto group, or Z_1 and Z_2 together are sulphur (in combination with Y = sulphur). Suitable reagents III belonging to this type of compounds are, for example, phosgene, thiophosgene, haloformic esters such as ethylchloroformate, esters of carbonic acid such as dimethyl- or diethylcarbonate, urea and urea derivatives such as thiourea or N,N'-carbonyl-di-imidazole, and carbondisulphide.

Preferably methylenehalide or formaldehyde (in water) is used as the reagent III in the present condensation reaction if the starting compound II does not contain a keto group (Q = H_2), because they yield the desired final product according to the invention in a direct way.

If a reagent according to the formula III, in which Y represents oxygen or sulphur and/or a starting compound II, in which Q stands for oxygen is (are) used, the resulting compound must be reduced additionally to obtain the desired final product. For such a reduction any suitable reducing agent can be used, for example, metal hydrides such as sodium hydride, lithium aluminium hydride or diborane. Said reduction can also be preformed catalytically by hydrogenation in the presence of a metal or a metal compound.

If Z_1 and/or Z_2 represent halogen, an agent capable of eliminating the hydrogenhalide formed during the

condensation reaction, such as pyridine, triethylamine, etc., is usually added to the reaction mixture.

The condensation reaction can be performed in any suitable solvent. Where methylenehalide is used as the reagent III, special preference is given to an aprotic polar solvent, such as dimethylsulfoxide, sulfolane or acetonitril. It is also possible, however, to perform the condensation exclusively in the reagent III, so ina(additional) solvent. In certain cases, e.g. in the absence of any (additional) urea is used as the reagent III, the condensation can be carried out in a melt.

The starting substances of formula II required in the present invention can be prepared by any process described for similar compounds. Thus, for example, the compound 6-chloro-methyl-11H-dibenzo[b,e]azepine can be reacted with a cyanate, for example sodiumcyanate. The resulting nitrile may then either be reduced to the corresponding amino compound optionally followed by introduction of the desired R_3-group, so yielding a compound II with Q = H_2, or be hydrolysed and optionally followed by introduction of the R_3-group, so forming a compound II in which Q = oxygen.

The acid addition salts of the compounds according to the invention are prepared in conventional manner by reacting the free base with a pharmaceutically acceptable acid such as hydrochloric acid, hydrobromic acid or hydroiodic acid, phosphoric acid, acetic acid, propionic acid, glycollic acid, maleic acid, malonic aicd, succinic acid, tartaric acid, citric acid, ascorbic acid, salicylic acid or benzoic acid.

The pharmaceutically acceptable quaternary ammonium compounds, in particular the lower (1–4C) alkyl quaternary ammonium compounds, are obtained by reacting the compounds of the general formula I with an alkyl halide, for example methyl iodide or methyl bromide.

From the above general formula I it appears that the compounds according to the invention possess an asymmetrical carbon. Consequently optical antipodes are possible, also forming part of this invention. Said optical antipodes can be isolated from the racemic mixtue in a conventional manner. It is also possible to resolve the racemic starting product II into its optical antipodes and to perform the condensation reaction after that, or to resolve an intermediate product obtained during the aforesaid synthesis of the compounds I.

It is of course possible to introduce or modify the substituents at one or both phenyl nuclei after the condensation reaction. Thus, for example, a hydroxy group present can be acylated or converted into an alkoxy group, an amino group into a halogen group, a methyoxy group into a hydroxy group, etc.

The substituent (R_3) at the N^{10}-nitrogen atom can also be obtained after the condensation reaction by alkylating or aralkylating the unsubstituted nitrogen atom (R_3 = H) or by acylating the unsubstituted nitrogen atom followed by a reduction of the carbonyl moiety of the N-acyl compound thus obtained.

It is also quite obvious and well-known in the art to convert the aklyl- or aralkyl substituted N^{10}-nitrogen atom (of formula I) into the unsubstituted nitrogen, for example by heating with chloroformic ester, followed by hydrolysis of the compound thus obtained.

The compounds according to the present invention have as already mentioned a completely different pharmacological profile with respect to the related known piperazinederivatives as described in the British Pat. No. 1,229,252.

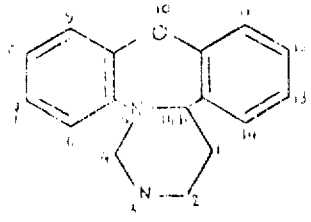
The present compounds show a positive effect in the reserpine-antagonism test and in the reserpine-reversal test, which means that they can be applied as antidepressive agents. The present compounds possess more generally strong CNS stimulatroy properties which together with their effects against agression means that the compounds of the present invention have also potent anxiolytic properties.

They can be administered both orally and parenterally, preferably in a dosage of between 0.01 and 10 mg per kg body weight. Mixed with suitable auxiliaries the compounds can be compressed into said dosage units, such as pills, tablets and coated tablets. They can also be processed into capsules, mixed with auxiliaries if desired. By means of suitable liquids the compounds I can be applied as injection preparations in the form of solutions, emulsions or suspensions.

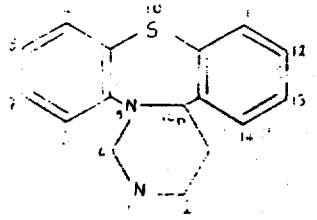
Compounds which are preferably used in the present invention are:

3-methyl-1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-a]debenzo-[c,f]azepine,
3-methyl-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]dibenzo-[b,f](1,4)oxazepine,
3,11-dimethyl-1,3,4,14b-tetrahydro-2H-pyrimidino-[3,4-d]dibenzo-[b,f](1,4e)oxazepine. HCl,
3-methyl-7-trifluoromethyl-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]dibenzo[b,f](1,4)thiazepine,
3-methyl-13-chloro-1,3,4,14b-tetrahydro-2H-pyrimidino-[3,4-d]dibenzo[b,f](1,4)oxazepine,
3, 10-dimethyl-13-methoxy-1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-d]dibenzo[b,f](1, 4)diazepine.

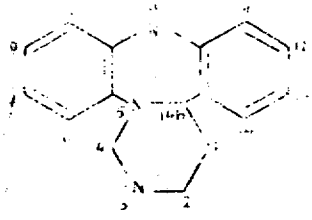
The following examples serve to illustrate the invention further. In the examples the following nomenclature and numbering have been used:



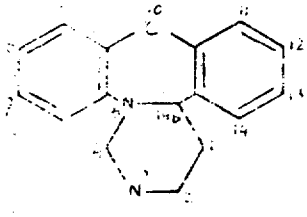
1,3,4,14b-tetrahydro-2H-pyrimidino [3,4-d] dibenzo[b,f](1,4)oxazepine.



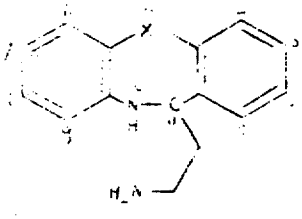
,3,4,14b-tetrahydro-4H-pyrimidino
,3,4-c] dibenzo[b,f](1,5)thiazepine.



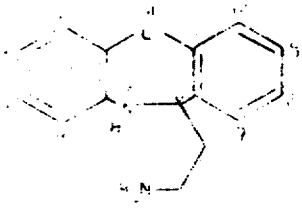
,,,4,10,14b-hexahydro-pyrimi
,3,4-a] dibenzo[b,f](1,4)diazepine.



1,2,3,4,10,14b-hexahydro-pyrimi
,3,4-a] dibenzo[c,f]azepine.



X = O: 11-aminoethyl-10,11-dihy
dibenzo[b,f](1,4)oxazepine
X = S: 11-aminoethyl-10,11-dihyd
dibenzo[b,f](1,4)thiazepine
X = N: 11-aminoethyl-10,11-dihy
5H-dibenzo[b,e](1,4)diazepi



6-aminoethyl-5,6-dihydro-11H-
dibenzo[b,e]azepine or
6-aminoethyl-5,6-dihydro-mo
thridine

EXAMPLE I

3-methyl-1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-a]dibenzo [c,f]azepine.fumarate

Two grams of the diamine 6-methylaminoethyl-5,6-dihydro11H-dibenzo[b,e]azepine (melting point 124-127°C) are dissolved in 25 ml of 96% ethanol. Then 10 ml of a 35% formaldehyde solution in water are added, after which the mixture is left to stand for 30 minutes. Then this mixture is poured into 250 ml of water, after which the mixture is extracted with methylene chloride.

The extract is washed with water and dried on sodium sulphate, after which the CH_2Cl_2-phase is evaporated (oil) and the residue dissolved in 10 ml of ethanol.

This solution is added to a solution of 1.5 g of fumaric acid in ethanol. The resulting precipitate is filtered, washed and dried (1.7 g) and then recrystallized from ethanol.

Melting point: 189°–192°C.
Rf in benzene:methanol (9:1) = 0.48 on SiO_2.

EXAMPLE II

1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-a]-dibenzo[c,f]-azepine and HCL salt

In the same manner as described in example I 2 g of the diamine 6-aminoethyl-5,6-dihydro-11H-dibenzo[b,e]-azepine (m.p. 152°–153°C) are dissolved in 10 ml of a 35% formaldehyde solution in water. The solution is set aside at 20°C for 30 minutes, after which it is poured out into 250 ml of water and extracted 3x with methylene chloride, washed with water and evaporated by means of a film evaporator. The remaining oil is purified by means of a chromatographic column (the solvent mixture is benzene:methanol (9:1)). Rf in benzene:methanol (8:2) = 0.50 on SiO_2.

Then the resulting oil is dissolved in as little HCL-containing alcohol as possible, after which the solution is cooled down. The crystals formed are filtered off.

Melting point: 212°–217°C.

EXAMPLE III

Resolution of: 3-methyl-1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-a]-dibenzo[c,f]-azepine

Racemic 3-methyl-1,2,3,4,10,14b-hexahydro-pyrimidino-[3,4-a]-dibenzo[c,f]-azepine (oil from example I, 1.7 g) is dissolved in 20 ml of ethanol. To this solution a solution of 1.3 g of (+)-dibenzoyl tartaric acid, also in 20 ml of ethanol, is added. After 4 days the precipitate formed is filtered and washed with ethanol. Then the precipitate is treated with an 1N sodium hydroxide solution and ether. The ether layer is separated out, washed with water, dried over sodium sulphate and evaporated. Of the remaining oil the rotation is determined.

$[\alpha_D]^{25} = -437°$ ($c = 0.1$ in ethanol).

The treatment of the oil described above is repeated twice to obtain a compound of $[\alpha_D]^{25} = -496°$ ($c = 0.1$ in ethanol). Melting point: 101°–103°C.

In the same manner the (+) rotating isomer is obtained by reacting the racemate with (−)-dibenzoyl tartaric acid. $[\alpha_D]^{25} = +492°$ ($c = 0.1$ in methanol).

EXAMPLE IV

By the process described in example I the following substances are prepared:

1. 3-methyl-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]dibenzo[b,f](1,4)oxazepine.HCl, melting point: 215°–218°C;
2. 13-chloro-3-methyl-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]dibenzo[b,f](1,4)oxazepine.HCl, melting point: 220°–222°C;
3. 3,11-dimethyl-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]-dibenzo[b,f](1,4)oxazepine.HCl, melting point: 219°–222°C;
4. 3-methyl-7-trifluoromethyl-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]dibenzo[b,f](1,4)thiazepine.HBr, melting point: 190°–193°C;
5. 3,7-dimethyl-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]-dibenzo[b,f](1,4)oxazepine.-maleate, melting point: 164°–166°C;
6. 3, 13-dimethyl-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]-dibenzo[b,f](1,4)oxazepine.

EXAMPLE V

3, 10-dimethyl-1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-d]dibenzo[b,f](1,4)diazepine derivatives

One gram of the diamine 5-methyl-11-methylaminoethyl-10,11-dihydro-5H-dibenzo[b-,e](1,4)diazepine is dissolved in 20 ml of 90% ethanol. To this solution 5 ml of a 35% formaldehyde solution in water is added. The mixture is left to stand for 1 hour at room temperature and after that poured out into 150 ml of water. Extraction with methylene chloride and evaporation of this CH_2Cl_2-phase gives the free base as an oil.

Rf in methanol = 0.35 on SiO_2. Iodomethylate: melting point 212°–215°C.

Starting from the diamine: 2-methoxy-5-methyl-11-methyl-aminoethyl- 10,11-dihydro-5H-dibenzo[b,e](1,4)diazepine (melting point HBr-salt 207°–208°) the free base 3,10-dimethyl-13-methoxy-1,2,3,4,14b-hexahydro-pyrimidino[3,4-d]-dibenzo[b,f](1,4)diazepine is obtained as an oil in the same way. Melting point picrate 103°–108°C.

Rf in methanol = 0.45 on SiO_2.

A quantity of this substance is the converted into the fumarate (see example I), melting point 210°–215°C, another quantity into the iodomethylate (melting point: 204°–207°C) by means of CH_3J.

EXAMPLE VI

By the same process as described in example II are prepared:

1. 1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]dibenzo[b,f](1,4)oxazepine.HCl; melting point 199°–204°C. RF in methanol = 0.90 on SiO_2.
2. 7-trifluoromethyl-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]dibenzo[b,f](1,4)thiazepine; melting point 123°–126°C. RF in benzene:ethyl acetate (7:3) = 0.25 on SiO_2.
3. 10-methyl-13-methoxy-1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-d]dibenzo[b,f](1,4)diazepine (oil). Rf in methanol = 0.51 on SiO_2. Rf in ethyl acetate = 0.40 on SiO_2.
4. 11-methyl-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]-dibenzo[b,f](1,4)oxazepine.maleate; melting point 177°–179°C.
5. 8-methoxy-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]dibenzo[b,f](1,4)oxazepine (oil). Rf in methanol = 0.45 on SiO_2.
6. 8-hydroxy-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]dibenzo[b,f](1,4)oxazepine. Rf in methanol = 0.25 on SiO_2.
7. 7-methyl-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]dibenzo[b,f](1,4)oxazepine.maleate; melting point 164°–166°C.
8. 3,7-dimethyl-13-chloro-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]dibenzo[b,f](1,4)oxazepine (oil).

EXAMPLE VII

3-ethyl-1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-a]dibenzo[c,f]azepine.HCl (direct route)

In the same manner as described in example I the diamine 6-ethylaminoethyl-5,6-dihydro-11H-dibenzo[b,e]azepine is dissolved in ethanol. The solution is treated with a formaldehyde solution and the mixture extracted with methylene chloride. The methylene chloride extracts are washed and dried, after which the resulting residue is dissolved in HCl-containing ethanol. The resulting crystals are recrystallized from ethanol.

Yield 72%; melting point: 198°–200°C.

Rf in ethylacetate = 0.15 on SiO_2.

In the same manner the corresponding 3-benzyl and 3-phenyl derivatives are prepared.

EXAMPLE VIII

3-ethyl-1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-a]dibenzo[c,f]azepine.HCl (indirect route)

1.3 g of 1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-a]dibenzo[c,f]azepine (example II) are acylated in benzene by means of 2 ml of acetic anhydride.

After 30 minutes' stirring at 20°C, the solution is evaporated and the residue purified by means of column chromatography (solvent ethylacetate; column silicagel).

The resulting oil, the N-acetyl derivative of the starting substance, has an Rf value of 0.48 in ethylacetate.

Of this oil 0.8 g is dissolved in 10 ml of tetrahydrofuran and gently added to a suspension of 0.5 g of $LiAlH_4$ in 25 ml of tetrahydrofuran. Then the mixture is refluxed for one hour, after which it is cooled down. Then 2 ml of water are added.

The precipitate formed is filtered off and the filtrate evaporated. The resulting residue is dissolved in HCl-containing alcohol, after which the product is allowed to crystallise out.

Yield 0.5 g. Melting point: 196°–200°C.
Rf in ethylacetate = 0.16 on SiO_2.

A mixture of the substances (3-ethyl derivatives) prepared in examples VII and VIII melts at 196°–200°C.

EXAMPLE IX

3-methyl-1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-a]dibenzo [c,f]azepine

A mixture of 2.4 g of 6-methylaminoethyl-5,6-dihydro-11H-dibenzo[b,e]azepine, 10 ml methylene chloride, 2 ml of triethylamine (TEA) and 10 ml of dimethylsulfoxide (DMSO) is refluxed for 5 hours. The excess of methylene chloride, TEA and a large quantity of the DMSO are distilled off in vacuum. The remaining liquid is diluted with water and then extracted with ether. The etherial solution is then washed with water, dried and evaporated to dryness.

The residue is treated with fumaric acid in ethanol. Melting point fumarate: 188°–191°C.

EXAMPLE X

In the same manner as described in example IX are prepared:

1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-a]dibenzo[c,f]azepine.HCl (melting point: 215°–216°C)

3,7-dimethyl-1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-a]dibenzo[c,f]azepine, (oil)

3-methyl-8-methoxy-1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-a]dibenzo[c,f]azepine, (oil)

3-methyl-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]dibenzo[b,f](1,4)oxazepine.HCl (melting point: 215°–218°C)

13-chloro-3-methyl-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]dibenzo[b,f](1,4)oxazepine.HCl (melting point: 220°–222°C)

3,11-dimethyl-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]dibenzo[b,f](1,4)oxazepine.HCl (melting point: 219°–222°C)

3-methyl-7-trifluoromethyl-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d]dibenzo[b,f](1,4)thiazepine.HBr (melting point: 190°–193°C)

3,7-dimethyl-1,3,4,14b-tetrahydri-2H-pyrimidino[3,4-d]dibenzo[b,f](1,4)oxazepine.maleate (melting point: 164°–166°C)

3,13-dimethyl-1,3,4,14b-tetrahydro-2H-pyrimidino[3,4-d] dibenzo[b,f](1,4)oxazepine.

EXAMPLE XI

1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-a]dibenzo[c,f]azepine.HCl

A. A solution of 1.2 g of thiophosgene in 10 ml of toluene is gently added, at 0°C, to a solution of 2.4 g of 6-aminoethyl-5,6-dihydro-11H-dibenzo[b,e]azepine in 20 ml of toluene to which 5 ml of pyridine have been added. The reaction mixture is left to stand for 1 hour and after that 20 ml of water are added. The mixture is stirred vigorously, after which the water layer is separated from the toluene layer. The toluene phase is washed with water, then with 0.2 M sulphuric acid and finally with water.

The toluene solution is then dried and evaporated to dryness. The residue is recrystallized from ethanol (2.2 g).

Melting point 1,2,3,4,10,14b-hexahydro-4-thione-pyrimidino[3,4-a]dibenzo[c,f]azepine: 196°–198°C.

B. Two grams of the substance obtained in A are added to a suspension of 4 g of $LiAlH_4$ in 50 ml of dioxane. The mixture is refluxed for 1.5 hours. After being cooled down the mixture is added dropwise to 15 ml of water. The mixture is filtered and the filtrate evaporated to dryness in vacuum. The residue is dissolved in hydrochloric acid-containing alcohol, after which the solution is cooled down to obtain a precipitate. Melting point: 213°–217°C. Yield 0.9 g.

C. The same compound is obtained in two steps, if, instead of thiophosgene in toluene, carbondisulphide is used as reagent and solvent as well.

EXAMPLE XII

3-methyl-1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-a]dibenzo[c,f]azepine

By the process described in example XI A 1 g of phosgene and 2.5 g of 6-methylaminoethyl-5,6-dihydro-11H-dibenzo[b,e]-azepine are converted into 3-methyl-1,2,3,4,10,14b-hexahydro-4-keto-pyrimidino[3,4-a]dibenzo[c,f]azepine.

This substance is reduced with $LiAlH_4$ in tetrahydrofuran by the process described in example XI B.

Melting point fumarate: 192°–193°C.

EXAMPLE XIII

3-methyl-1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-a]dibenzo[c,f]azepine

To 2.4 g of 6-methylaminoethyl-5,6-dihydro-11H-dibenzo[b,e]azepine (melting point: 124°–126°C), dissolved in 50 ml of tetrahydrofuran, a solution of 2 g of N,N'-carbonyldiimidazol in 30 ml of tetrahydrofuran is added, while stirring. After 1.5 hours' stirring at room temperature about 65 ml of tetrahydrofuran are distilled off, after which the residue is diluted with water. Extraction of this mixture with benzene, washing of the extracts with water, drying on sodium sulphate and evaporation of the benzene solution gives 2.4 g of 3-methyl-1,2,3,4,10,14b-hexahydro-4-keto-pyrimidino[3,4-a]dibenzo[c,f]azepine.

This substance is dissolved in 80 ml of tetrahydrofuran, after which a solution of 0.8 g of diboran in 50 ml of tetrahydrofuran is added. The mixture is heated in a sealed ampoule for 5 hours, at 45°C. After that alcohol is added to the mixture, whereupon it is stirred for some time. After that the mixture is partly evaporated, then acidified with dilute acid (0.1 N HCl) and extracted with benzene.

The benzene extracts are processed in the conventional manner.

Melting point fumarate: 190°–192°C.

EXAMPLE XIV

a.

2-keto-1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-a]dibenzo[c,f]azepine

10 g of 6-carboxamidomethyl-5,6-dihydromorphanthridine is dissolved in 300 ml ethanol (70%), after which 100 ml of a 37% formaldehyde solution in water is added. The mixture is refluxed for 6 hours, after which the solvent is substantially evaporated. The residue obtained is filtered and the solid substance dried.

Melting point: 181°–185°C, yield 85%.
Rf in ethylacetate = 0.3 on SiO_2.

b.

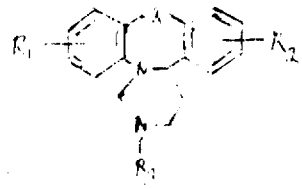
1,2,3,4,10,14b-hexahydro-pyrimidino[3,4-a]dibenzo[c,f]azepine.HCl

8 g of the compound obtained in a. is dissolved in 75 ml tetrahydrofurane (THF). The solution is gently added to a suspension of 4 g $LiAlH_4$ in 100 ml THF. The mixture is refluxed for 3 hours and after that cooled down to 0°C. To this cooled mixture 16 ml water is gently added, whereupon the mixture is filtered. The filtrate obtained is evaporated and the residual oil dissolved in HCl/EtOH. The solution is filtered and the solid substance obtained is dried.

Melting point HCl-salt: 214°–218°C; yield 88%.

What is claimed is:

1. A compound of the formula:



in which

X is selected from the group consisting of oxygen, sulfur, the group NR_4 and $—CH_2—$;

R_1 and R_2 are selected from the group consisting of hydrogen, halogen, hydroxy, alkyl having 1–6 carbon atoms, alkoxy having 1–6 carbon atoms, and trifluoromethyl;

R_3 is selected from the group consisting of hydrogen, alkyl having 1–6 carbon atoms, and

R_4 is selected from the group consisting of hydrogen and alkyl having 1–6 carbon atoms, and the pharmaceutically acceptable acid addition salts and quaternary ammonium compounds thereof.

2. A compound according to claim 1 in which X is $—CH_2—$.

3. A compound according to claim 1 in which X is oxygen.

* * * * *

UNITED STATES PATENT OFFICE

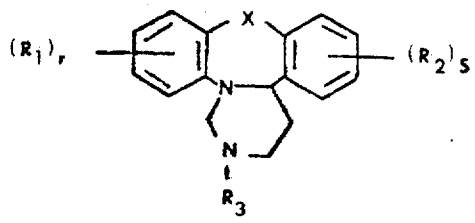
CERTIFICATE OF CORRECTION

Patent No. 3,892,695 Dated July 1, 1975

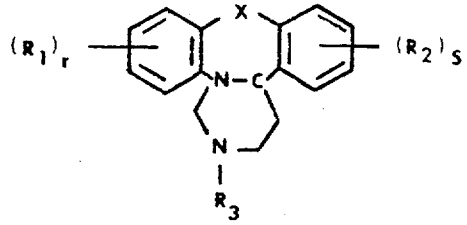
Inventor(s) Willem Jacob Van Der Burg

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

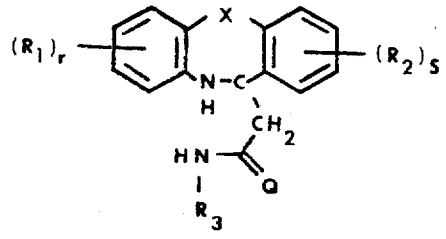
In the Abstract, the formula should read as shown below:



Column 1, lines 15-23, the formula should read as shown below:



Column 1, lines 55-63, the formula should read as shown below:



USCOMM-DC 60376-P69
U.S. GOVERNMENT PRINTING OFFICE: 869-930

UNITED STATES PATENT OFFICE

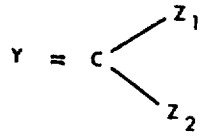
CERTIFICATE OF CORRECTION

Patent No. 3,892,695 Dated July 1, 1975

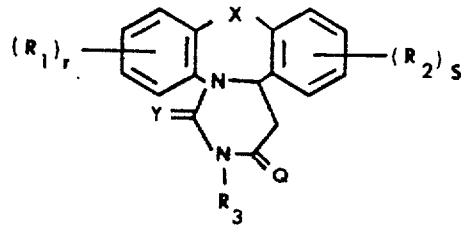
Inventor(s) Willem Jacob Van Der Burg Page 2

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

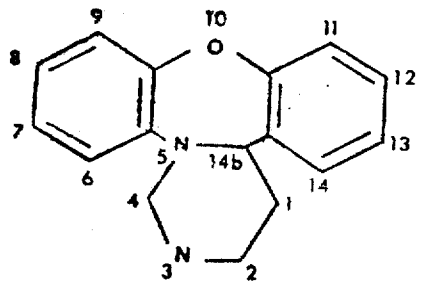
Column 2, lines 4-8, the formula should read as shown below:



Column 2, lines 18-25, the formula should read as shown below:



Column 3, after line 55, the formula should read as shown below:



USCOMM-DC 60376-P69
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UNITED STATES PATENT OFFICE

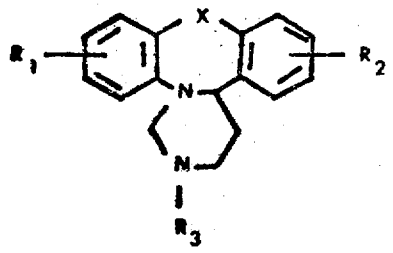
CERTIFICATE OF CORRECTION

Patent No. 3,892,695 Dated July 1, 1975

Inventor(s) Willem Jacob Van Der Burg

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 12, lines 5-12, Claim 1, the formula should read as shown below:



UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

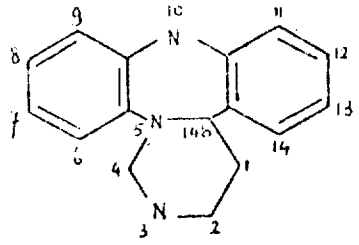
Patent No. 3,892,695 Dated July 1, 1975

Inventor(s) Willem Jacob Van Der Burg

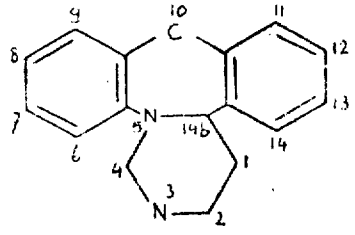
It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Columns 5 and 6, lines 1 through 49 should read as shown below:

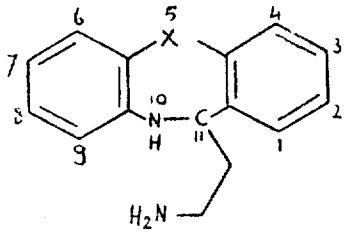
5 6



1,2,3,4,10,14b-hexahydro-pyrimidino [3,4-d] dibenzo[b,f](1,4)diazepine.



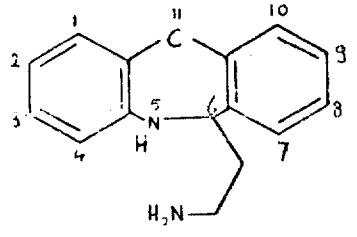
1,2,3,4,10,14b-hexahydro-pyrimidino [3,4-a] dibenzo[c,f]azepine.



X = O: 11-aminoethyl-10,11-dihydro-dibenzo[b,f](1,4)oxazepine

X = S: 11-aminoethyl-10,11-dihydro-dibenzo[b,f](1,4)thiazepine

X = N: 11-aminoethyl-10,11-dihydro-5H-dibenzo[b,e](1,4)diazepine.



6-aminoethyl-5,6-dihydro-11H-dibenzo[b,e]azepine or

6-aminoethyl-5,6-dihydro-morphanthridine

Signed and Sealed this

thirtieth **Day of** *December 1975*

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks