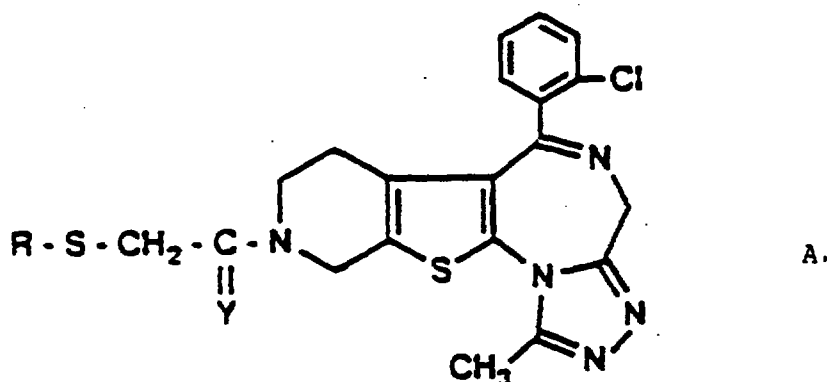


TITLE:**Preparation of Thieno-triazolo-diazepine Derivatives****DESCRIPTION:**

The invention relates to a process for the preparation of derivatives of thieno-triazolo-diazepine.

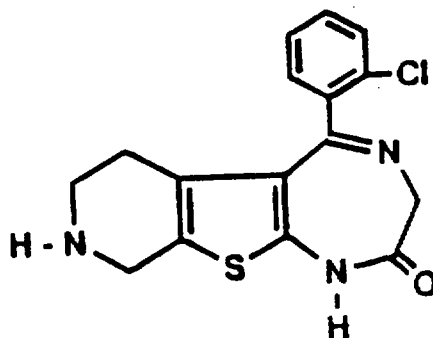
More particularly, the invention relates to a process for the preparation of thieno-triazolo-diazepine derivatives of the general formula A



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; a phenyl group substituted by one or more of 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, a trifluoromethyl group or an optionally substituted phenoxy group; or a furyl or thienyl group.

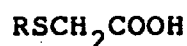
These compounds are described and claimed in our copending Application No. 9010403.5 (Patent No. 2231330). As described therein, they are anti-ischemic, anti-asthmatic and anti-allergic agents and gastro-intestinal protectors.

The invention provides a process for the preparation of the thieno-triazolo-diazepine derivatives of the general formula A as above defined, the process comprising reacting the thieno-triazolo-diazepine derivative of the formula B



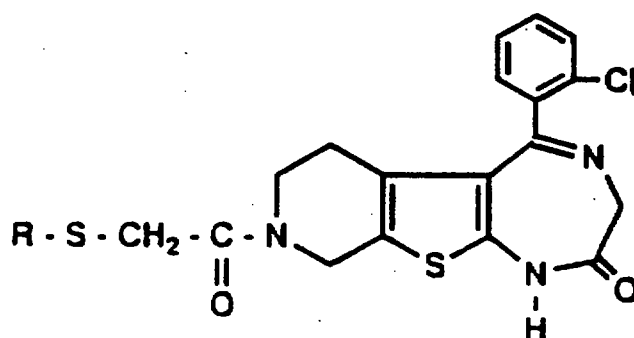
B.

with a stoichiometric amount of a compound of the general formula C



C.

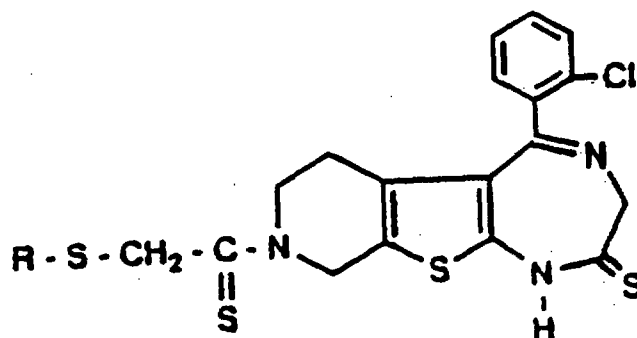
wherein R is as above defined, in the presence of a slight stoichiometric excess of the dicyclohexylcarbodiimide to obtain a compound of the general formula D



D.

wherein R is as above defined;

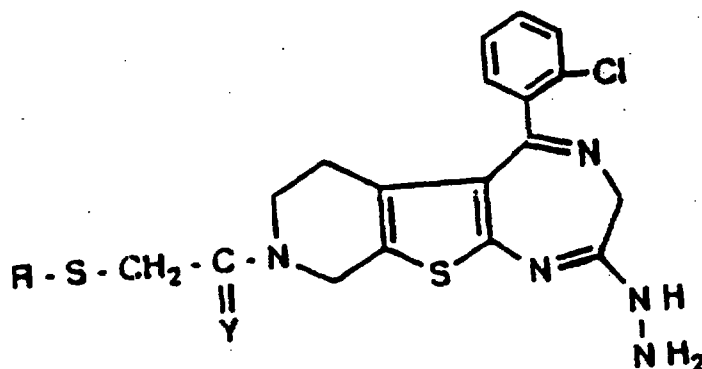
and, if the desired thieno-triazolo-diazepine derivative of the general formula A is one in which Y represents a sulphur atom, reacting the compound of the general formula D with phosphorus pentasulphide or with Lawesson's reagent to obtain a compound of the general formula D'



D'.

wherein R is as above defined;

reacting the compound of the general formula D or D' with a stoichiometric excess of hydrazine hydrate to obtain a compound of the general formula E

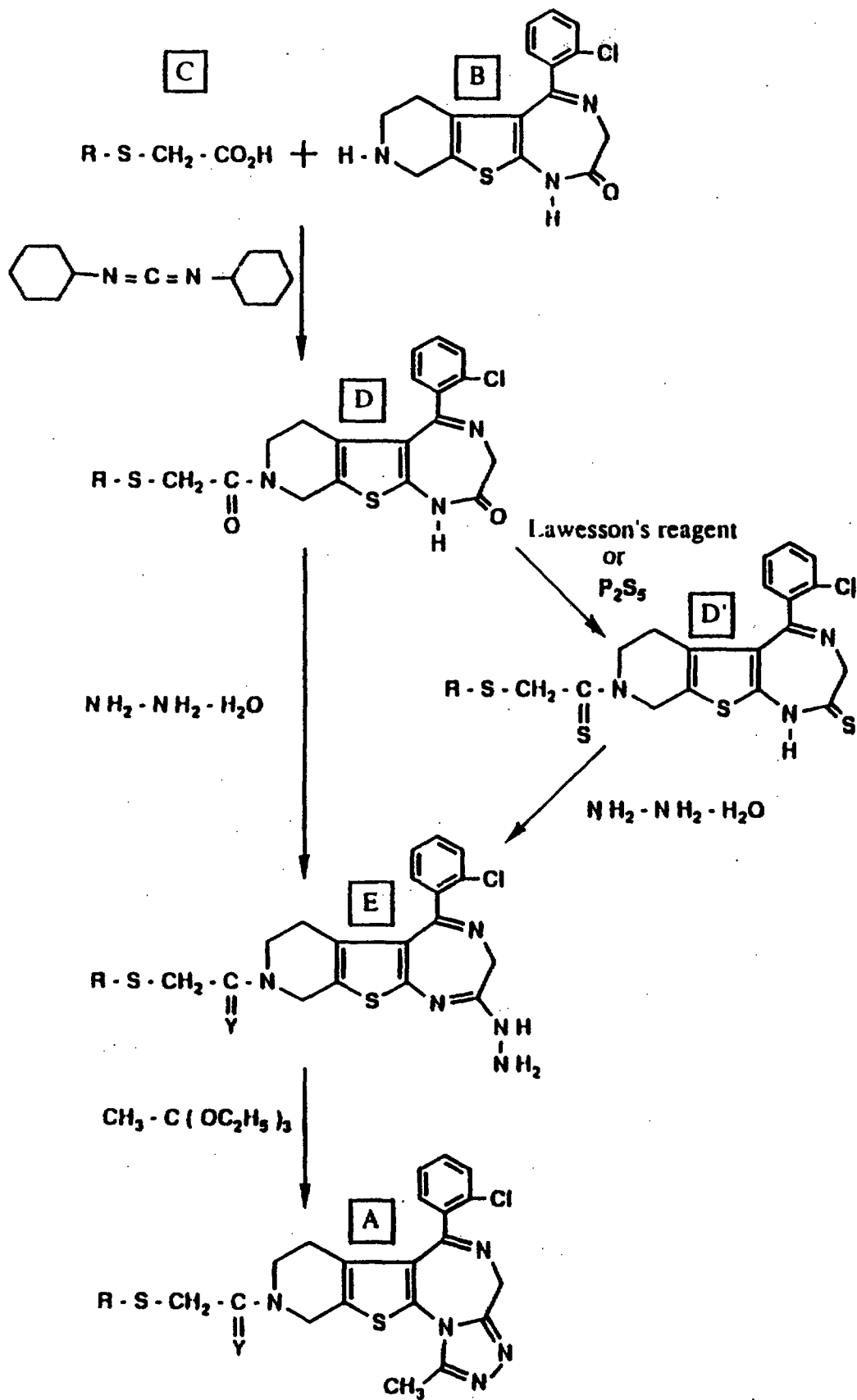


E.

wherein Y and R are as above defined;

and cyclising the compound of the general formula E with a trialkylorthoacetate.

The process is illustrated by the following reaction scheme:

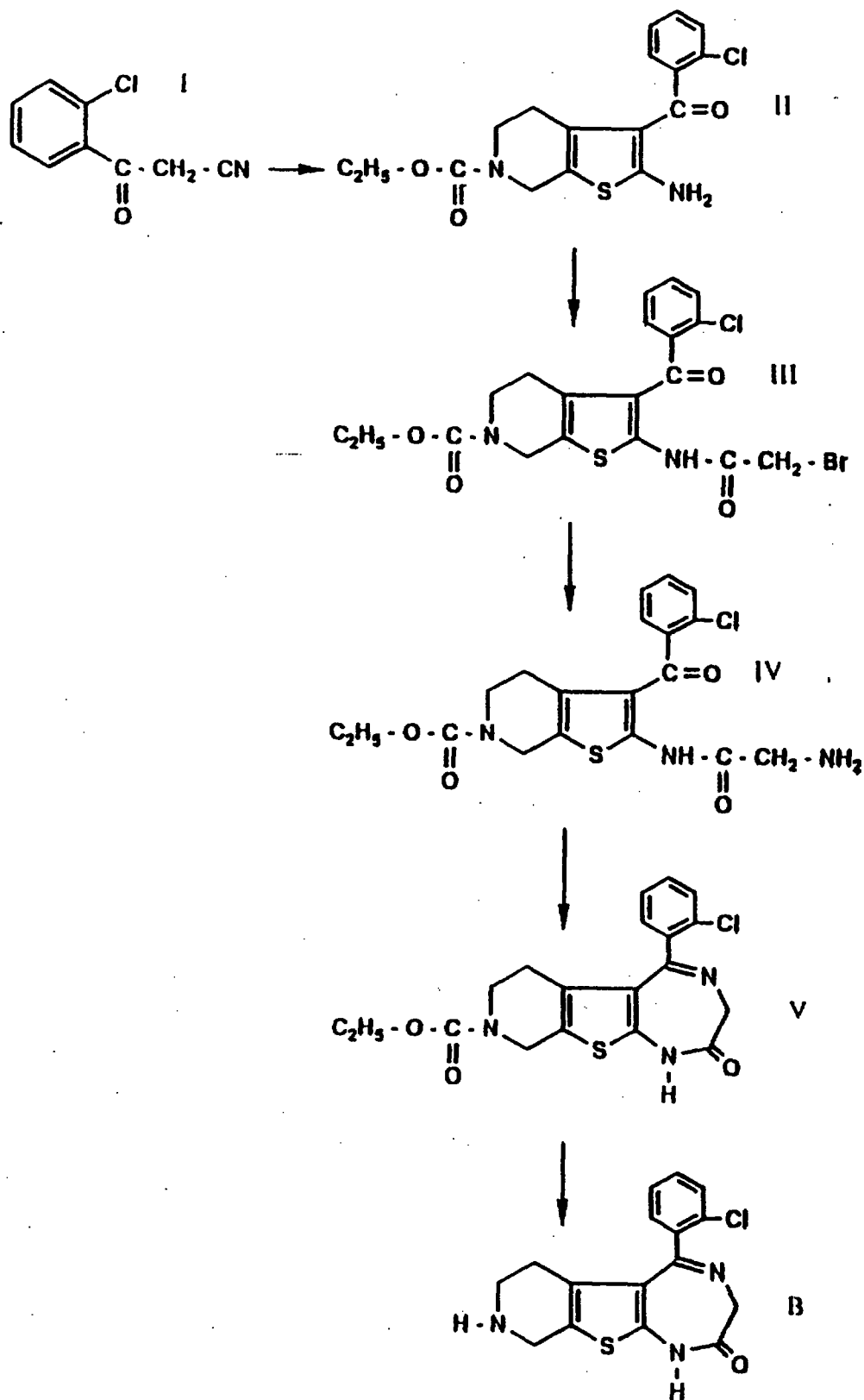


Preferably, the reaction of the compounds of the general formulae B and C is performed in an aprotic solvent at a temperature of from 0 to 60°C. The sulphuration of the compound of the general formula D is suitably performed with three to five stoichiometric equivalents of phosphorus pentasulphide or Lawesson's reagent in an aprotic solvent at a temperature of from 10°C to the reflux temperature of the reaction mixture. The reaction of the compound of the general formula D or D' with hydrazine hydrate is preferably performed in a protic solvent with from three to five stoichiometric equivalents of hydrazine hydrate at a temperature of from ambient temperature to 50°C.

The cyclisation of the compound of the general formula E may be performed with from 1 to 3 stoichiometric equivalents of the trialkylorthoacetate, which is preferably triethylorthoacetate. It may be performed in a protic solvent at a temperature of from ambient temperature to the reflux temperature of the reaction mixture.

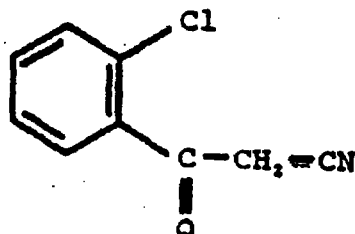
The reactions described above are preferably carried out under an inert atmosphere.

The starting compound of the formula B may be prepared according to the following reaction scheme:



These steps are further described in the following preparative examples I to VI.

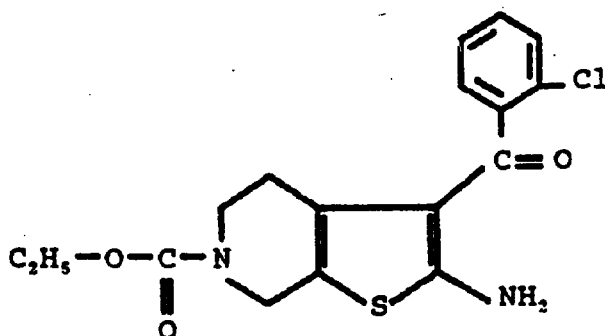
I - (2-chloro)benzoylmethyl cyanide.



7 litres of anhydrous tetrahydrofuran (THF) and 115.9 g (1.36 mol) of previously dried cyanoacetic acid were poured into an appropriate reactor under nitrogen circulation at -70°C . 1715 ml (2.74 mol) of a 1.6 M solution of butyllithium in hexane was added dropwise, while allowing the temperature to rise from -70°C to 0°C . The reaction mixture was then stirred for one hour. Thereafter the reaction mixture was once more cooled to -70°C and a solution of 120 g (0.685 mol) of 2-chloro-benzoyl chloride in 1 litre of anhydrous THF was added dropwise.

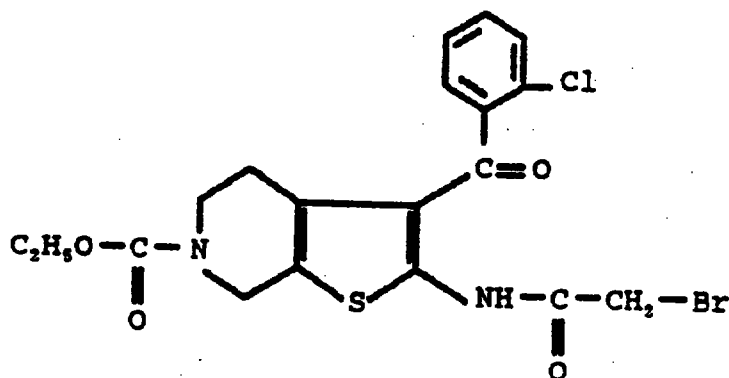
After stirring for one hour at -70°C , the temperature was allowed to rise from -70°C to 0°C for one hour. Then there was added dropwise 3 litres of 1N hydrochloric acid. After stirring for a few minutes, the reaction mixture was extracted with chloroform. The organic phase was washed with a 10% aqueous sodium bicarbonate solution, then with a saturated sodium chloride solution, dried and filtered. The solvent was evaporated off to give 135 g of residue. 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 - 2-amino-3-(2-chlorobenzoyl)-6-ethoxycarbonyl-4,5,6,7-tetrahydro-pyrido [3,4-b] thiophene.



Into a two litre erlen flask 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 flowers of sulphur 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 precipitated. It was filtered off, washed with ethanol, then with diethyl ether and dried to yield 155.4 g (85%) of the title compound.

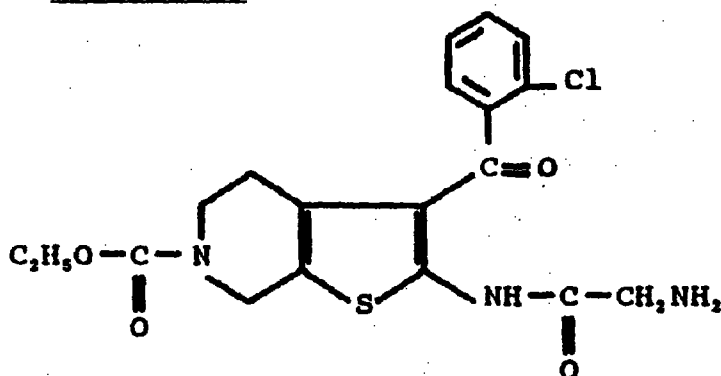
III - 2-bromoacetamido-3-(2-chlorobenzoyl)-6-ethoxycarbonyl-4,5,6,7-tetrahydro-pyrido [3,4-b] thiophene.



Into a five litre reactor fitted with appropriate means and with a separating funnel, were poured 2.5 litres of chloroform and 146 g (0.400 mol) of (II). 87.7 g (0.43 mol) of bromoacetyl bromide contained in the separating funnel were added dropwise. The reaction mixture was stirred for one hour at room temperature and then washed

with 300 ml of iced water. 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.

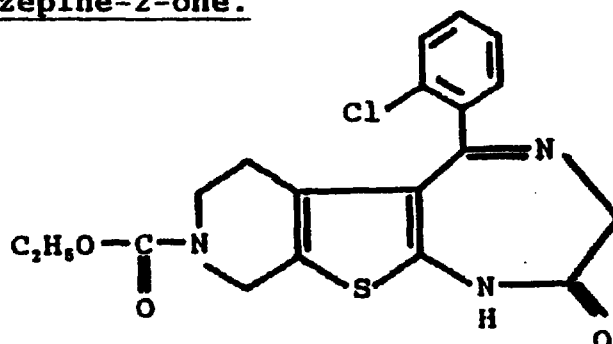


Into a five litre reactor fitted with a gas-injector were poured 174.8 g (0.36 mol) of (III) and 3 litres of THF. The suspension was cooled to 0°C and then gaseous ammonia previously dried over potassium hydroxide was added. The addition was conducted in 8 hours. (60 g of ammonia were absorbed). The mixture was stirred overnight at 0°C. 2 litres of THF were then 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 using a rotary evaporator. The precipitate was allowed to stand overnight in a 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 litres of diethyl ether:THF (3:1 by volume) to give 14.6 g of the title compound (overall yield 88%).

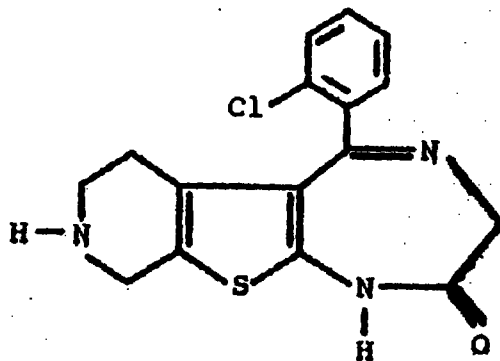
V - 5-(2-chlorophenyl)-8-ethoxycarbonyl-6,7,8,9-tetrahydro-3-H-pyrido [4',3' : 4,5] thieno [3,2-f] 1,4-diazepine-2-one.



126.6 g (0.3 mol) of (IV) and 800 ml of pyridine were poured into a two litre-reactor fitted with stirring, cooling and warming means and under nitrogen circulation. The reaction mixture was refluxed for 18 hours. After having checked that all the starting material had reacted, the pyridine was partially evaporated off using a rotary evaporator under reduced pressure.

The dark brown oil obtained was dissolved in 1 litre of ethanol. After cooling in an ice-bath, there was obtained a precipitate which was filtered off, washed with ethanol and diisopropyl oxide to yield 101.3 g (83.6%) of the title compound.

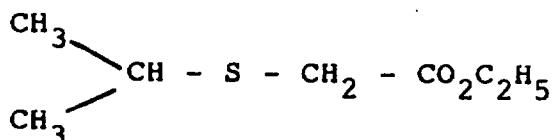
VI - 5-(2-chlorophenyl)-6,7,8,9-tetrahydro-3H-pyrido
[4',3':4,5] thieno [3,2-f] 1,4-diazepine-2-one.



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 monoethylether were poured into a reactor fitted with warming means and under nitrogen circulation. 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 hydrochloric acid (d=1.18) at pH 5.3. Then potassium carbonate was added to adjust the pH to 8.3. The solution was then extracted three times with 500 ml of methylene dichloride. 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 diisopropyl ether and drying, there were obtained 55.9 g of the title compound (yield = 72%).

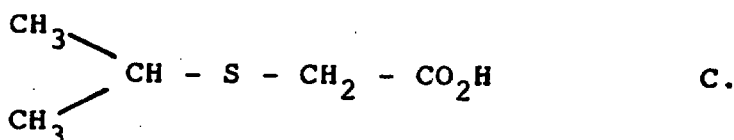
The following preparative examples I' and II' illustrate the preparation of one of the starting compounds of the general formula C, in particular that one in which R represents an isopropyl group.

I' - Ethyl isopropylthio-acetate.



300 ml of methanol and 25.4 g (0.333 mol) of isopropylthiol were poured into a 1 litre reactor fitted with appropriate means. 57.3 g (0.333 mol) of ethyl bromoacetate were added dropwise at room temperature and the mixture was stirred for four hours at room temperature. 135 ml of 2.5N sodium hydroxide solution was then added dropwise such that the pH did not reach a value above 7-7.5. Thereafter the mixture was stirred overnight and then the methanol was evaporated off. The residue was treated with 100 ml of water, and the resultant 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 over anhydrous magnesium sulphate. After filtration and evaporation on a rotary evaporator, there was obtained 46 g of the title compound (yield 85%).

II' - Isopropylthio-acetic acid



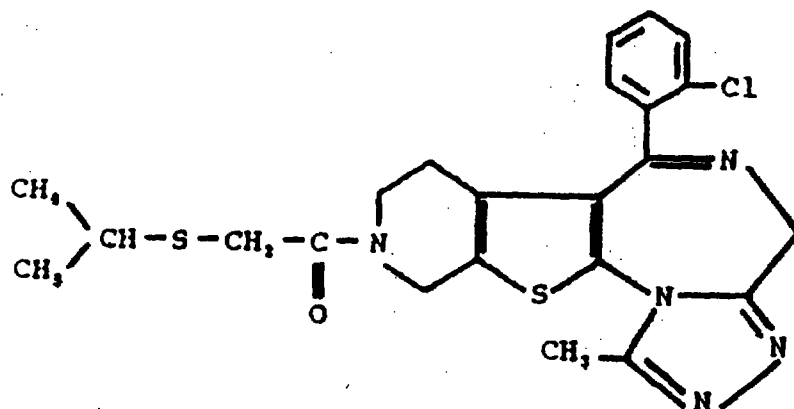
40 g (0.236 mol) of ethyl isopropylthio-acetate and 380 ml of methanol were poured into a 2 litre reactor fitted with appropriate means. A solution of 20.7 g (0.369 mol) of potassium hydroxide in 380 ml of water was then added dropwise. The temperature rose and was then maintained for two hours at 35-38°C. Thereafter the

methanol was evaporated off and the resulting residue was treated with about 500 ml of iced water. The solution was then acidified to pH 3 by addition of a 10% hydrochloric acid solution. The precipitate was filtered off, washed with water until neutrality and dried. The resultant compound was crystallized with 200 ml of a mixture of diisopropyl acetate:diisopropyl ether (4:6 by volume). The solution was filtered hot and allowed to crystallize. After filtration and washing with diisopropyl ether, there was obtained 26.7 g of the title compound (yield 80.5%).

The following Examples illustrate the invention.

EXAMPLE 1

6-(2-chlorophenyl)-9-isopropylthiomethyl-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 = 0, R - isopropyl.



1st step B + C → D:

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

49.8 g (0.150 mol) of 5-(2-chlorophenyl)-6,7,8,9-tetra-
hydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine-

-2-one and 250 ml of dichloroethane were poured into a two litre reactor fitted with appropriate means. The suspension was cooled to 5°C. There were then 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 the temperature at 10°C. The mixture was allowed to stand for 30 minutes in an ice bath. It was then brought to room temperature and warmed to 50°C to homogenize. Thereafter the mixture was stirred overnight at room temperature and the dichloroethane was evaporated off.

The residue obtained was treated with 600 ml of N,N-dimethylformamide. 150 ml of water were then added and the mixture was stirred for two hours. The dicyclohexylurea which had formed was filtered off and the solution was washed with N,N-dimethylformamide. The N,N-dimethylformamide was partially evaporated off. The residue obtained was treated with iced water and precipitation occurred. 0.150 mol of acetic acid were then 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 ethyl acetate. The solution was cooled and allowed to stand for three hours in a 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-(isopropylthiomethyl-carbonyl)-2-hydrazino-6,7,8,9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine

42.5 g (0.095 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, 1 litre of methanol and 19.06 g (0.376 mol) of hydrazine hydrate were poured into a two litre reactor fitted with appropriate means and placed under nitrogen circulation. The suspension was allowed to stand for 90 minutes at room temperature (25°C). The presence of starting material was proved by CCM analysis. The mixture was then heated to 40°C for 30 minutes and subsequently 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.

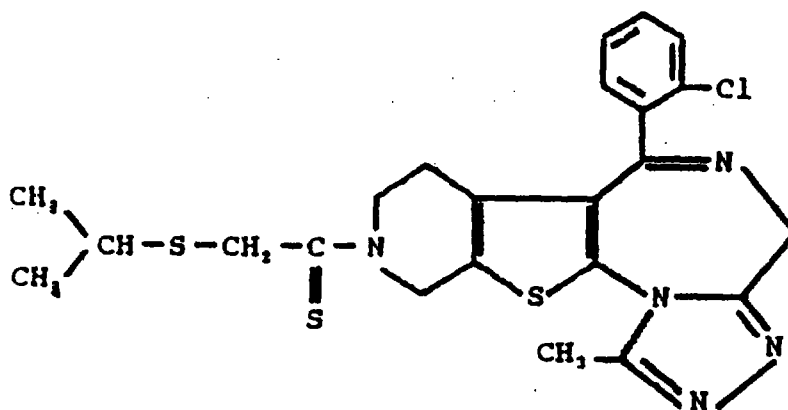
Preparation of 6-(2-chlorophenyl)-9-(isopropylthiomethyl-carbonyl)-7,8,9,10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine.

32.4 g (0.070 mol) of 5-(2-chlorophenyl)-8-isopropylthiomethyl-carbonyl)-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 were poured into a 1 litre reactor fitted with cooling means and placed under nitrogen circulation. The suspension was refluxed for 90 minutes; after 15 minutes of reflux, there was obtained a solution and precipitation occurred after 45 minutes of reflux. All

of the starting material had reacted. The mixture was then cooled. The precipitate was filtered off and washed with methanol and 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] diazepine
Y = S, R = isopropyl.



1st step B + C → D:

Preparation of 5-(2-chlorophenyl)-8-(isopropylthio-
methyl-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 detail in Example 1 (first step).

2nd step D → D':

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

40.3 g (0.090 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 and 1.25 litres of 1,2-dimethoxy-ethane were poured into a five litre reactor fitted with appropriate means and placed under nitrogen circulation. The suspension was warmed to 60°C. 87.1 g (0.392 mol) of phosphorus pentasulphide and 65.4 g (0.785 mol) of sodium bicarbonate were then added over a period of 15 minutes. After this addition 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 litres of iced water were added. The mixture was then poured into a 5 litre beaker and 0.4 M sodium bicarbonate solution was added until the pH reached 8. The mixture was stirred for 30 minutes. The resultant precipitate was filtered off, washed with water, ethanol and diethyl ether, and treated with 1 litre of dichloromethane. Insoluble matter was filtered off. The mixture was then washed with 300 ml of dichloromethane, which was subsequently 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-isopropylthiomethyl-thiocarbonyl-2-hydrazino-6,7,8,9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine

19.7 g (0.041 mol) of 5-(2-chlorophenyl)-8-(isopropylthiomethyl-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 were poured into a two litre reactor fitted with appropriate means and placed under nitrogen circulation. The suspension was allowed to stand for

90 minutes at room temperature (25°C). The presence of starting material was proven by CCM analysis. The mixture was therefore 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, after washing and with diethyl ether, 16.4 g of the title compound (yield 84%).

4th step E → A:

Preparation of 6-(2-chlorophenyl)-9-(isopropylthio-methyl-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

12 g (0.025 mol) of 5-(2-chlorophenyl)-8-(isopropylthio-methyl-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 were poured into a 1 litre reactor fitted with cooling means and placed under nitrogen circulation. The suspension was refluxed for 90 minutes; after 15 minutes of reflux, there was obtained a solution and precipitation occurred after 45 minutes of reflux. All of the starting material had reacted. The mixture was then cooled. The precipitate was filtered off and washed with methanol and 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 RSCH₂CO₂H 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-(phenylthiomethyl-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- (phenylthiomethyl-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-chlorophenyl)-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-car-
bonyl)-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-thio-
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 = 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- furylthiomethyl-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- furylthiomethyl-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- thienylthiomethyl-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-thienylthiomethyl-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.

US Patent No. 4621083 (and the equivalent European Patent No. 176927) disclose thieno-triazolo-diazepine derivatives having PAF-antagonistic activity. The compounds prepared by the process of this invention present a PAF-antagonistic activity from ten to a thousand times greater than the diazepines disclosed in the abovementioned Patent, and also a more potent effectiveness.

TOXICITY

The compounds of the invention are not toxic on mice 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 in Table I (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 aggregation 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 ³H-RO-15-1788 and ³H-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 Table I (right hand column).

3) Global ischemia on gerbils

For this test, males gerbils 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 seconds, aliquots of 50 µl each of this preparation were incubated in each 1 ml of TRIS-HCl buffer containing ³H-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 ³H-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 in Table II.

PRESENTATION - POSOLOGY

In human therapy, the compounds of the invention are preferably administered by the oral route. Preferred 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. The preferred unit dose is 50 mg, associated with appropriate carriers and agents. They may also be administered 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

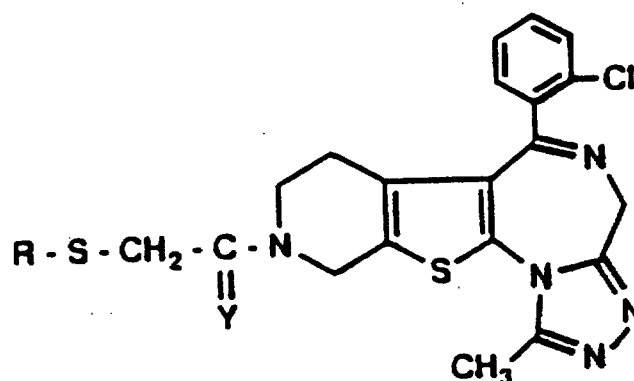
EXAMPLES	Global protection in %
1	54.2 ***
2	36.3 **
3	34.3 **
4	38.1 **
5	29.4 **
6	27.8 **
7	14.8 NS
8	26.2 *
9	31.2 **
10	10.3 NS
11	46.5 ***
12	34.1 **
13	32.1 **
14	19.7 NS
15	35.8 **
16	29.3 **
17	11.1 NS
18	12.6 NS
19	45.6 ***
20	32.7 **

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 **

CLAIMS:

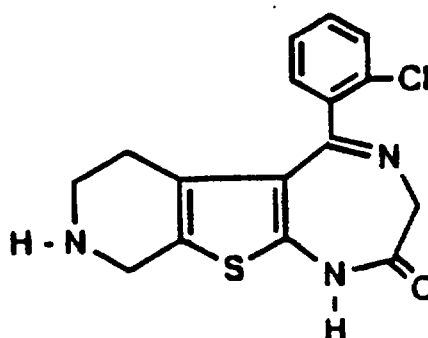
1. A process for the preparation of a thieno-triazolo-diazepine derivative of the general formula A



A.

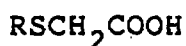
wherein Y represents an oxygen or sulphur atom and R represents a straight chain or branched chain alkyl group having from 1 to 20 carbon atoms; a phenyl group; a phenyl group substituted by one or more of a straight chain or branched chain alkyl group having from 1 to 5 carbon atoms, an alkoxy group having from 1 to 5 carbon atoms, a halogen atom, a trifluoromethyl group or an optionally substituted phenoxy group; or a furyl or thienyl group;

the process comprising reacting the thieno-triazolo-diazepine compound of the general formula B



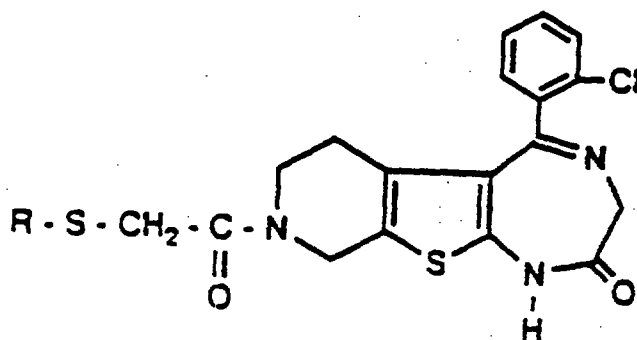
B.

with a stoichiometric amount of a compound of the general formula C



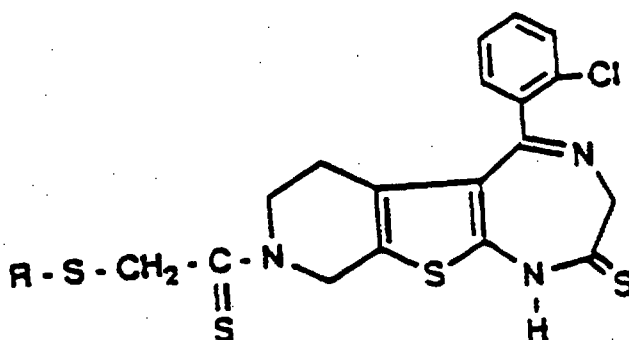
C.

wherein R is as defined in this claim in the presence of a slight stoichiometric excess of dicyclohexylcarbodiimide to obtain a compound of the general formula D



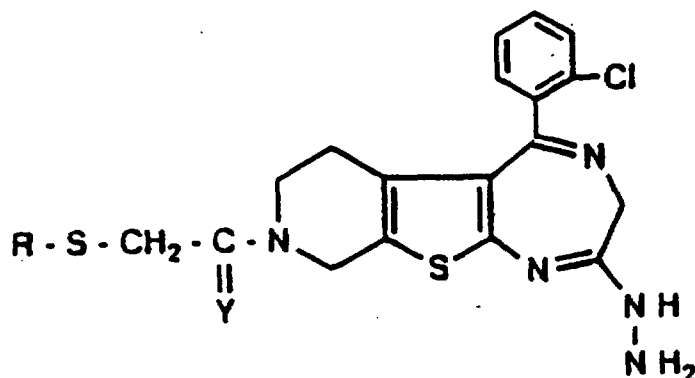
wherein R is as defined in this claim;

and, if the desired thieno-triazolo-diazepine derivative of the general formula A is one in which Y represents a sulphur atom, reacting the compound of the general formula D with phosphorus pentasulphide or with Lawesson's reagent to obtain a compound of the general formula D'



wherein R is as defined in this claim;

reacting the compound of the general formula D or D' with a stoichiometric excess of hydrazine hydrate to obtain a compound of the general formula E



E.

wherein Y and R are as defined in this claim;
and cyclising the compound of the general formula E
with a trialkylorthoacetate.

2. A process according to claim 1 wherein the reaction
of the compounds of the general formulae B and C is
performed in an aprotic solvent at a temperature of
from 0 to 60°C.

3. A process according to claim 1 or claim 2 wherein
the sulphuration of the compound of the general formula
D is performed with three to five stoichiometric
equivalents of phosphorus pentasulphide or Lawesson's
reagent in an aprotic solvent at a temperature of from
10°C to the reflux temperature of the reaction mixture.

4. A process according to any preceding claim wherein
the reaction of the compound of the general formula D
or D' with hydrazine hydrate is performed in a protic
solvent with from three to five stoichiometric
equivalents of hydrazine hydrate at a temperature of
from ambient temperature to 50°C.

5. A process according to any preceding claim wherein
the cyclization of the compound of the general formula
E is performed with from 1 to 3 stoichiometric
equivalents of triethylorthoacetate.



6. A process according to any preceding claim wherein the cyclization of the compound of the general formula E is performed in a protic solvent at a temperature of from ambient temperature to the reflux temperature of the reaction mixture.

7. A process according to any preceding claim wherein any or all of the reactions are performed under an inert atmosphere.

8. A process according to claim 1, the process being substantially as described herein with reference to any of the Examples.
