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Preparation of thieno-triazolo-diazepine derivatives

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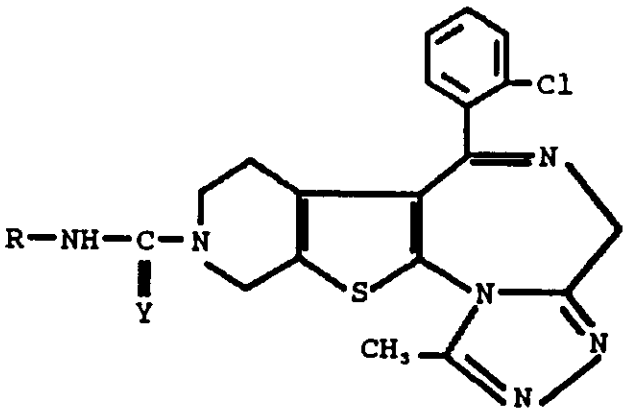
TITLE:

Preparation of Thieno-triazolo-diazepine Derivatives

DESCRIPTION:

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

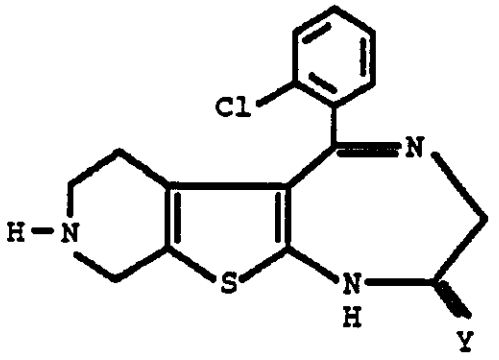
More particularly, the invention relates to a process for the preparation of thieno-triazolo-diazepine derivatives of the general formula I



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 cycloalkyl group having from 3 to 6 carbon atoms,
a straight chain alkenyl group having from 2 to 5 carbon atoms,
a straight chain or branched chain alkyl group having from 1 to 5 carbon atoms and being substituted by an aryl or heteroaryl group,
a phenyl group substituted by one or more of an alkyl group, a lower alkoxy group having from 1 to 5 carbon atoms, a phenoxy group, an alkylsulphonyl group having from 1 to 5 carbon atoms, a fluorine atom, a chlorine atom or a trifluoromethyl group,
a heterobicyclic group, or
a sulphonyl group substituted by a phenyl group, a heteroaryl group or a bicyclic group.

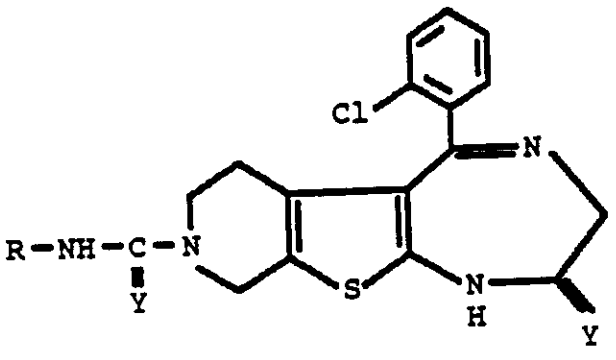
These compounds are described and claimed in our British Patent No. 2229723. They are anti-asthmatic and anti-allergic agents and gastro-intestinal protectors.

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



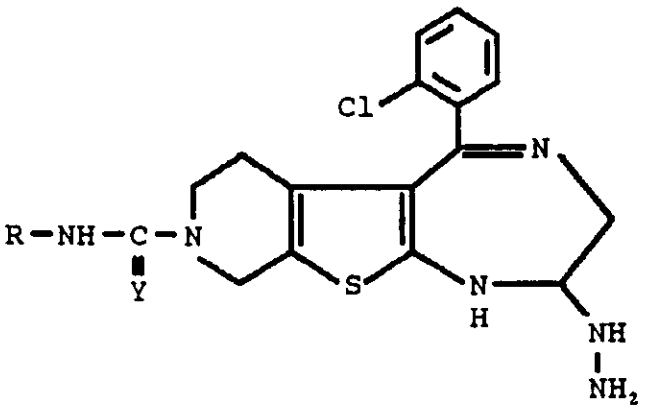
A.

wherein Y is as above defined
with stoichiometric excess of a compound of the general formula R-N=C=Y wherein R and Y are as above defined; reacting the resultant compound of the general formula B:



B.

wherein R and Y are as above defined with a stoichiometric excess of hydrazine hydrate; and cyclizing the resultant compound of the general formula C:



C.

wherein R and Y are as above defined with a stoichiometric excess of triethylorthoacetate.

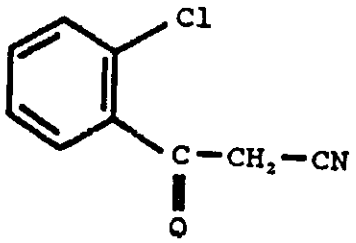
The reaction of compound A with R-N=C=Y is suitably performed under nitrogen circulation in a protic solvent under reflux for from ½ to 24 hours. Only a slight stoichiometric excess of R-N=C=Y is needed.

The reaction of compound B with hydrazine hydrate is suitably performed under nitrogen circulation in an aprotic solvent at a temperature of from 0°C to room temperature. From 5 to about 60 minutes suffices. Only a slight stoichiometric excess of hydrazine hydrate is needed.

The cyclization is preferably performed under nitrogen circulation in a protic solvent. The cyclization may be commenced at room temperature for from 15 minutes to 3 hours, but is preferably completed under reflux for from ½ to 5 hours. A fourfold stoichiometric excess of triethylorthoacetate is desirable.

The starting compound of the formula (A) may be prepared as described in the following steps:

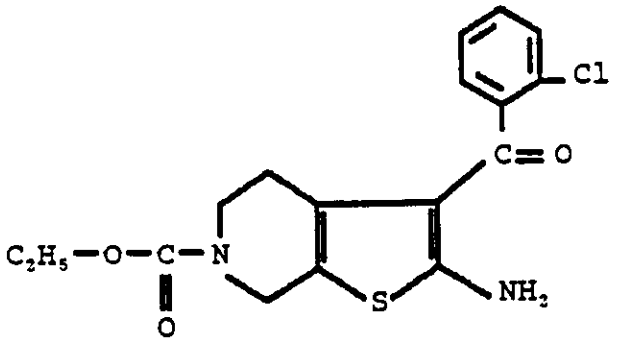
I - (2-chloro)benzoylmethyl cyanide.



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.

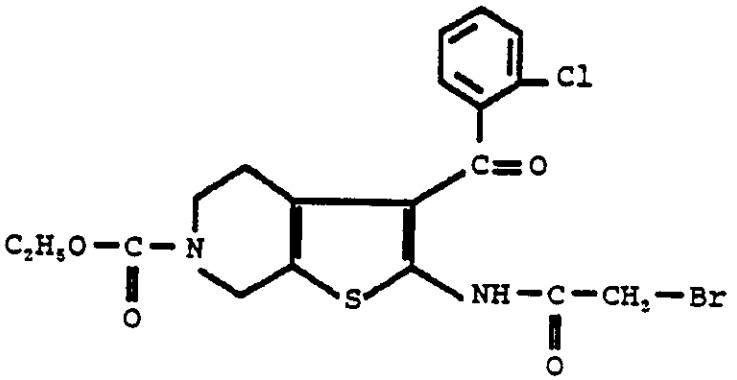
After stirring for one hour at -70°C, the temperature was allowed to rise from -70°C to 0°C for one hour. Then there was added dropwise 3 litres of 1N hydrochloric acid. After stirring for a few minutes, the reaction mixture was extracted with chloroform. The organic phase was washed with a 10% aqueous 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.

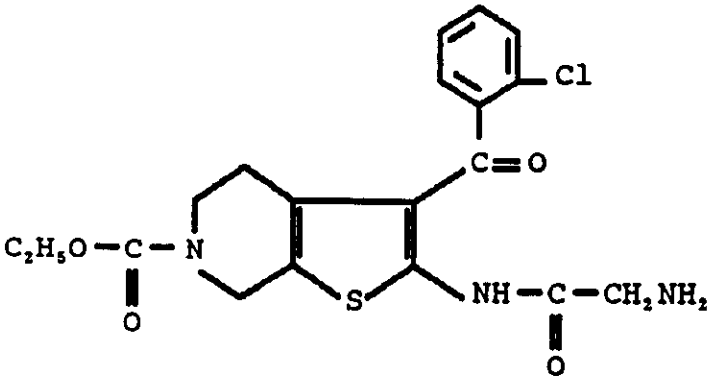
III - 2-bromo-acetamido-3-(2-chlorobenzoyl)-6-ethoxycarbonyl-4,5,6,7-tetrahydro-pyrido [3,4-b] thiophene.



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 bromoacetylbromide 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-ethoxy-carbonyl-4,5,6,7-tetrahydro-pyrido [3,4-b] thiophene.**

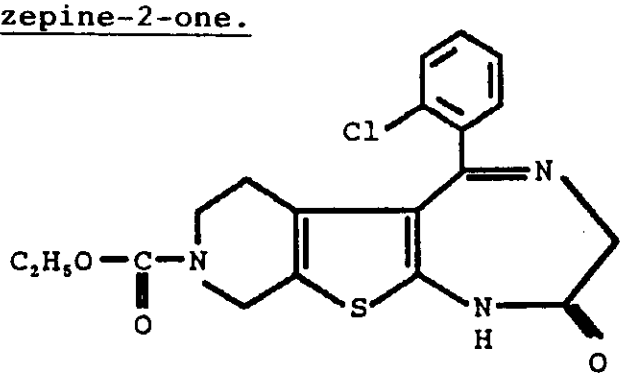


Into a five litre reactor fitted with a gas-injector were poured 174.8 g (0.36 mol) of (III) and 3 litres of THF. The suspension was cooled to 0°C and then gaseous ammonia previously dried over potassium hydroxide was added. The addition was conducted in 8 hours. (60 g of ammonia were absorbed). The 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%).

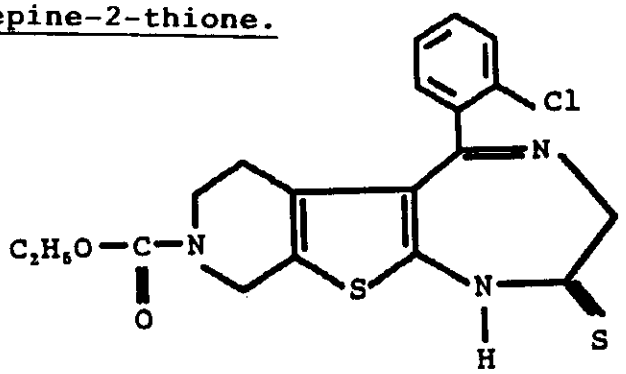
V - 5-(2-chlorophenyl)-8-ethoxycarbonyl-6,7,8,9-tetra hydro-3-H-pyrido [4',3' : 4,5] thieno [3,2-f] 1,4--diazepine-2-one.



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.

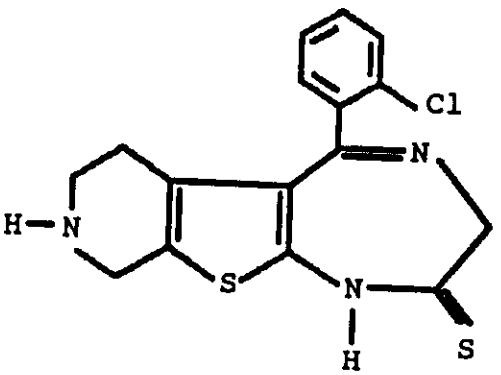
The dark brown oil obtained was dissolved in 1 litre of ethanol. After cooling in an ice-bath, there was obtained a precipitate which was filtered off, washed with ethanol and diisopropyloxide to yield 101.3 g (83.6%) of the title compound.

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



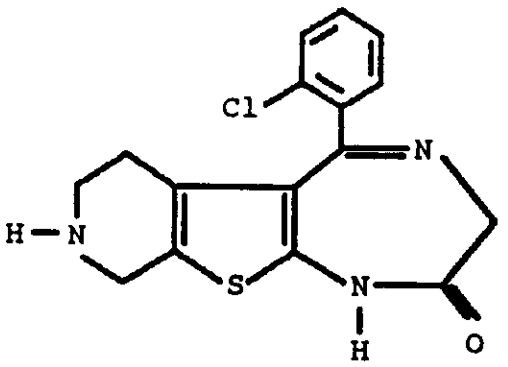
93 g (0.230 mol) of V and 1.75 litres of pyridine were poured into a three litre-reactor fitted with appropriate means. After solubilization, there were added 56.3 g (0.25 mol) of phosphorus pentasulphide, and the reaction mixture was then stirred for three hours at 80-85°C. Thereafter, the pyridine was evaporated off and the obtained residue treated with icy-water. The mixture was then extracted by methylene dichloride, dried with anhydrous magnesium sulphate, filtered, evaporated and treated with diethyl ether. The resulting product was filtered off, and treated with 700 ml of acetonitrile. The suspension was heated at 60°C for 30 minutes and then allowed to cool. After filtration, and washing with acetonitrile and then with diethyl ether, the residue was dried to yield 80.2 g (83%) of the title compound.

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



71.4 g (0.17 mol) of (VI), 116 g (1.30 mol) of (85%) pelleted potassium hydroxide and 1 litre of a mixture of ethanol:water (19:1 by volume) were poured into a two litre reactor fitted with appropriate means. The reaction mixture was refluxed for 18 hours. After having checked that all the starting material had reacted, the ethanol was evaporated off and the residue was treated with iced water. The mixture was then extracted twice with chloroform. The aqueous phase was acidified to pH 6.5 with acetic acid, and the pH was then adjusted to 7.5 by addition of sodium bicarbonate. The precipitate was filtered off, washed twice with water, twice with ethanol and once with diethyl ether, and then washed under reflux with 500 ml of a mixture of dichloromethane:ethanol (3:1 by volume) for 30 minutes. After filtration, washing with diethyl ether and drying under reduced pressure, there were obtained 47.3 g of the title compound (yield 80%).

VIII - 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 Examples illustrate the invention.

EXAMPLE 1

6-(2-chlorophenyl)-9-(4-methoxyphenylthiocarbamoyl)--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

First Step

Preparation of 5-(2-chlorophenyl)-8-(4-methoxyphenyl-thiocarbamoyl)-6,7,8,9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine-2-thione B: Y=S, R=4-methoxyphenyl)

40 g (0.115 mol) of 5-(2-chlorophenyl)-6,7,8,9-tetrahydro--3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine-2--thione (93%) (A: Y=S) and 500 ml of methanol were poured into a 1 litre reactor fitted with stirring and cooling means and under nitrogen circulation.

18.5 ml (0.123 mol) of 4-methoxyphenylisothiocyanate were added to the orange suspension which was then refluxed for two hours. After having checked that all the starting material had reacted, the mixture was cooled. After filtration, the residue was washed with ethanol and then with diisopropylether. It was dried overnight

at 65°C to yield 49 g (83%) of the title compound.

Second Step

Preparation of 5-(2-chlorophenyl)-8-(4-methoxyphenyl-thiocarbamoyl)-2-hydrazino-6,7,8,9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine (C: Y=S, R=4-methoxyphenyl)

40 g (0.078 mol) of 5-(2-chlorophenyl)-8-(4-methoxyphenyl-thiocarbamoyl)-6,7,8,9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine-2-thione and 350 ml of tetrahydrofuran were poured into a 1 litre reactor fitted with stirring and cooling means and under nitrogen circulation. The mixture was cooled to 10°C, and 4.1 ml (0.081 mol) of hydrazine hydrate were added. The addition was conducted in 15 minutes. There was thus obtained a red-brown solution with a dark slight precipitate which was then filtered off. Thereafter 9/10 of the tetrahydrofuran was evaporated off, and 400 ml of absolute ethanol were added to the residue. Precipitation occurred after priming. The mixture was stirred on an ice-bath for 1 hour. The precipitate was then filtered off, washed with ethanol, then with diisopropyl ether, and dried overnight under reduced pressure at 65°C to give 29.7 g of the title compound. The washing-liquors were concentratated and the resulting residue was treated with ethanol, filtered, washed with ethanol then with diethyl ether to give 4.5 g of the title compound (overall yield 86%).

Third Step

Preparation of the title compound

25.5 g (0.05 mol) of 5-(2-chlorophenyl)-8-(4-methoxy-phenylthiocarbamoyl)-2-hydrazino-6,7,8,9-tetrahydro-3H--pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine and 500 ml of absolute ethanol were poured into a 1 litre reactor fitted with stirring and cooling means and under nitrogen circulation. 37 ml (0.20 mol) of triethylorthoacetate

were added. After 30 minutes, the solution became red, and was then refluxed for two hours (precipitation started at 70°C). The mixture was cooled to 10°C and the precipitate filtered off, washed with ethanol and then with diethyl ether. It was dried under reduced pressure at 90°C to yield 24.6 g (92%) of the title compound.

The following compounds have been prepared as described in Example 1 when Y=S; when Y=0, the reaction is also carried out in 3 steps in the same conditions as described in Example 1 but starting with 5-(2-chlorophenyl)-6,7,8,9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine-2-one [instead of 5-(2-chlorophenyl)-6,7,8,9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine-2-thione] and reacting on the appropriate isocyanate derivative instead of the isothiocyanate derivative.

EXAMPLE 2

6-(2-chlorophenyl)-9-(4-methoxyphenyl carbamoyl)-
-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=4-methoxyphenyl

EXAMPLE 3

6-(2-chlorophenyl)-9-t.butylcarbamoyl-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=t.butyl

EXAMPLE 4

6-(2-chlorophenyl)-9-t.butylthiocarbamoyl-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-hexadecylthiocarbamoyl -7,8,9,10--tetra-hydro-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 6

6-(2-chlorophenyl)-9-isopropylcarbamoyl-7,8,9,10-tetra-hydro-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

EXAMPLE 7

6-(2-chlorophenyl)-9-isopropylthiocarbamoyl-7,8,9,10--tetra-hydro-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.

EXAMPLE 8 :

6-(2-chlorophenyl) - 9-(3,4,5-trimethoxyphenylcarbamoyl) -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 9 :

6-(2-chlorophenyl) - 9-(3,4,5-trimethoxyphenylthiocarbamoyl)- - 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 10 :

6-(2-chlorophenyl) - 9-(4-t.butylphenylcarbamoyl) - 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 11:

6-(2-chlorophenyl) - 9-(4-t.butylphenylthiocarbamoyl)- -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 12 :

6-(2-chlorophenyl) - 9-(2-trifluoromethylphenylthiocarbamoyl)- 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 13 :

6-(2-chlorophenyl) - 9-(3-trifluoromethylphenylthiocarbamoyl)- 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 14 :

6-(2-chlorophenyl) - 9-(4-trifluoromethylphenylcarbamoyl)--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-trifluoromethyl phenyl

EXAMPLE 15 :

6-(2-chlorophenyl) - 9-(4-trifluoromethylphenylthiocarbamoyl)- 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 16 :

6-(2-chlorophenyl) - 9-(4-fluorophenylthiocarbamoyl) - 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-fluoro phenyl

EXAMPLE 17 :

6-(2-chlorophenyl) - 9-(2,3-dichlorophenylcarbamoyl) - 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-dichloro phenyl

EXAMPLE 18 :

6-(2-chlorophenyl) - 9-(4-phenoxyphenylcarbamoyl) - 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-phenoxy phenyl

EXAMPLE 19 :

6-(2-chlorophenyl) - 9-(α-methylphenethylthiocarbamoyl) - -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 = α-methylphenethyl

EXAMPLE 20 :

6-(2-chlorophenyl) - 9-(β-methylphenethylthiocarbamoyl) - -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 = β-methylphenethyl

EXAMPLE 21 :

6-(2-chlorophenyl)- 9-(4-methylsulphonyl phenylthiocarbamoyl)- - 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-methylsulphonylphenyl

EXAMPLE 22 :

6-(2-chlorophenyl) - 9-(2,4-di-t.butylphenylthiocarbamoyl)-
- 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 = 2,4-di-t.butylphenyl

EXAMPLE 23 :

6-(2-chlorophenyl) - 9-benzylcarbamoyl - 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 = benzyl

EXAMPLE 24 :

6-(2-chlorophenyl) - 9-(2-furfurylthiocarbamoyl) - 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-furfuryl

EXAMPLE 25 :

6-(2-chlorophenyl) - 9-(3-quinolylthiocarbamoyl) - 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-quinolyl

EXAMPLE 26 :

6-(2-chlorophenyl) - 9-cyclohexylthiocarbamoyl - 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 = cyclohexyl

EXAMPLE 27 :

6-(2-chlorophenyl) - 9-cyclohexylcarbamoyl - 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 = cyclohexyl

EXAMPLE 28 :

6-(2-chlorophenyl) - 9-allylthiocarbamoyl - 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 = allyl

EXAMPLE 29 :

6-(2-chlorophenyl) - 9-(2,4-difluorophenylcarbamoyl) - 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 = 2,4-difluorophenyl

EXAMPLE 30 :

6-(2-chlorophenyl) - 9-(phenylsulphonylthiocarbamoyl)- 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 = phenylsulphonyl

EXAMPLE 31 :

6-(2-chlorophenyl) - 9-(2-furylsulphonylthiocarbamoyl) -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- furylsulphonyl

EXAMPLE 32 :

6-(2-chlorophenyl) - 9-(2-thienylsulphonyl)carbamoyl - 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- thienylsulphonyl

EXAMPLE 33 :

6-(2-chlorophenyl) - 9-(2-pyrrolylsulphonylthiocarbamoyl)--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-pyrrolylsulphonyl

EXAMPLE 34 :

6-(2-chlorophenyl) - 9-(3-pyridylsulphonylcarbamoyl) - 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- pyridyl sulphonyl

EXAMPLE 35 :

6-(2-chlorophenyl) - 9-(4-quinolylsulphonylthiocarbamoyl) --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- quinolylsulphonyl

EXAMPLE 36 :

6-(2-chlorophenyl) - 9-(4-morpholinylsulphonylcarbamoyl) --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- morpholinylsulphonyl

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 per os at the dose of 1 g/kg. By the IP route on the mice, only the compounds of Examples 10, 17, 18 and 33 showed a LD_{50} between 0.4 and 1 g/kg and all the others were not toxic at 1 g/kg.

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 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 intereaction 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 Table I (right hand column).

3) Action on the bronchospasm induced by the PAF

The PAF intravenous injection in anaesthetized guinea-pigs induces a bronchoconstriction with a leucopeny and a thrombocytopeny, according to the method described in S. DESQUAND, C. TOUVAY, J. RANDON, V. LAGENTE, B. VILAIN, I. MARIDONNEAU-PARINI, A. ETIENNE, J. LEFORT, P. BRAQUET and B. VARGAFTIG. Interference of BN 52021 (Ginkolide B) with the bronchopulmonary effects of PAF-acether in the guinea-pig. Eur. J. Pharmacol. 127 : 83-95, 1986.

Male Hartley guinea-pigs (400-450 g) (Charles River) anaesthetized with urethane (2 g/kg IP), then are thracheotomized and submitted to a forced respiration with a breathing pump : 70-80 strokes/mn, 1 ml of air/100 g per stroke. A catheter is introduced in the jugular vein for the injections, an other is introduced in the carotic artery for blood takings. The initial resistance is kept constant under the pressure of 10 cm of water in accordance with the Konzett and Rössler method and the air in excess is measured with a transducor for bronchospasm UGO BASILE together with an enregistror GEMINI. The guinea-pigs had received an IV injection of pancuronium (Pavulon) to inhibit their spontaneous respiration.

The compound according to the invention and the reference compound WEB 2086 (see the above cited Boehringer patent) have been prepared as suspension in gummy water and administrated orally 1 hour before the stimulation by the PAF.

The bronchoconstriction is determined by the calculation of the percentage of bronchoconstriction $\frac{A}{B} \times 100$ wherein A stands for induced bronchoconstriction in mm and B stands for maximum bronchoconstriction in mm.

The results are reported in table II.

PRESENTATION - POSOLOGY

In human therapy, the compounds of the invention are preferably administered 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.

TABLE I A

EXAMPLES	IC_{50}		BDZ receptors	
1	3.01	10^{-7}	2	10^{-6}
2	1.27	10^{-7}	7.7	10^{-5}
3	1.71	10^{-8}	4.3	10^{-7}
4	8.82	10^{-9}	1.35	10^{-7}
5	2.97	10^{-7}	6.3	10^{-5}
6	2.35	10^{-8}	6.6	10^{-5}
7	3.28	10^{-8}	7	10^{-6}
8	1.15	10^{-8}	1.5	10^{-6}
9	3.87	10^{-8}	4.5	10^{-6}
10	8.8	10^{-9}	5.25	10^{-6}
11	9.44	10^{-9}	1.2	10^{-6}
12	1.71	10^{-7}	3.5	10^{-6}

TABLE I B

EXAMPLES	IC_{50}		BDZ receptors	
13	1.71	10^{-7}	6.25	10^{-6}
14	1.5	10^{-7}	7.05	10^{-5}
15	2.2	10^{-7}	1.25	10^{-6}
16	6.4	10^{-8}	7.	10^{-7}
17	5.5	10^{-8}	9.2	10^{-7}
18	3.3	10^{-8}	8.6	10^{-7}
19	4.25	10^{-8}	3.6	10^{-7}
20	6.17	10^{-9}	7.2	10^{-7}
21	2.4	10^{-8}	1.1	10^{-6}
22	3.66	10^{-7}	6.3	10^{-7}
23	6.68	10^{-8}	1.6	10^{-6}
24	4.8	10^{-8}	6.5	10^{-7}

TABLE I C

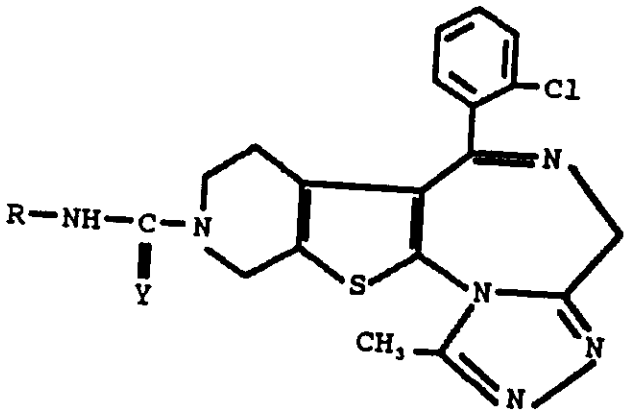
EXAMPLES	IC_{50}		BDZ receptors	
25	1.82	10^{-7}	3.5	10^{-7}
26	5.33	10^{-8}	4.1	10^{-6}
27	4.52	10^{-8}	2.	10^{-6}
28	9.05	10^{-9}	1.4	10^{-7}
29	5.86	10^{-8}	2.2	10^{-7}
30	1.1	10^{-8}	6.3	10^{-7}
31	8.15	10^{-9}	6.15	10^{-7}
32	6.66	10^{-8}	4.33	10^{-6}
33	2.05	10^{-7}	9.1	10^{-6}
34	1.0	10^{-7}	4.	10^{-5}
35	3.4	10^{-8}	2.2	10^{-6}
36	6.10	10^{-9}	7.25	10^{-6}

TABLE II

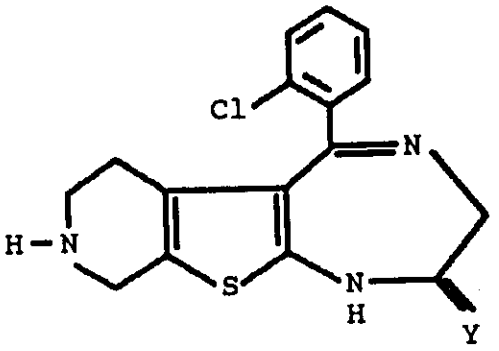
Examples	Percentage of bronchoconstriction	Percentage of action
Controls	79. + 5.55	-
WEB 2086	25.3 + 11.56 ***	- 68.0
1	13 + 4.39 ***	- 83.5
3	28.7 + 9.30 ***	- 63.7
5	30.3 + 8.80 ***	- 61.6
7	23.4 + 10.50 ***	- 70.4
8	16.2 + 8.38 ***	- 79.5
10	26.7 + 11.0 ***	- 66.2
14	48.6 + 14.32 **	- 38.5
18	14.1 + 11.25 ***	- 81.8
22	25.5 + 13.2 ***	- 67.7
24	33.3 + 12.8 ***	- 57.9
30	37.2 + 14.95 ***	- 52.9
33	22.4 + 9.8 ***	- 71.7

CLAIMS:

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

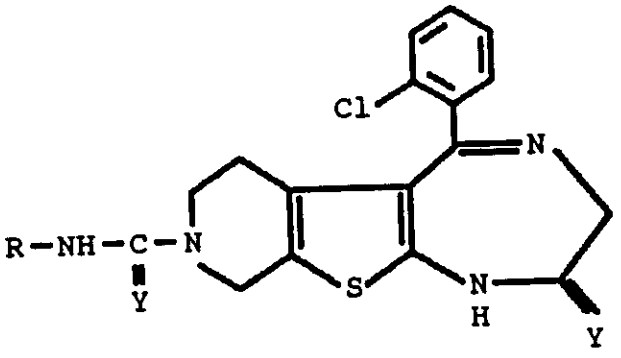


wherein Y represents an oxygen or sulphur atom and R represents a straight chain or branched chain alkyl group having from 1 to 20 carbon atoms,
a cycloalkyl group having from 3 to 6 carbon atoms,
a straight chain alkenyl group having from 2 to 5 carbon atoms,
a straight chain or branched chain alkyl group having from 1 to 5 carbon atoms and being substituted by an aryl or heteroaryl group,
a phenyl group substituted by one or more of an alkyl group, a lower alkoxy group having from 1 to 5 carbon atoms, a phenoxy group, an alkylsulphonyl group having from 1 to 5 carbon atoms, a fluorine atom, a chlorine atom or a trifluoromethyl group,
a heterobicyclic group, or
a sulphonyl group substituted by a phenyl group, a heteroaryl group or a bicyclic group,
the process comprising reacting the thieno-triazolo--diazepine compound of the general formula A



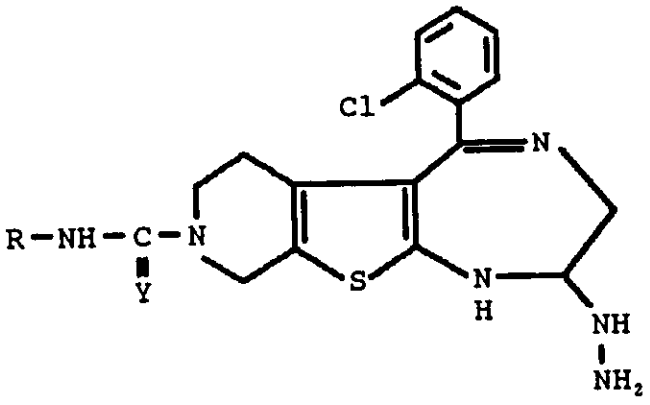
A.

wherein Y is as defined in this claim with a stoichiometric excess of a compound of the general formula R-N=C=Y wherein R and Y are as defined in this claim; reacting the resultant compound of the general formula B



B.

wherein R and Y are as defined in this claim with a stoichiometric excess of hydrazine hydrate; and cyclizing the resultant compound of the general formula C



C.

wherein R and Y are as above defined with a stoichiometric excess of triethylorthoacetate.

2. A process according to claim 1 wherein the reaction of compound A with R-N=C=Y is performed under nitrogen circulation in a protic solvent under reflux for from ½ to 24 hours.

3. A process according to claim 1 or claim 2 wherein the reaction of compound B with hydrazine hydrate is performed under nitrogen circulation in an aprotic solvent at a temperature of from 0°C to room temperature for from 5 to 60 minutes.

4. A process according to any preceding claim wherein the cyclization of compound C is performed with a fourfold excess of triethylorthoacetate.

5. A process according to any preceding claim wherein the cyclization of compound C is performed under nitrogen circulation in a protic solvent first at room temperature for from 15 minutes to three hours and then under reflux for from ½ to 5 hours.

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

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