3/

(NON-CONVENTION. By one or more persons and/or a Company.) Form 1.

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

620513

APPLICATION FOR A PATENT

(1) Here insert (in full) Name or Names of Applicant or Applicants, followed by Address(es).

~~I~~/We (1) SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S.) of 51/53 rue du Docteur Blanche, 75016 Paris, France

(2) Here insert Title of Invention.

hereby apply for the grant of a Patent for an invention entitled: (2) PREPARATION PROCESS OF THIENO-TRIAZOLO-DIAZEPINE DERIVATIVES

which is described in the accompanying ~~PROVISIONAL~~/COMPLETE specification.

~~My~~/Our address for service is WATERMARK PATENT & TRADEMARK ATTORNEYS 290 Burwood Road, Hawthorn, Victoria, Australia.

DATED this 10th day of May 1990

REPRINT OF RECEIPT
FO16427 11/05/90

(3) Signature(s) of Applicant(s) or Seal of Company and Signatures of its Officers as prescribed by its Articles of Association.

(3) SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S.)

by

Ian A. Scott

Registered Patent Attorney

To: THE COMMISSIONER OF PATENTS.

WATERMARK PATENT & TRADEMARK ATTORNEYS

(CONVENTION. Company.) Form 8

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1962

DECLARATION IN SUPPORT OF A ~~CONVENTION~~ APPLICATION FOR A PATENT OR PATENT OF ADDITION

(1) Here insert (in full) Name of Company.

In support of the ~~Convention~~ Application made by(1) SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S.), a French Société Anonyme, 51/53 rue du Docteur Blanche 75016 PARIS (FRANCE), duly represented by its General Manager, Mr. Gérard BEAUFOUR (hereinafter referred to as the applicant) for a Patent

(2) Here insert title of Invention.

for an invention entitled:(2) PREPARATION PROCESS OF THIENO-TRIAZOLO-DIAZEPINE DERIVATIVES

(3) Here insert full Name and Address, of Company official authorized to make declaration.

I,(3) GERARD BEAUFOUR

of 51/53 rue du Docteur Blanche, 75016 Paris, France

do solemnly and sincerely declare as follows:

1. I am authorised by the applicant for the patent to make this declaration on its behalf.

~~2. The basic application as defined by Section 141 of the Act was~~ made in(4)

(4) Here insert basic Country or Countries followed by date or dates and basic Applicant or Applicants.

on the day of 19, by

~~on the day of 19, by~~

(5) Here insert (in full) Name and Address of Actual Inventor or Inventors.

3.(5) PIERRE BRAQUET, 8, rue des Suisses, 92380 Garches; ANDRE ESANU, 5, avenue d'Erlanger, 75016 Paris, JEAN-PIERRE LAURENT, 159, rue Blomet 75015 Paris and JACQUES POMMIER, 93, avenue Henri Barbusse, 92700 Colombes, all in France

~~is~~/are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follow:

The applicant is the assignee of the invention from the said actual inventors

~~4. The basic application referred to in paragraph 2 of this Declaration~~ was the first application made in a Convention country in ~~respect of the invention the subject of the application~~.

DECLARED at Paris

this 23 day of April 19 90

(CONVENTION. Company.) Form 8

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1962

DECLARATION IN SUPPORT OF A ~~CONVENTION~~ APPLICATION FOR A PATENT OR PATENT OF ADDITION

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~~is~~/are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follow:

The applicant is the assignee of the invention from the said actual inventors

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DECLARED at Paris

this 23 day of April 19 90

(12) PATENT ABRIDGMENT (11) Document No. AU-B-54930/90
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 620513

(54) Title
PREPARATION PROCESS OF THIENO-TRIAZOLO-DIAZEPINE DERIVATIVES

International Patent Classification(s)
(51)[5] C07D 495/22

(21) Application No. : 54930/90 (22) Application Date : 11.05.90

(43) Publication Date : 05.12.91

(44) Publication Date of Accepted Application : 20.02.92

(71) Applicant(s)
SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S.)

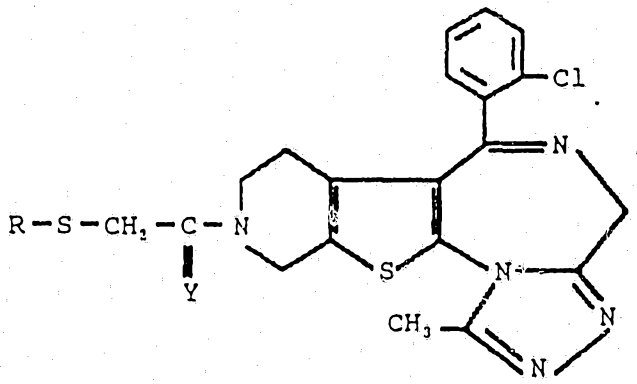
(72) Inventor(s)
PIERRE BRAQUET; ANDRE ESANU; JEAN-PIERRE LAURENT; JACQUES POMMIER

(74) Attorney or Agent
WATERMARK PATENT & TRADEMARK ATTORNEYS , Locked Bag 5, HAWTHORN VIC 3122

(56) Prior Art Documents
AU 43761/89 C07D 495/14 495/22 A61K 031/55
AU 54931/90 C07D 495/22 A61K 031/55
AU 76015/87 C07D 495/22 495/14 A61K 031/55

(57) Claim

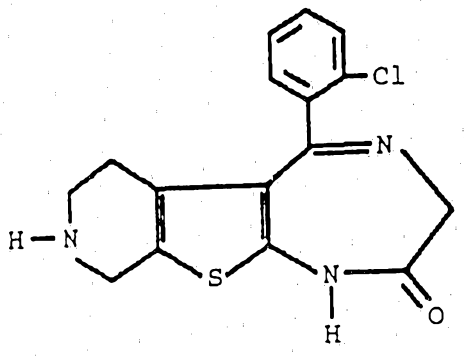
1) Preparation process of the thieno-triazolo-diazepine derivatives of the formula A



A.

wherein Y represents an oxygen or suiphur atom and R represents a straight chain or branched chain alkyl group having from 1 to 20 carbon atoms ; a phenyl group, unsubstituted or substituted by a straight chain or branched chain alkyl group having from 1 to 5 carbon atoms, an alkoxy group having from 1 to 5 carbon atoms, a halogen atom, trifluoromethyl group or an optionally substituted phenoxy group ; or a furan or thiophene ring,
consisting in reacting the ~~thieno-triazolo-~~ pyrido-thieno-diazepine compound of the formula B

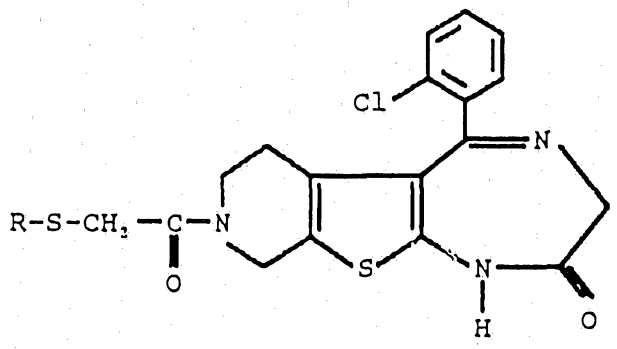
.../2



B.

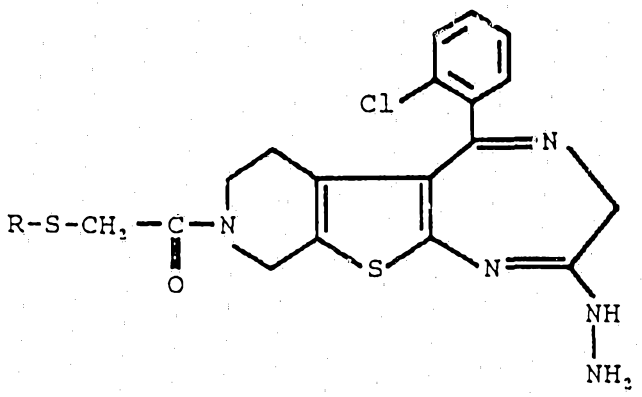
with a stoichiometric amount of $RSCH_2COOH$ derivative C wherein R is as above defined in an aprotic solvent, in the presence of a slight stoichiometric excess of dicyclohexylcarbodiimine at a temperature of from 0 to 60°C,

then reacting the resulting compound of the formula :



D.

wherein R is as above defined, with three to five stoichiometric equivalents of hydrazine hydrate in a protic solvent at a temperature of from room temperature to 50°C, and finally cyclizing in a protic solvent the thus obtained compound of the formula :



E.

with a one to three stoichiometric equivalents of triortho-acetate at a temperature of from room temperature to reflux temperature of the reacting mixture to obtain the thieno-triazolo-diazepine derivative of the general formula A wherein Y is an oxygen atom, and optionnally proceeding with a sulphuration reaction step [D → D'], consisting in reacting the thieno-diazepine derivative of the formula D, on three to five stoichiometric equivalents of phosphorus pentasulfide in an aprotic solvent at a temperature of from 10°C to reflux temperature of the reacting mixture, to obtain the corresponding thieno-triazolo-diazepine wherein Y stands for sulphur atom.

Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

620513

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority :

Related Art :

Name of Applicant : SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S.)

Address of Applicant : 51/53 rue du Docteur Blanche, 75016 Paris, France

Actual Inventor : PIERRE M. BRAQUET, ANDRE M. ESANU, JEAN-PIERRE M. LAURENT and JACQUES M. POMMIER

Address for Service : **WATERMARK PATENT & TRADEMARK ATTORNEYS.**
LOCKED BAG NO. 5, HAWTHORN, VICTORIA 3122, AUSTRALIA

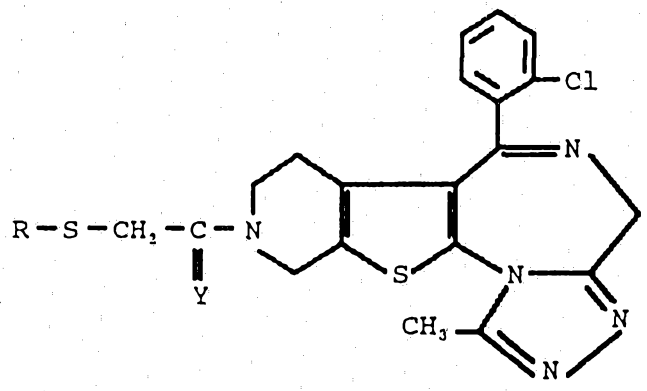
Complete Specification for the invention entitled:

PREPARATION PROCESS OF THIENO-TRIAZOLO-DIAZEPINE DERIVATIVES

The following statement is a full description of this invention, including the best method of performing it known to :- us

The invention relates to a preparation process of new derivatives of thieno-triazolodiazepine which are particularly interesting as anti-ischemic, anti-asthmatic and anti-allergic agents and as gastro-intestinal protectors. The compounds of the present invention are more particularly interesting in the treatment of ischemia.

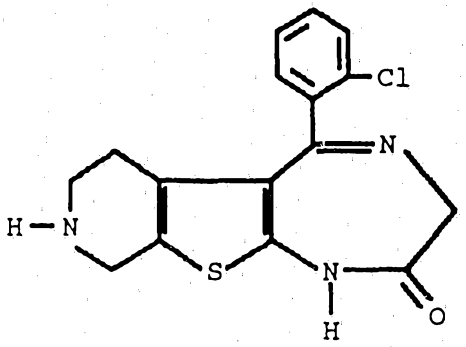
The invention relates more particularly to a preparation process of thieno-triazolo-diazepine derivatives of the general formula A



A.

wherein Y represents an oxygen or sulphur atom and R represents a straight chain or branched chain alkyl group having from 1 to 20 carbon atoms ; a phenyl group, unsubstituted or substituted by a straight chain or branched chain alkyl group having from 1 to 5 carbon atoms, an alkoxy group having from 1 to 5 carbon atoms, a halogen atom, trifluoromethyl group or an optionally substituted phenoxy group ; or a furan or thiophene ring,
and of therapeutic salts thereof.

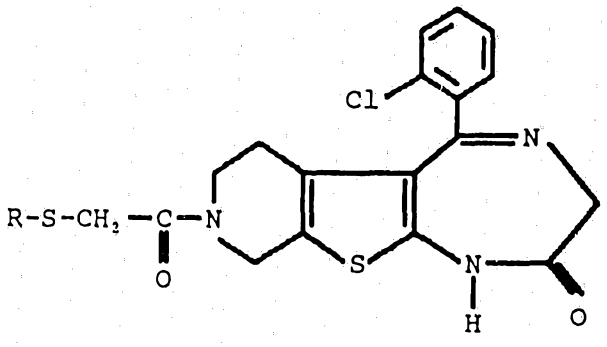
According to the invention, these compounds may be readily prepared by treating the ~~thieno-triazolo-~~ pyrido-thieno-diazepine compound of the formula B



B.

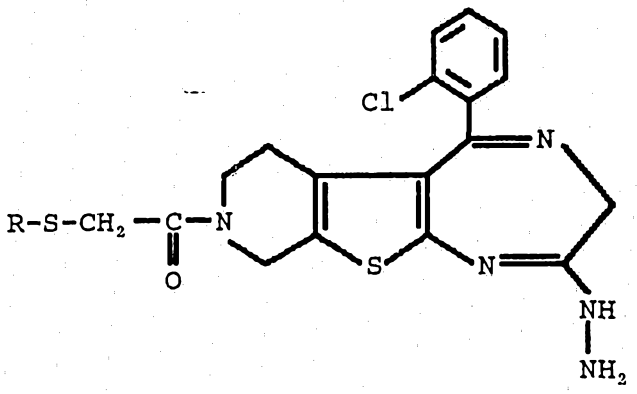
with a stoichiometric amount of $RSCH_2COOH$ derivative C wherein R is as above defined, in an aprotic solvent, in the presence of a slight stoichiometric excess of dicyclohexylcarbodiimide at a temperature of from 0 to 60°C,

then reacting the resulting compound of the formula :



D.

with three to five stoichiometric equivalents of hydrazine hydrate, in a protic solvent, at a temperature of from room temperature to 50°C, and, finally, cyclizing, in a protic solvent, the thus obtained compound of the formula :



E.

with a one to three stoichiometric equivalents of triorthoacetate at a temperature of from room temperature to reflux temperature of the reacting mixture to obtain the thieno-triazolo-diazepine derivative of the general formula A wherein Y is a oxygen atom, and optionnally proceeding with a sulphuration reaction step [D → D'], consisting in reacting the thieno-diazepine derivative of the formula D, on three to five stoichiometric equivalents of phosphorus pentasulfide in an aprotic solvent at a temperature of from 10°C to reflux temperature of the reacting mixture, to obtain the corresponding thieno-triazolo-diazepine wherein Y stands for sulphur atom. The corresponding sequence of reaction is summed up in the enclosed drawing sheet 1.

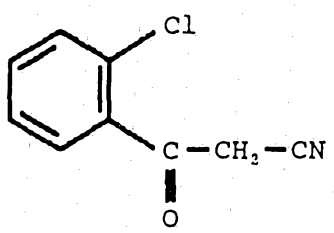
The reactions of the preparation process of thieno-triazolo-diazepine derivatives of the present invention are preferably carried out in an inert atmosphere.

The prior art in the field of this invention, may be illustrated by US patent 4 621 083 (or E.P. 176 927) in which thieno-triazolo-diazepine having PAF-antagonistic acitivity are disclosed.

These new compounds present a PAF-antagonistic acitivity from 10 to 1000 times greater than this one of the diazepines disclosed in the above mentionned patent and also a more potent effectiveness.

The obtention of starting compound B is dercribed in the following sequence of preparative examples (from I to VI) which is reported in drawing sheet 2.

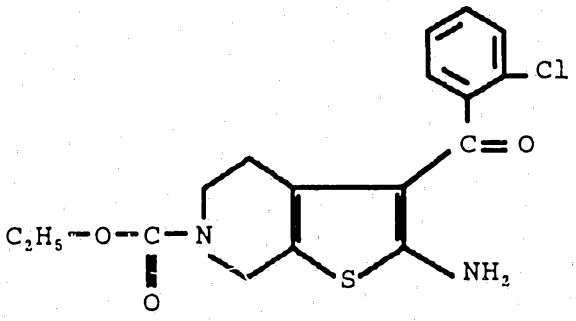
I - <u>(2-chloro)benzoylmethyl cyanide</u>.



In an appropriate reactor placed under nitrogen circulation at - 70°C were poured 7 l of anhydrous THF and 115.9 g (1.36 mol) of previously dried cyanoacetic acid. Then were thus added dropwise 1 715 ml (2.74 mol) of 1,6 M solution of butyllithium in hexane, while allowing temperature to rise from - 70°C to 0°C. The reactional mixture was then stirred for one hour. Thereafter the reactional mixture was once more cooled at - 70°C and a solution of 120 g (0.685 mol) of chloro-2 benzoyle chloride in 1 l of anhydrous THF, was added dropwise.

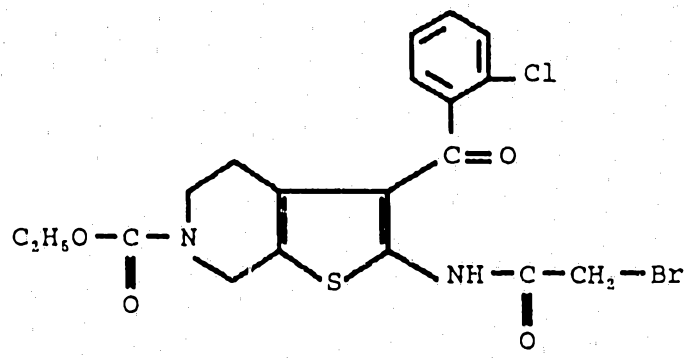
After stirring for one hour always at - 70°C, the temperature was allowed to rise from - 70°C to 0°C for one hour. Then there was added dropwise 3 l of 1N HCl solution and after stirring for a few minutes, the reacted mixture was extracted by chloroform. The organic phase was washed with a 10 % aqueous sodium bicarbonate solution, then with a saturated sodium chloride solution, dried, filtered and the solvent was evaporated off to give 135 g of residue. The crystallization was effected by the addition of diisopropyl ether, and the product was filtered off, and washed with hexane to give 97.2 g of the title compound (Yield 79 %).

II - <u>**2-amino - 3-(2-chlorobenzoyl) - 6-(ethoxycarbonyl)-4, 5,6,7-tetrahydro-pyrido [3,4 - b] thiophene**</u>.



In a two litre-erlen fitted with a cooler, were poured 85.5 g (0.501 mol) of N-carbethoxy-4-piperidone, 90 g (0.501 mol) of (I), 19.3 g (0.600 mol) of flower of sulfur and 44.4 g (0.501 mol) of morpholine, in 550 ml of methanol. The mixture was refluxed for one hour. After evaporation of 250 ml of solvent, the desired compound precipitates, was filtered off, washed with ethanol, then with diethyl ether and dried to yield 155.4 g (85 %) of the title compound.

III - <u>2-(bromoacetamido) - 3-(2-chlorobenzoyl) - 6-(ethoxy-carbonyl) - 4,5,6,7-tetrahydro-pyrido [3,4-b] thiophene</u>.

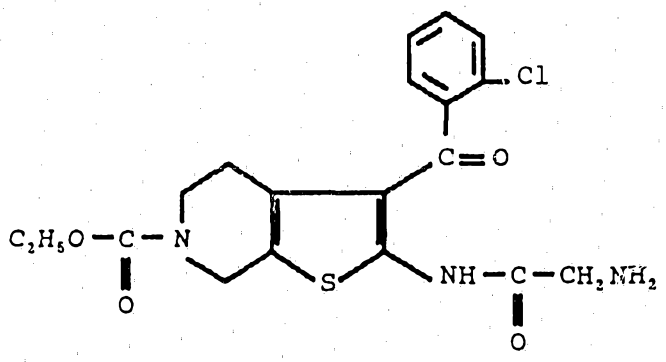


In a five litre-reactor fitted with appropriate means and with separating funnel, were poured 2.5 l of chloroform and 146 g (0.400 mol) of (II).

Then, 87.7 g (0.43 mol) of bromoacetylbromide contained in the separating funnel were added dropwise.

The reactional mixture was stirred for one hour at room temperature, then washed with 300 ml of icy-water, and the organic phase was dried with anhydrous magnesium sulphate and filtered. The chloroform was evaporated off and the residue was treated with ethanol. The resulting precipitate was filtered off, washed with ethanol, then with diethyl ether, and dried to yield 184.6 g (95 %) of the title compound.

IV - 2-(aminoacetamido) - 3-(2-chlorobenzoyl) - 6-(ethoxycarbonyl) - 4,5,6,7-tetrahydro - pyrido [3,4 - b] thiophene.

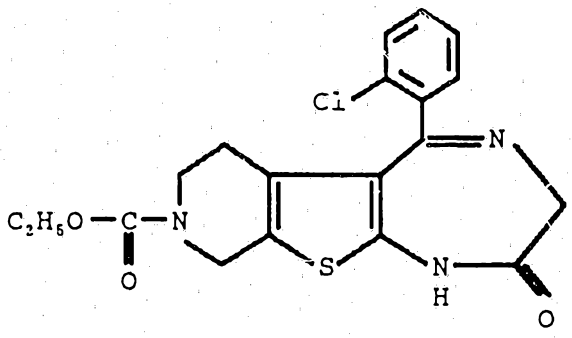


In a five litre-reactor fitted with a gaz-injector were poured 174.8 g (0.36 mol) of (III) and 3 litres of THF. The suspension was cooled at 0°C and then gazeous ammonia previously dried over potassium hydroxide was added. The addition was conducted in 8 hours. (60 g of ammonia were absorbed). The mixture was stirred overnight at 0°C, then 2 litres of THF was evaporated off under reduced pressure, and 750 ml of ethyl acetate were added. After decantation, the organic phase was washed once with 300 ml of a 10 % sodium chloride solution, three times with 300 ml of water, and dried with anhydrous magnesium sulphate. After filtration, the solvent was partially evaporated off at rotavapor. The precipitate was allowed to stand overnight in refrigerator.

After filtration, the precipitate was washed with diethyl ether and dried to give 119 g of the title compound.

The remaining organic phase was concentrated and treated with a mixture of 1.5 l of diethyl ether/THF (3/1 by volume) to give 14.6 g of the title compound (overall yield 88 %).

V - 5-(2-chlorophenyl) - 8-(ethoxycarbonyl) - 6,7,8,9-tetrahydro - 3H - pyrido [4',3' : 4,5] thieno [3,2 - f] 1,4-diazepine - 2-one.

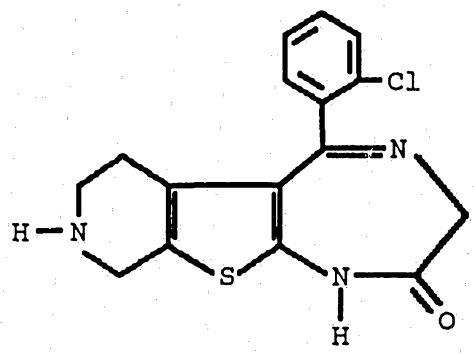


In a two litre-reactor fitted with stirring, cooling and warming means and placed under nitrogen circulation were poured 126.6 g (0.3 mol) (IV) and 800 ml of pyridine. The reaction mixture was refluxed for 18 hours.

After having checked that all the starting material had reacted, the pyridine was partially evaporated at a rotavapor under reduced pressure. The obtained (dark brown) oil was dissolved with 1 litre of ethanol.

After cooling in an ice-bath, there was obtained a precipitate which was filtered off, washed with ethanol and diisopropyloxide to yield 101.3 g (83.6 %) of the title compound.

VI - 5-(2-chlorophenyl) - 6, 7, 8, 9-tetrahydro-3H- pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine - 2-one.

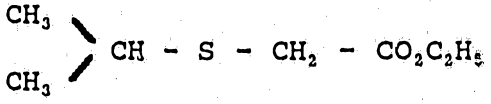


B.

In a reactor fitted with warming means and placed under nitrogen circulation, were poured 94.5 g (0.234 mol) of V, 152.1 g (2.34 mol) of pelleted (90 %) potassium hydroxide and 900 ml of ethylene glycol monomethylether. The mixture was warmed over one hour to reflux temperature and reflux was maintained for one hour. The solution was then added to 1.2 kg of cracked-ice and acidified with (d = 1.18) chlorhydric acid at pH 5.3. Then potassium carbonate was added to ajuste pH at 8.3. The solution was then extracted three times with 500 ml of methylene chloride. The organic phase was washed with 450 ml of a 10 % aqueous sodium chloride solution, dried with anhydrous magnesium sulphate, filtered and evaporated. The resulting residue was treated with diisopropyl-ether. After washing with diisopropylether and drying, there was obtained 55.9 g of the title compound (yield 72 %).

Second sequence of preparative examples (from I' to II') : Preparation of isopropylthio-acetic acid ($R-S-CH_2CO_2H$ derivative wherein R = isopropyl).

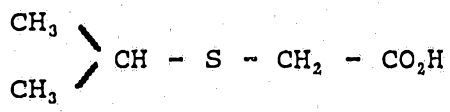
I' - <u>Ethyl-isopropylthioacetate</u>.



In a 1 litre reactor fitted with appropriate means, were poured 300 ml of methanol and 25.4 g (0.333 mol) of isopropylthiol.

Then 57.3 g (0.333 mol) of ethyl-bromoacetate were added dropwise at room temperature and the mixture was stirred for four hours at always room temperature. Then 135 ml of 2,5N sodium hydroxide solution was added dropwise without pH reached a value above 7-7.5. Thereafter the mixture was stirred overnight and then methanol was evaporated off. The residue was treated with 100 ml of water, and the obtained mixture extracted with 350 ml of diethyl-ether. The organic phase was washed once with a 5 % sodium hydroxide solution, then three times with water and dried with anhydrous magnesium sulphate. After filtration and evaporation at rotavapor, there was obtained 46 g of the title compound (yield 85 %).

II' - Isopropylthio acetic acid



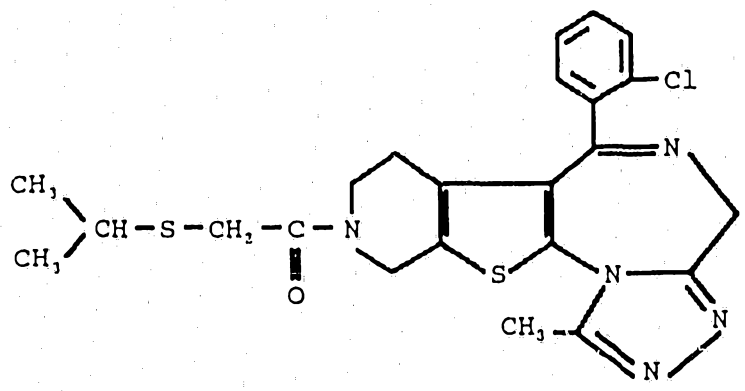
C.

In a 2 litre reactor fitted with appropriate means were poured 40 g (0.246 mol) of ethyl-isopropylthioacetate and 380 ml of methanol. Then a solution of 20.7 g (0.369 mol) of potassium hydroxide in 380 ml of water, was added dropwise. The temperature rose and was then maintained for two hours at 35-38°C. Thereafter the methanol was evaporated off and the resulting residue treated with about 500 ml of icy-water. The solution was then acidified at pH 3 by addition of a 10 % chlorhydric acid solution. The precipitate was filtered off, washed with water until neutrality and dried. The thus obtained compound was crystallized with 200 ml of mixture of diisopropyl acetate/diisopropylether (4/6 by volume). The solution was filtered hot and allowed to crystallize. After filtration and washing with diisopropyloxide, there was obtained 26.7 g of the title compound (yield 80.5 %).

The invention will be better understrood from the decription of the following examples.

EXAMPLE 1 :

6 -(2-chlorophenyl)- 9-(isopropyl-thiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = isopropyl.



1st step B + C → D :
Preparation of 5 -(2-chlorophenyl)- 8-(isopropyl-thiomethyl-carbonyl)-6, 7, 8, 9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine-2-one

In a two litre reactor fitted with appropriate means, were poured 49.8 g (0.150 mol) of 5-(2-chlorophenyl)-6, 7, 8, 9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine-2-one and 250 ml of dichloroethane. The suspension was cooled to 5°C. Then there were added simultaneously 34 g (1.65 mol) of carbodicyclohexylimide, 400 ml of dichloroethane, 20.1 g (0.150 mol) of isopropylthio acetic acid and 400 ml of dichloroethane while maintaining temperature at 10°C. The mixture was allowed to stand for 30 minutes in an ice-bath, then brought to room temperature and warmed to 50°C to homogenize. Thereafter the mixture was stirred overnight at room temperature and dichloroethane was evaporated off.

The obtained residue was treated with 600 ml of N,N-dimethylformamide. Then 150 ml of water were added and the mixture was stirred for two hours. The formed dicyclohexylurea was filtered off and the solution was washed with N,N-dimethylformamide. The N,N-dimethylformamide was partially evaporated off. The obtained residue was treated with icy-water and precipitation occured. Then 0.150 mol of acetic acid were added and the mixture was stirred.

The precipitate was filtered off, washed with a 10 % aqueous acetic acid solution, with water and then with a 10 % aqueous sodium bicarbonate solution, dried under reduced pressure and then treated with 600 ml of boiling ethylacetate. The solution was cooled and allowed to stand for three hours in refrigerator. After filtration, washing with ethyl-acetate then with diethyl-ether and drying, there was obtained 45.7 g of the title compound (yield 68 %).

2nd step D → E :

Preparation of 5 -(2-chlorophenyl)- 8-(isopropyl-thiomethyl carbonyl)-2-hydrazino-6, 7, 8, 9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine

In a two litre reactor fitted with appropriate means and placed under nitrogen circulation, were poured 42.5 g (0.095 mol) of 5-(2-chlorophenyl)-8-(isopropyl-thiomethyl-carbonyl)-6, 7, 8, 9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine-2-one, 1 litre of methanol and 18.06 g (0.376 mol) of hydrazine hydrate. The suspension was allowed to stand for 90 minutes at room temperature (25°C). The presence of starting material was proved by CCM analysis. Thus the mixture was heated to 40°C for 30 minutes and then maintained at room temperature for one hour for the completion of the reaction.

The mixture was filtered and there was obtained 36.4 g of the title compound after washing with methanol and with diethyl-ether (yield 83 %).

3rd step E → A : Title compound.

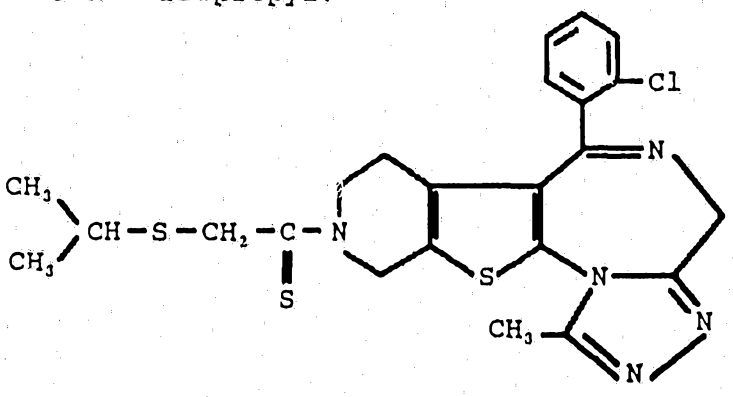
Preparation of 6 -(2-chlorophenyl)- 9-(isopropyl-thiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

In a 1 litre reactor fitted with cooling means and placed under nitrogen circulation, were poured 32.4 g (0.070 mol) of 5 -(2-chlorophenyl)- 8-(isopropyl-thiomethyl-thiocarbonyl)-2-hydrazino-6, 7, 8, 9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine, 600 ml of methanol and 45 g (0.28 mol) of triethylorthoacetate. The suspension was refluxed for 90 minutes : after 15 minutes of reflux, there was obtained a solution and precipitation occured after 45 minutes of reflux. All of the starting material had reacted. The mixture was then cooled and the precipitate filtered off, washed with methanol then with diethyl-ether. After drying at room temperature and then at 110°C overnight under reduced pressure, there was obtained 30.3 g of the title compound (yield 89 %).

EXAMPLE 2 :

6 -(2-chlorophenyl)- 9-(isopropylthiomethyl-thiocarbonyl)-7,8,9,10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

Y = S R = isopropyl.



1st step B + C → D :
Preparation of 5 -(2-chlorophenyl)- 8-(isopropyl-thiomethyl-carbonyl)-6, 7, 8, 9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine-2-one

This reaction is described in details in the example 1 (first step).

2nd step D → D' :
Preparation of 5-(2-chlorophenyl)- 8-(isopropyl thiomethyl thiocarbonyl)-6, 7, 8, 9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine-2-thione

In a five litre reactor fitted with appropriate means and placed under nitrogen circulation, were poured 40.3 g (0.090 mol) of 5-(2-chlorophenyl)- 8-(isopropylthiomethyl carbonyl)-6, 7, 8, 9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine-2-one and 1.25 l of 1,2-dimethoxy ethane. The suspension was warmed to 60°C then were added 87.1 g (0.392 mol) of phosphorus pentasulfide and 65.4 g (0.785 mol) of sodium bicarbonate. The addition was conducted in 15 minutes. Then the temperature was maintained at 70°C for 90 minutes. Because CCM analysis showed traces of intermediates, the mixture was then refluxed for 30 minutes for the completion of the reaction. Thereafter the mixture was cooled to 15°C and 2.5 l of icy-water were added. The mixture was then poured into a 5 litre beaker in which a 0.4M sodium bicarbonate solution was added to reach pH 8. The mixture was stirred for 30 minutes and the obtained precipitate was filtered off, washed with water, with ethanol then with diethyl-ether and treated with 1 l of dichloromethane. An insoluble matter was filtered off. Thereafter the mixture was washed with 300 ml of dichloromethane and dichloromethane was then evaporated off. The resulting residue was treated with acetonitrile and then allowed to stand overnight in an icebox.

After filtration, washing with acetonitrile then with diethyl-ether and drying, there was obtained 28.1 g of the title compound (yield 65 %).

3rd step D' → E :

Preparation of 5 -(2-chlorophenyl)- 8-(isopropyl-thiomethyl thiocarbonyl)-2-hydrazino-6, 7, 8, 9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine

In a two litre reactor fitted with appropriate means and placed under nitrogen circulation, were poured 19.7 g (0.041 mol) of 5-(2-chlorophenyl)-8-(isopropyl-thiomethyl-thiocarbonyl)-6, 7, 8, 9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine-2-thione, 500 ml of methanol and 8.22 g (0.162 mol) of hydrazine hydrate.The suspension was allowed to stand for 90 minutes at room temperature (25°C). The presence of starting material was proved by CCM analysis. Thus the mixture was heated to 40°C for 30 minutes and then maintained at room temperature for one hour for the completion of the reaction. The mixture was filtered and there was obtained 16.4 g of the title compound after washing with methanol and with diethyl-ether (yield 84 %).

4th step E → A :

Preparation of 6 -(2-chlorophenyl)- 9-(isopropyl-thiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

In a 1 litre reactor fitted with cooling means and placed under nitrogen circulation, were poured 12 g (0.025 mol) of 5 -(2-chlorophenyl)- 8-(isopropyl-thiomethyl-thiocarbonyl)-2-hydrazino-6, 7, 8, 9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine, 250 ml of methanol and 16.1 g (0.100 mol) of triethylorthoacetate.

The suspension was refluxed for 90 minutes : after 15 minutes of reflux, there was obtained a solution and precipitation occured after 45 minutes of reflux. All of the starting material had reacted. The mixture was then cooled and the precipitate filtered off, washed with methanol then with diethyl-ether. After drying at room temperature and then at 110°C overnight under reduced pressure, there was obtained 11.1 g of the title compound (yield 88 %).

The following compounds have been prepared as described in example 1 wherein Y = O, and as described in example 2 wherein Y = S, but starting with the appropriate $R-S-CH_2CO_2H$ derivative.

EXAMPLE 3 :

6-(2-chlorophenyl)-9-(t.butylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = t.butyl.

EXAMPLE 4 :

6-(2-chlorophenyl)-9-(t.butylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S R = t.butyl.

EXAMPLE 5 :

6-(2-chlorophenyl)-9-(hexadecylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = hexadecyl.

EXAMPLE 6 :

6 -(2-chlorophenyl)- 9-(hexadecylthiomethyl-thiocarbonyl)7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S R = hexadecyl.

EXAMPLE 7 :

6-(2-chlorophenyl)- 9-(phenyl-thiomethyl-carbonyl)- 7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = phenyl.

EXAMPLE 8 :

6 -(2-chorophenyl)-9 -(phenyl-thiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S R = phenyl.

EXAMPLE 9 :

6-(2-chlorophenyl)- 9-(4-methoxyphenylthiomethyl-carbonyl)- 7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = 4-methoxyphenyl.

EXAMPLE 10 :

6-(2-chorophenyl)-9-(4-methoxyphenylthiomethyl-thiocarbonyl) -7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S R = 4-methoxyphenyl.

EXAMPLE 11 :

6- (2-chlorophenyl)- 9-(3,4-dimethoxyphenylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = 3,4-dimethoxyphenyl.

EXAMPLE 12 :

6 -(2-chlorophenyl)- 9-(3,4-dimethoxyphenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S R = 3,4-dimethoxyphenyl.

EXAMPLE 13 :

6-(2-chlorophenyl)- 9-(3, 4, 5-trimethoxyphenylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = 3,4,5-trimethoxyphenyl.

EXAMPLE 14 :

6-(2-chlorophenyl)-9-(3,4,5-trimethoxyphenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S R = 3,4,5-trimethoxyphenyl.

EXAMPLE 15 :

6-(2-chlorophenyl)-9-(2,3,4-trimethoxyphenylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = 2,3,4-trimethoxyphenyl.

EXAMPLE 16 :

6 -(2-chlorophenyl)- 9-(2,3,4-trimethoxyphenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S R = 2,3,4-trimethoxyphenyl.

EXAMPLE 17 :

6-(2-chlorophenyl)- 9-(4-t.butylphenylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = 4-t.butylphenyl.

EXAMPLE 18 :

6 -(2-chlorophenyl)- 9-(4-t.butylphenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S R = 4-t.butylphenyl.

EXAMPLE 19 :

6 -(2-chlorophenyl)- 9-(2-trifluoromethylphenylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = 2-trifluoromethylphenyl.

EXAMPLE 20 :

6 -(2-chlorophenyl)- 9-(2-trifluoromethylphenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S R = 2-trifluoromethylphenyl.

EXAMPLE 21 :

6 -(2-chlorophenyl)- 9-(3-trifluoromethylphenylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = 3-trifluoromethylphenyl.

EXAMPLE 22 :

6 -(2-chlorophenyl)- 9-(3-trifluoromethylphenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S R = 3-trifluoromethylphenyl.

EXAMPLE 23 :

6 -(2-chlorophenyl)- 9-(4-trifluoromethylphenylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = 4-trifluoromethylphenyl.

EXAMPLE 24 :

6 -(2-chlorophenyl)- 9-(4-trifluoromethylphenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S R = 4-trifluoromethylphenyl.

EXAMPLE 25 :

6 -(2-chlorophenyl)- 9-(4-fluorophenylthiomethyl-carbonyl) -7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = 4-fluorophenyl.

EXAMPLE 26 :

6 -(2-chlorophenyl)- 9-(4-fluorophenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S R = 4-fluorophenyl.

EXAMPLE 27 :

6 -(2-chlorophenyl)- 9-(2,3-dichlorophenylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = 2,3-dichlorophenyl.

EXAMPLE 28 :

6 -(2-chlorophenyl)- 9-(2,3-dichlorophenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S R = 2,3-dichlorophenyl.

EXAMPLE 29 :

6 -(2-chlorophenyl)- 9-(4-phenoxyphenylthiomethyl-carbonyl) 7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = 4-phenoxyphenyl.

EXAMPLE 30 :

6 -(2-chlorophenyl)-9 -(4-phenoxyphenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S R = 4-phenoxyphenyl.

EXAMPLE 31 :

6 -(2-chlorophenyl)- 9-(2-furyl-thiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

Y = O R = 2-furyl

EXAMPLE 32 :

6 -(2-chlorophenyl)- 9-(2-furyl-thiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

Y = S R = 2-furyl.

EXAMPLE 33 :

6 -(2-chlorophenyl)- 9-(2-thienyl-thiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

Y = O R = 2-thienyl.

EXAMPLE 34 :

6 -(2-chlorophenyl)- 9-(2-thienyl-thiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

Y = S R = 2-thienyl.

TOXICITY

The compounds of the invention are not toxic on the mice per os at the dose of 1 g/kg, by the IP or oral routes.

PHARMACOLOGY

Various pharmacological determinations have been made on these compounds ; they are summarized as follows :

1) Inhibition of platelet agregation induced by PAF

This experimentation was conducted according to the method of R. KINLOUGH. RATHBONE, J.P. CAZENAVE, M. PACKHAM and F. MUSTARD, Lab. Invest. 48, 98, 1980. In this test, New Zealand rabbits were used (male New Zealand rabbits of an average weight of 5 kg).

The determinations are made on a chrono-log Coultronics agregometer, at 57°C coupled with a graphic recorder ; the results of these determinations (in molecular concentration) are reported on the table I on the central column.

2) Inhibition of the binding to benzodiazepine receptors

The interest of the previous experimentation depends on the results obtained in this experimentation : as a compound of the invention has a benzodiazepine like structure, it is important to check whether the specific benzodiazepine activity would not appear at the dose where platelet agregation was inhibited.

Therefore, this experimentation has been conducted according to the method of MOHLER H. and RICHARD J.G. Agonist and antagonist benzodiazepine receptor interaction in vitro, Nature, vol. 294, 763-765, 1981.

This experimentation was conducted on rat brains incubated 1 h 30 at 4°C using ^{3}H-RO-15-1788 and ^{3}H-RO-5-4864 (NEN) as tracers and RO-15-4788 and RO-5-4864 as reference antagonists.

The results in molecular concentration are reported in the table I, on the right hand column.

3) Global ischemia on gerbilles

For this test, males gerbilles were anaesthetized with brietal at the doses of 35 mg/kg IP ; thereafter, both carotides were clamped for 10 minutes, then the clamping was released. Treated animals received each 10 mg/kg of the compounds of one of the examples.

One week later, the animals were killed and both hippocampes were taken, weighed and frozen at -80°C.

After crushing with 1 ml of TRIS-HCl pH 7.4 for 30 secondes, aliquots of each 50 µl of this preparation were incubed in each 1 ml of TRIS-HCl buffer containing ^{3}H-PK 11195 at 2 nM (90 Ci/mmole, NENE, Germany) for 1 hour at 25°C.

For each preparation, 3 determinations were made. The density of omega 3 sites (marked by the specific ^{3}H-PK 11195 marker) are expressed in f-moles of PK 11195/mg of fresh tissues and converted in percentage of protection compared to control.

The results of this experimentation are reported on the following table II.

PRESENTATION - POSOLOGY

In human therapy, the compounds of the invention are preferably administrated by oral route. Prefered forms of administration include tablets, gelatine capsules and the like. Usual posology is from 50 mg to 500 mg per diem according to the case.

Prefered unit dose is 50 mg, associated with appropriate carriers and agents. They may be adminitrated by injection route. Usual posology is from 5 mg to 100 mg per diem according to the case. Unit doses are from 1 to 20 mg.

TABLE I A

EXAMPLES	IC_{50}		BDZ receptors	
1	2.53	10^{-8}	6.7	10^{-6}
2	2.81	10^{-8}	4.82	10^{-5}
3	1.68	10^{-8}	2.3	10^{-6}
4	4.97	10^{-7}	1.55	10^{-6}
5	7.43	10^{-9}	1.21	10^{-7}
6	9.46	10^{-9}	9.1	10^{-7}
7	5.11	10^{-7}	2.1	10^{-6}
8	1.05	10^{-8}	7.33	10^{-6}
9	3.37	10^{-8}	2.7	10^{-6}
10	1.71	10^{-7}	6.6	10^{-5}
11	2.64	10^{-8}	1.4	10^{-6}
12	3.14	10^{-8}	8.7	10^{-7}

TABLE I B

EXAMPLES	IC_{50}	BDZ receptors
13	$1.85\ 10^{-8}$	$5.5\ 10^{-5}$
14	$9.22\ 10^{-9}$	$1.5\ 10^{-6}$
15	$1.2\ 10^{-7}$	$3.6\ 10^{-6}$
16	$5.35\ 10^{-8}$	$6.\ 10^{-7}$
17	$8.75\ 10^{-9}$	$4.7\ 10^{-6}$
18	$2.3\ 10^{-8}$	$4.41\ 10^{-5}$
19	$6.36\ 10^{-9}$	$2.7\ 10^{-7}$
20	$1.46\ 10^{-7}$	$1.6\ 10^{-6}$
21	$8.66\ 10^{-9}$	$8.1\ 10^{-7}$
22	$8.18\ 10^{-9}$	$6.1\ 10^{-7}$
23	$1.24\ 10^{-8}$	$1.2\ 10^{-6}$
24	$3.27\ 10^{-8}$	$3.3\ 10^{-6}$

TABLE I C

EXAMPLES	IC_{50}		BDZ receptors	
25	1.13	10^{-8}	6.3	10^{-7}
26	6.56	10^{-9}	6.1	10^{-7}
27	8.45	10^{-9}	4.8	10^{-5}
28	9.06	10^{-9}	4.3	10^{-6}
29	9.05	10^{-9}	1.23	10^{-6}
30	1.04	10^{-7}	3.6	10^{-7}
31	7.10	10^{-9}	2.3	10^{-7}
32	8.75	10^{-9}	1.3	10^{-6}
33	4.12	10^{-8}	5.7	10^{-6}
34	1.28	10^{-7}	7.2	10^{-7}

TABLE II A

EXAMPLES	Global protection in %
1	54.2 ***
2	36.3 **
3	34.3 **
4	38.1 **
5	29.4 **
6	27.8 **
7	14.8 NS
8	26.2 *
9	31.2 **
10	10.3 NS
11	46.5 ***
12	34.1 **
13	32.1 **
14	19.7 NS
15	35.8 **
16	29.3 **
17	11.1 NS
18	12.6 NS
19	45.6 ***
20	32.7 **

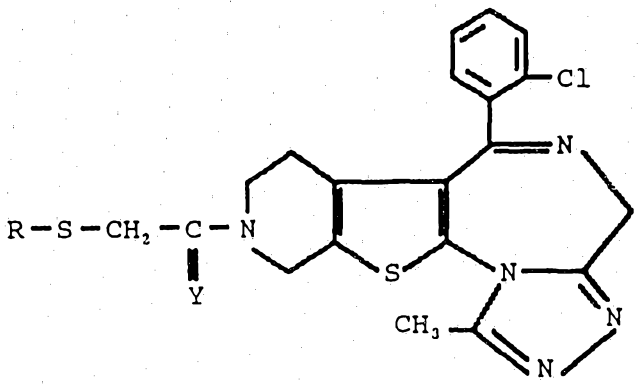
TABLE II B

EXAMPLES	Global protection in %
21	34.1 **
22	48.1 ***
23	37.5 **
24	38.7 **
25	14.7 NS
26	26.5 *
27	33.3 **
28	35.3 **
29	51.6 ***
30	16.1 NS
31	36.2 **
32	30.3 **
33	24.8 *
34	34.7 **

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

~~CxLxAxIxMxSxxx~~

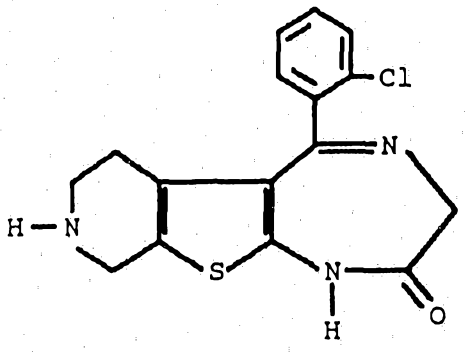
1) Preparation process of the thieno-triazolo-diazepine derivatives of the formula A



A.

wherein Y represents an oxygen or sulphur atom and R represents a straight chain or branched chain alkyl group having from 1 to 20 carbon atoms ; a phenyl group, unsubstituted or substituted by a straight chain or branched chain alkyl group having from 1 to 5 carbon atoms, an alkoxy group having from 1 to 5 carbon atoms, a halogen atom, trifluoromethyl group or an optionally substituted phenoxy group ; or a furan or thiophene ring,

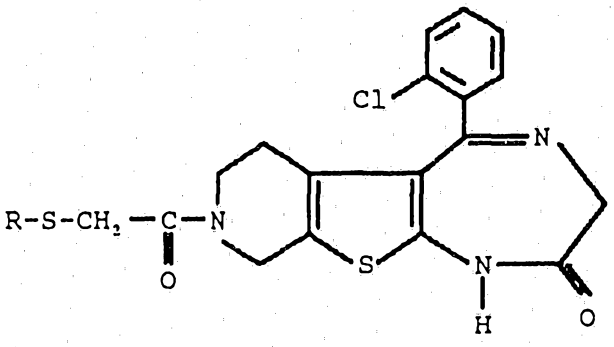
consisting in reacting the ~~thieno-triazolo-~~ pyrido-thieno-diazepine compound of the formula B



B.

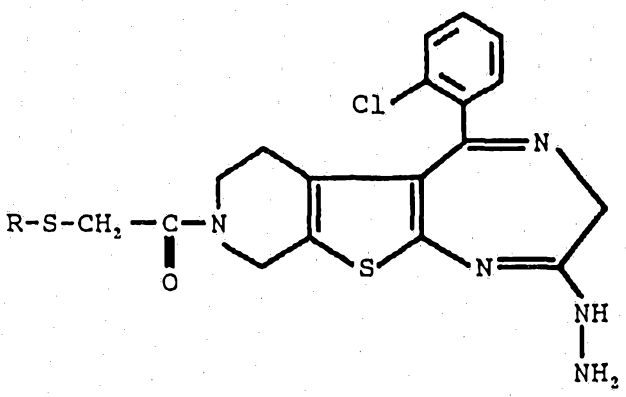
with a stoichiometric amount of $RSCH_2COOH$ derivative C wherein R is as above defined in an aprotic solvent, in the presence of a slight stoichiometric excess of dicyclohexylcarbodiimine at a temperature of from 0 to 60°C,

then reacting the resulting compound of the formula :



D.

wherein R is as above defined, with three to five stoichiometric equivalents of hydrazine hydrate in a protic solvent at a temperature of from room temperature to 50°C, and finally cyclizing in a protic solvent the thus obtained compound of the formula :



E.

with a one to three stoichiometric equivalents of triortho-acetate at a temperature of from room temperature to reflux temperature of the reacting mixture to obtain the thieno-triazolo-diazepine derivative of the general formula A wherein Y is an oxygen atom, and optionnally proceeding with a sulphuration reaction step [D → D'], consisting in reacting the thieno-diazepine derivative of the formula D, on three to five stoichiometric equivalents of phosphorus pentasulfide in an aprotic solvent at a temperature of from 10°C to reflux temperature of the reacting mixture, to obtain the corresponding thieno-triazolo-diazepine wherein Y stands for sulphur atom.

2) A preparation process of claim 1 wherein the reactionnal steps are preferably carried out in an inert atmosphere.

DATED this 10th day of May 1990.

SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICAITONS SCIENTIFIQUES (S.C.R.A.S.)

WATERMARK PATENT & TRADEMARK ATTORNEYS
"THE ATRIUM"
290 BURWOOD ROAD
HAWTHORN. VIC. 3122.