

[54] **TRANQUILIZING AND ANTI-ANXIETY PHARMACEUTICAL COMPOSITIONS**

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Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 173,305, Aug. 19, 1971, Pat. No. 3,799,920.

[30] **Foreign Application Priority Data**

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[52] **U.S. Cl.**..... **424/244**, 424/248, 424/250, 424/267, 424/274

[51] **Int. Cl.**..... **A61k 27/00**

[58] **Field of Search** 424/248, 250, 267, 274

[56] **References Cited**

UNITED STATES PATENTS

3,296,249 1/1967 Bell..... 260/239.3 D

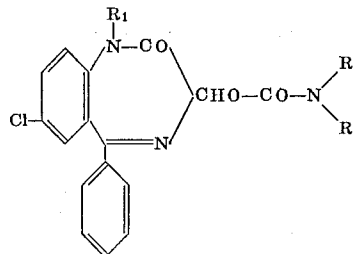
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[57] **ABSTRACT**

Tranquillizing and anti-anxiety pharmaceutical com-

positions are disclosed comprising, as the active ingredient, a 1,4-benzo-diazepine derivative containing a carbamic ester group, having the general formula:



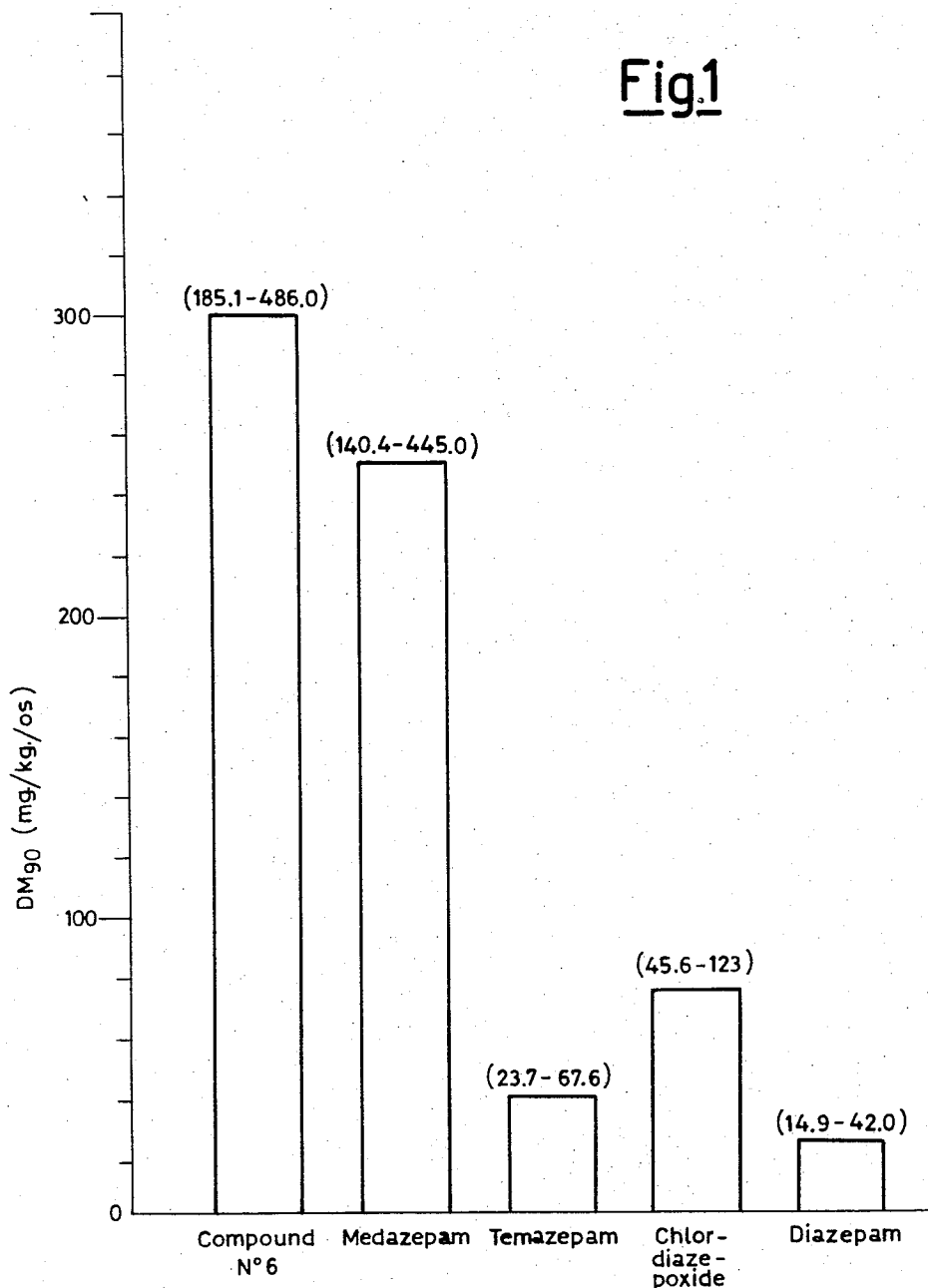
(I)

wherein R₁ is hydrogen or a lower alkyl of 1 to 4 carbon atoms, and R₂ and R₃ are, each, hydrogen, a lower alkyl of 1 to 4 carbon atoms, a cycloalkyl or lower alkyl bearing as a substituent an amine or hydroxy group, and R₂ and R₃ can also form a polymethylene chain, possibly containing one hetero-atom; these compositions have low toxicity and are devoid of objectionable side effects, such as the asthenizing and myorelaxing effect characteristic of the prior art compounds of the class of the 1,4-benzodiazepines.

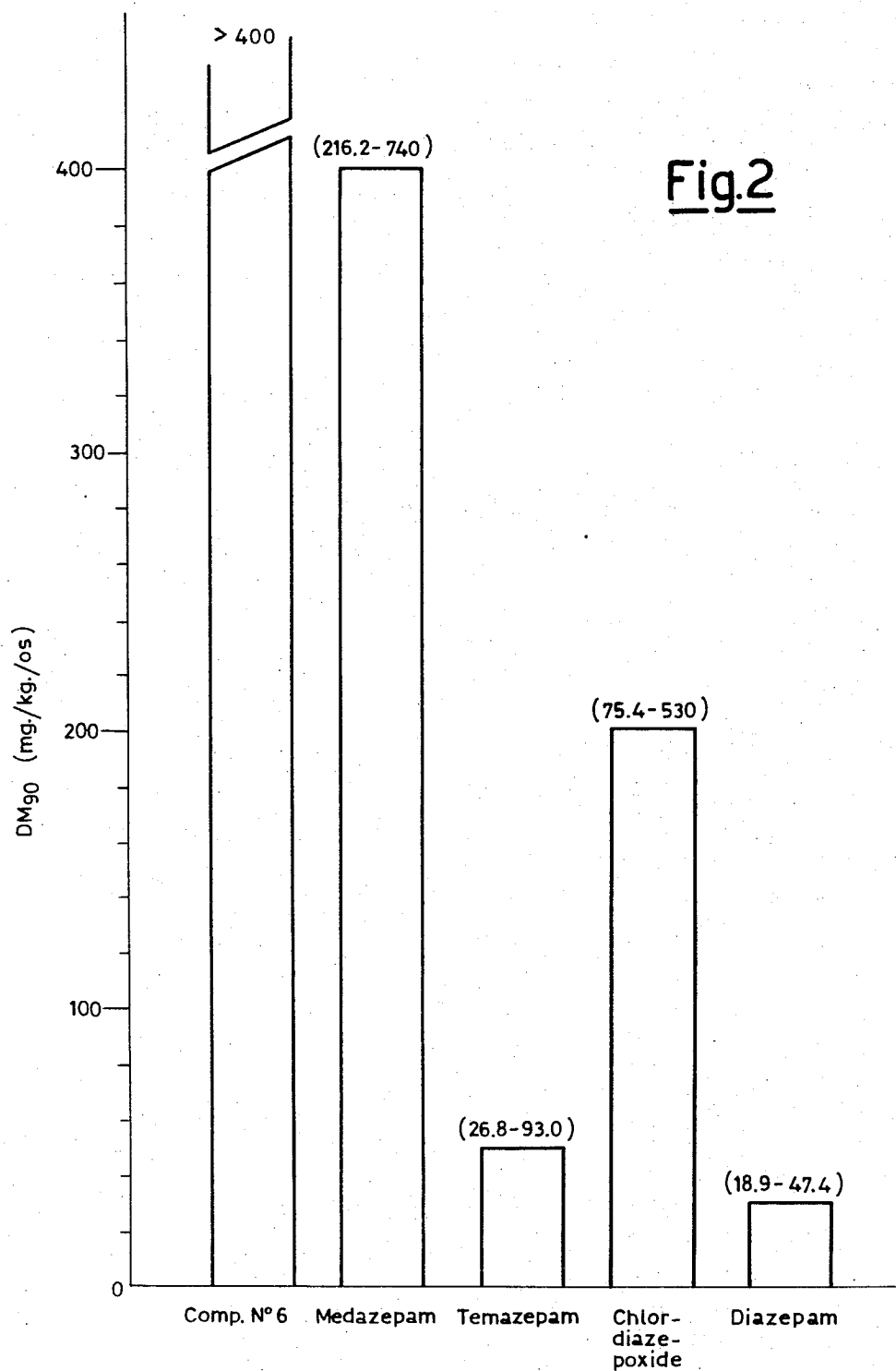
The therapeutic method is also described.

13 Claims, 4 Drawing Figures

Fig.1



Effect of comp. N°6 and of some other benzodiazepine compounds on the traction test in the mouse.
 MD₅₀ = doses in mg/kg/os which cause the myorelaxing effect in the 90% of the mice.



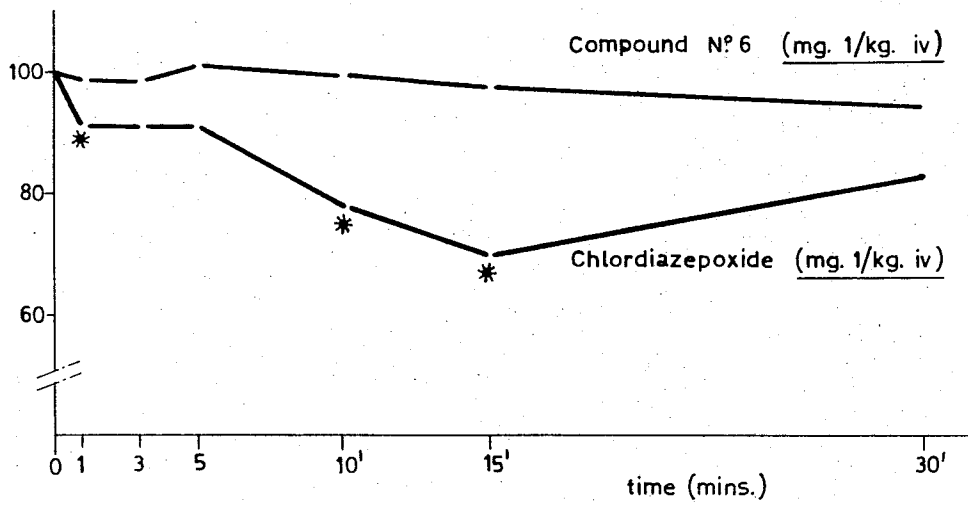
Effect of compound N°6 and of some other benzodiazepine compounds in the rotarod test in the mouse.

MD₅₀ = doses in mg./kg./os which cause the myorelaxing effect in the 90% the mice.

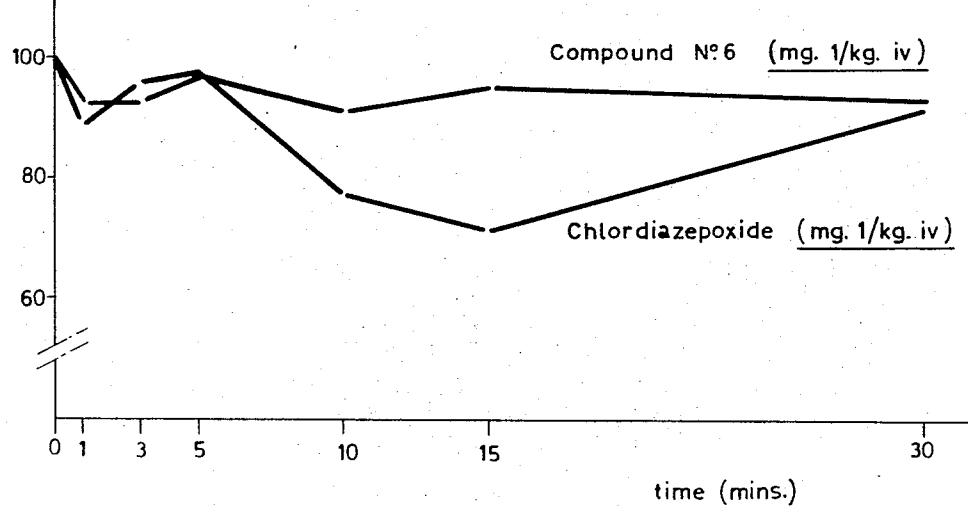
Effects on the left ventricular pressure (pvs) and dp/dt in the awake dog.

Fig.3

% variation
of pvs



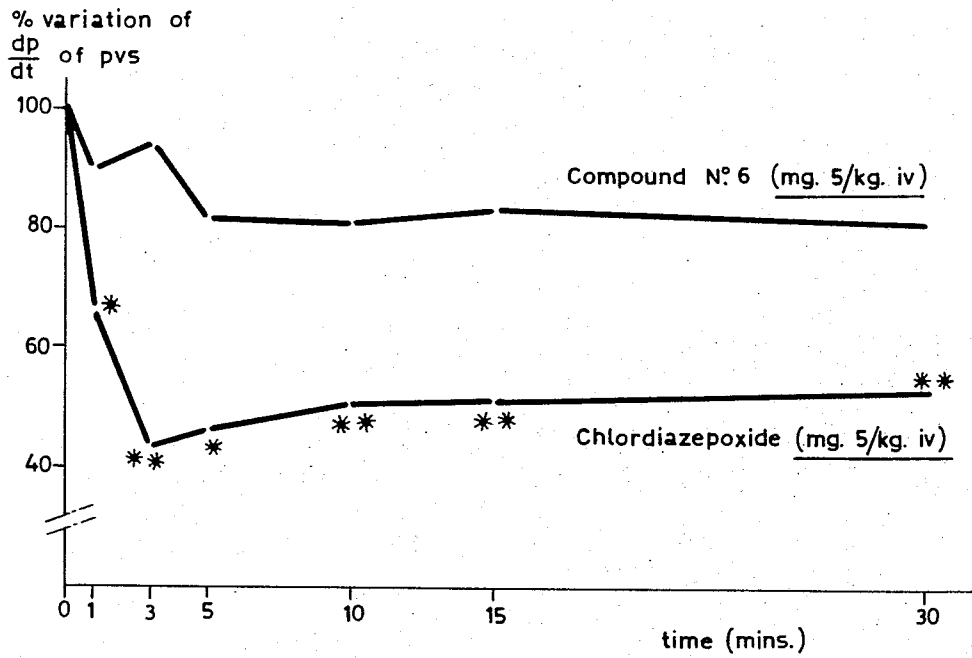
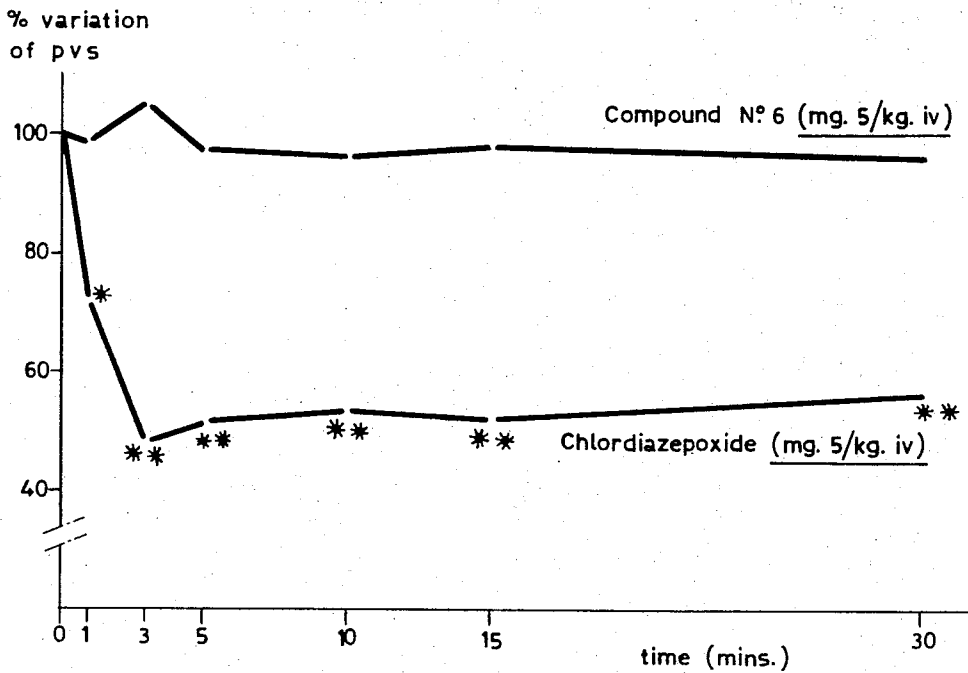
% variation of
 $\frac{dp}{dt}$ of pvs



* P < 0,05

Effects on the left ventricular pressure (pvs) and dp/dt in the awake dog.

Fig.4



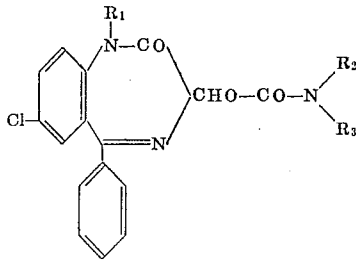
* P < 0,05

** P < 0,01

TRANQUILIZING AND ANTI-ANXIETY PHARMACEUTICAL COMPOSITIONS

This Application is a continuation-in-part of the U.S. application Ser. No. 173,305 filed Aug. 19, 1971, now U.S. Pat. No. 3,799,920.

This invention relates to pharmaceutical compositions containing, as the active ingredient, an 1,4-benzodiazepine derivative having the general formula:



(I)

wherein R_1 is hydrogen, or a lower alkyl having 1 to 4 carbon atoms, and R_2 and R_3 are, each, hydrogen, a lower alkyl of 1 to 4 carbon atoms, a cycloalkyl or lower alkyl bearing as a substituent an amine or hydroxy group, and R_2 and R_3 can also form, conjointly, a polymethylene chain or also a polymethylene chain containing one heteroatom.

Since 1962 the class of the 1,4-benzodiazepine has been extensively investigated as to their possible application as psychopharmacological agents and several compounds of this class have achieved a widespread therapeutic use.

However some problems and disadvantages arose with respect to their long term therapeutical use, namely:

their toxicity is rather high, so that a great deal of care is needed as to their administration; some objectionable side effects are induced by their use, namely exceedingly high sedative action and muscle relaxation liable to induce depression, drowsiness, fatigue and reduced working capability.

It has surprisingly been found that some compounds having the above formula (I), when used as the active ingredient of a tranquillizer and anti-anxiety drug, show considerably improved properties, and are both weakly toxic and devoid of objectionable side effects, thus permitting a more intense therapy without the asthenizing effect, characteristic of the prior art compounds.

These and other objects are achieved, according to the present invention, by means of a pharmaceutical composition, useful for tranquillizing and anti-anxiety use, as well as for the treatment of depressing moods, psychoneuroses and psychosomatic ailments, characterized in that the active ingredient is selected amongst the compounds of the formula (I) above referred to, said compound being present at a dosage of 5 to 30 milligrams.

The pharmaceutical compositions of the present invention can be embodied as tablets, dragees and capsules, for the oral administration, solutions and suspensions both for oral and parenteral use, and suppositories.

These pharmaceutical compositions can be prepared by using an 1,4-benzodiazepine derivative having the above formula (I), at dosage levels of 5 to 30 mg, so as to permit the administration of daily total doses of 5 to 90 mg in 1 to 3 times.

In the pharmaceutical compositions the aforesaid 1,4-benzodiazepine derivatives can be present alone or, alternatively, in combination with other active principles, so as to obtain a composition useful both for the treatment of anxious states and for the treatment of functional troubles, the cause of which is at least partially attributable to the same anxious mood. For example, a benzodiazepine derivative could be usefully associated to an antispasmodic drug, e.g., a compound of the group of the atropine or synthetic analogues, and/or of the group of the papaverine and its synthetic analogues. Lastly the compounds of the present invention can be combined with antianginous drugs, as for example pentaerythritol tetranitrate.

The pharmaceutical compositions of the present invention can be formulated with suitable excipients and diluents, so as to obtain a sustained release, and therefore to extend the effect of the active principles and reduce the number of daily administrations.

The following examples are illustrative of two possible embodiments for the formulation of pharmaceutical compositions containing one of the aforesaid benzodiazepine derivatives, namely 3-N,N-dimethylcarbamoyloxy-1-methyl-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one.

EXAMPLE I

3-N,N-Dimethylcarbamoyloxy-1-methyl-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (20 g) is dissolved in 1.6 l of tetrahydrofurfuryl alcohol-polyethylene glycol ether (Glycofurol); the solution is made up to 2 l with distilled, pyrogen-free water, then divided in ampules, each containing 2 ml, which are sealed and sterilized by heating at 112°C for 20 min. A dosage form containing 20 mg of the active principle and suitable for parenteral administration is thus obtained.

EXAMPLE II

3-N,N-Dimethylcarbamoyloxy-1-methyl-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (100 g) is thoroughly mixed with 600 g of carboxymethylcellulose, 40 g of talc, 50 g of silica gel (e.g., Gesilite) and 10 g of magnesium stearate; the mixture is sieved through a 200-mesh sieve and compressed in tablets weighing 80 mg; these are coated by the usual technique to give sugar-coated tablets, each weighing 160 mg and containing 10 mg of the active principle.

The present invention relates also to the method for the treatment of patients suffering from anxious states according to which a composition containing 5 to 30 mg of a compound having the preceding formula (I) as the active ingredient is administered to the patient.

In a preferred embodiment, the method of the present invention comprises the treatment of the patients suffering from anxiety with a pharmaceutical composition, containing, besides pharmacologically acceptable carriers and excipients, doses of between 5 and 30 mg of 3-N,N-dimethylcarbamoyloxy-1-methyl-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one.

In the following the results of some pharmacological and clinical tests about some compounds of the preceding formula (I) are summarized in order to permit their outstanding properties and effects to be appreciated.

1. Effects on the spontaneous motility of grouped mice (Dews, Brit. J. Pharmacol. 8, 46 (1953)). Each tested compound has been administered, as a suspen-

sion in 5 percent carboxymethylcellulose and at a dose of 10 mg/kg per os, to several groups each of five Swiss white mice.

One hour after the administration, the animals have been introduced in the chamber of an actometer having a photoelectrical call detector and their movements have been recorded during 1 hour. In the Table 1 the percent reductions of motility are reported in comparison with a reference group of mice.

2. Effect on the hypermotility induced by amphetamine on grouped mice (Piala et al. *J. Pharmacol. Exptl. Ther.* 127, 55, (1959)).

By the same technique as the preceding test, each compound has been tested, at a dose of 10 mg/kg per os, on several groups of mice, which had been previously tested with amphetamine (10/kg i.p. 2 hours before the administration of the compounds being tested). The percent variation, i.e., either the increase and the decrease, with respect to a control group treated only with amphetamine are reported in Table 1.

3. Effect on the behaviour of rats subjected to luminous and acoustical stimuli (reactive motility, open field) (Brimblecome and Green, *Nature*, 194, 193 (1962)).

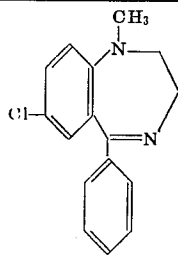
A rat is placed within a circular container, having a diameter of 83 cm and surrounded by a wall 20 cm high; the floor of the container is subdivided into zones having a surface area of 250 sq.cm. After a 30 second time for the rat to become familiarized, the rat is subjected to a luminous and acoustical continuous stimulus during about 3 minutes, and the number of zones run through by the rat is counted.

Groups of at least ten rats have been tested without administering any drug; after 24 hours the same rats have been treated with the compounds being tested, at a dose of 25 mg/kg per os.

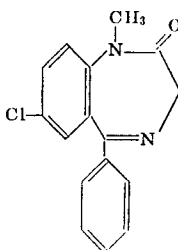
In the Table 1, the percent variation, i.e., either the increase or the decrease of the number of the zones run through after the administering of the drugs with respect to the number of zones run through in basal conditions are reported.

In the same Table 1, the results of the same tests as performed with known 1,4-benzodiazepine compounds, having a structural formula as much as possible close to that of the compounds used in the present invention are shown; these known compounds, which are commonly used in the therapy of anxious states are the following:

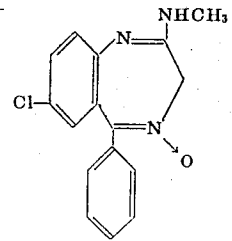
Medazepam.....



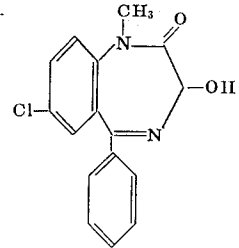
Diazepam.....



Chlordiazepoxide.....



Temazepam.....



The preceding three tests give an indication of the tranquillizing activity, such an indication directly ensuing from the reduced motility of the animals in the tests (1) and (3), whereas in the case of the test (2) an increased hypermotility induced by amphetamine (which is apparently paradoxical), is observed. However, such an effect is known to be characteristic of the benzodiazepines having anxiolytic and tranquillizing activity, as it is also reported in the literature (Taccardi, *Arch. Ital.Sci.Farmacol.*, 12, 3 (1962)); Fleury, *Arch.Sci.* 10, 107 (1957)).

Two further pharmacological tests (as hereinafter described at (4) and (5)) have been carried out, in order to evaluate the potential side effects of the compounds being tested. In fact, as it is well known in the related art, the objectionable side effects, which frequently occur in the therapeutical use of tranquillizing drugs containing the known 1,4-benzodiazepine compounds, are exceedingly high sedative action and muscle relaxation liable to induce depression, drowsiness, fatigue and reduced working capability.

4. Potentiation of barbiturate Hypnosis. Groups of ten Swiss white mice have been treated with the tested compounds, at a dose of 10 mg/kg per os, and then with 25 mg/kg of nembutal by intraperitoneal route; the duration of the sleep induced by nembutal has been recorded.

In the Table 1, the percent increase of the sleep duration with respect to that induced by the only administration of nembutal is reported.

5. Myorelaxing effect on the mouse by the "rotarod test" (Boissier, *Therapie*, 13, 1074 (1958)).

Mice treated with the compounds being tested have been evaluated, as to their capability of keeping their balance for a given time on a rotating rod, in comparison with untreated mice.

In the test, performed on groups of ten mice, the dose (MD 90) inducing the myorelaxing effect (i.e., the falling from the rod) in the 90 percent of the mice has been determined.

Upon considering the Table 1, most of the compounds according to the invention, corresponding to the general formula given in the heading of the same

Table, exhibit very interesting pharmacological activity.

In fact:

a. from the results of the tests (1), (2) and (3) the novel compounds show a pharmacological activity similar to that of the therapeutically useful benzodiazepines, but on the contrary their potential sedative action and myorelaxing effects, as indicated by the tests (4) and (5), are remarkably reduced.

b. The reduced or absent myorelaxing effects indicate, moreover, that the motility inhibiting actions, as shown in the tests (1) and (3), are not the consequence of the asthenia and of the ataxia originating from the muscle relaxation, but only the result of a tranquillizing activity.

It is also to be noticed that the acute toxicity of at least some of the claimed compounds, namely the compounds Nos. 1, 2, 4, 5, 6, 9, as tested in mice by oral administration is very low: in fact the LD₅₀ (lethal dose causing the death of 50 percent of the animals after the stated time) is always greater, after 48 hours, than 1,000 mg/kg. On the contrary the known benzodiazepines are more toxic, as proved by the data hereinafter reported.

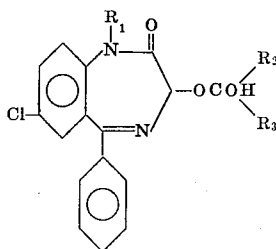
While the Table I does not contemplate all the compounds corresponding to the indicated meanings of the groups R₁, R₂ and R₃ of the formula (I), the pharmacological data therein reported confirm that, as a general rule, all the compounds corresponding to this general formula with the related meanings of the aforesaid groups are likely to exhibit essentially corresponding properties.

In view of the results and of the indications obtained from the pharmacological tests previously referred to, and taking it into account the foreseen therapeutical use, some further specific pharmacological tests have been carried out and the Applicant is able, for the time being, to furnish the data and the results relating to the compounds No. 6 of the Table 1, namely 3-N,N-dimethylcarbamoyloxy-1-methyl-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one.

The compound No. 6 has been firstly evaluated according to the tests 1 to 3 at several dose levels and in comparison with Medazepam, as well as with the other known 1,4-benzodiazepines.

By these tests further data and information about the relationship between dose and pharmacological effect have been obtained. The results of these tests are reported in the following Tables 2, 3 and 4.

TABLE NO. 1



PHARMACOLOGICAL ASSAY OF THE NEW 1,4-BENZODIAZEPINE DERIVATIVES CLAIMED IN THE INVENTION



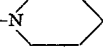

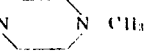
Test	R ₁	$\begin{matrix} R_2 \\ \\ -N \\ \\ R_3 \end{matrix}$	Spontaneous motility (inhibition percent)	Amphetamine hypermotility (variation percent)	Reactive motility (variation percent)	Barbiturate hypnosis (increase percent)	Myorelaxing effect (MD 90)
1.....	H	-NH ₂	-51	-2	-52	+75	300
2.....	CH ₃	-NH ₂	-40	-24	-45	+124	250
3.....	H	-NHCH ₃	-58	+30	-32	+56	>400
4.....	CH ₃	-NHCH ₃	-48	+72	-20	+126	300
5.....	H	$\begin{matrix} CH_3 \\ \\ -N \\ \\ CH_3 \end{matrix}$	-40	+56	-60	+32	250
6.....	CH ₃	Same as above	-58	+93	-42	+23	>400
7.....	H	-NHCH ₂ CH ₂ CH ₂ CH ₃	-5	-20	-30	+20	>400
8.....	H	-NH- 	-45	-15	-48	+94	250
9.....	H	-NHCH ₂ CH ₂ OH	-26	+100	+17	+32	>400
10.....	CH ₃		-31	+16	-34	+20	250
11.....	H		-21	+38	-10	+71	250
12.....	CH ₃	Same as above	-45	0	-26	+22	>400
13.....	CH ₃		-77	+113	+12	+28	250
14.....	H		-10	+35	-21	+30	>400
15.....	CH ₃	Same as above	-30	8	-35	+20	>400
Medazepam.....			-54	+47	-49	+77	400
Diazepam.....			-70	+26		+106	30
Chlordiazepoxide.....			-4	+51		+1	200
Temazepam.....			-70	+85	-60	+81	50

TABLE NO. 2

Spontaneous motility of grouped mice (number of mice used is indicated within brackets).						
Substance	% variation (with respect to the control animals) of the number of counts effected in 60 minutes in the photocell actometer - groups of five mice - doses mg/kg per os.					
	1	5	10	25	50	100
Compound No. 6	- 18 (10)	- 54 (10)	- 58 (10)	- 61 (5)	- 87 (5)	- 95 (5)
Medazepam	- 32 (15)	- 37.6 (20)	- 54 (20)	- 45 (5)	- 45 (5)	- 61 (5)
Diazepam	- 67 (5)	- 66 (5)	- 70 (5)	- 38 (5)	- 69 (5)	- 59 (5)
Chlordiazepoxide	- 3 (10)	- 6 (10)	- 4 (10)	- 63 (10)	- 56 (10)	- 70 (10)
Temazepam	- 33 (5)	- 36 (5)	- 70 (5)	- 96 (5)	- 88 (5)	- 99 (5)

TABLE NO. 3

Hypermotility induced by amphetamine in grouped mice (the number of mice used is indicated in brackets).						
Substance	% Variation (with respect to the control animals) of the number of counts effected in 60 minutes in the photocell actometer - groups of five mice - doses, mg/kg per os.					
	1	5	10	25	50	100
Compound No. 6	+ 3 (10)	+ 44 (10)	+ 93 (10)	+ 150 (5)	+ 15 (5)	+ 64 (5)
Medazepam	0 (15)	+ 27 (20)	+ 47 (20)	+ 292 (5)	+ 245 (5)	+ 330 (5)
Diazepam	+ 75 (5)	+ 152 (5)	+ 26 (5)	+ 44 (5)	+ 55 (5)	- 15 (5)
Chlordiazepoxide	+ 25 (10)	+ 20 (10)	+ 51 (10)	- 24 (10)	- 25 (10)	- 41 (10)
Temazepam	+ 42 (5)	+ 45 (5)	+ 85 (5)	- 25 (5)	- 49 (5)	- 33 (5)

TABLE NO. 4

Comparative effects of the compound No. 6 and of the other known 1,4-benzodiazepines on the reactive motility (open field) in the rat (the number of animals used is indicated within brackets).		
Substance	Doses (mg/kg/os)	% Variation with respect to the basal values
Compound No. 6	1 (15)	+ 65.3
	5 (15)	- 9.9
	10 (15)	- 26.7 **
	25 (15)	- 42.2 **
Medazepam	1 (10)	- 32.1 **
	5 (15)	- 38.5 **
	10 (20)	- 37.1 **
Temazepam	25 (15)	- 48.9 **
	1 (5)	- 15.6 *
	5 (10)	- 26.8 **
	10 (10)	- 40.5 *
	25 (10)	- 60.5 *

* P < 0.05

** P < 0.01

The aforesaid further tests were the following:

6. Traction test, relating to the myorelaxing effect (Boissier and Simon, Therapie, 15, 1170 (1,960)) in the mouse. The test essentially consists in observing whether or not the animals, suspended by the fore legs to a horizontally taut wire, are capable of raising, up to the height of the wire, the hindlegs. The oral doses (MD 90) of the tested compounds inducing to a myorelaxing effect (i.e., incapacity of raising up to the wire the hindlegs) in the 90 percent of the animals have been determined.

The results of this test plotted in the FIG. 1, are similar to those of the already cited "rotarod test", the results of the latter being also plotted in FIG. 2.

7. Effect on avoidance reaction in trained rats.

The test has been carried out on adult Sprague-Dawley white rats, both male and female and of 200-250 grams of weight.

An automatic programmed conditioning apparatus (made by the firm Basile, of Milan, Italy) has been used, comprising two adjacent compartments, interconnected by an opening and provided with an acoustical stimulator (bell) as well as with an electrical stimulator (electrical connection of a current source to the floor of the compartment).

The rat is left during about 15 minutes inside one compartment, so as to become familiarized; subsequently an acoustical stimulation is applied, for a time of 6 seconds, and after 3 seconds from the beginning thereof, also an electrical stimulation is applied to the animal; when the 6 second time has lapsed, a resting time of 2 seconds is allowed and thereafter the cycle is repeated.

If the rat enters the second compartment either during the first 3 second time of acoustical stimulation or during the remaining 3 seconds of both acoustical and electrical stimulation, the stimuli are automatically stopped. Each displacement from one compartment to the other compartment as well as the time at which such a displacement occurs are recorded by suitable counting and recording means, which are also adapted to distinguish the displacements caused only by the acoustical stimulus (conditioned reflexes) from those caused by the electrical stimulus.

The total number of stimuli, which each rat undergoes for each experimental session of about 20 minutes, is 60. As a consequence, each rat, if well conditioned, can at maximum give 60 conditioned responses.

By means of the above apparatus the rats have been conditioned, by undergoing each day an experimental session of 20 minutes for 15-20 days.

At the end of the conditioning period, the rats have been divided into two groups, namely:

1. those capable of giving 46 to 60 conditioned reactions;
2. those capable to give 16 to 30 conditioned reactions.

The compound No. 6 and the control compound (temazepam) have been administered by subcutaneous injection to the two groups of rats and, at several times from the administration, the rats have been subjected to the test.

The results are reported in the Table 5. ,160

Upon considering the preceding data, it is evident that a deconditioning marked effect of the tested compounds appears only at the dose of 400 mg/kg os for the highly conditioned rats (first group), whereas in the little conditioned rats (second group) at doses of between 10 and 100 mg/kg, an increase of the number of the avoidance conditioned reactions is observed. Similar effects are known for other tranquillizers, like diazepam, nitrazepam and chlordiazepoxide (Takaori S. et al., Jap. J.Pharmac. 19, 587, (1969)).

8. Effect on the EEG of the rabbit.

The rabbits have been prepared for the test and the EEG recorded according to the technique described by V. C. Longo (Electroencephalographic Atlas for Pharmacological Research, Elsevier, 1972).

The compound No. 6 and the comparison compound, medazepam, have been administered per os as an aqueous suspension in carboxymethylcellulose at doses ranging between 5 and 30 mg/kg.

After 30 minutes from the administration, a series of EEG has been recorded at intervals of 10 minutes, up to 120 minutes. Every 30 minutes, also the effect of the administered compound on the arousal reaction caused by acoustical, vibro-acoustical and painful stimuli, was determined.

The compound No. 6 caused the duration of the reaction to the various stimuli to be reduced. Such an effect, which was rather moderate at the small dose of 5 mg/kg, is progressively enhanced at the higher doses, and the reaction to the stimuli was sometimes completely absent at doses of 15-20 mg/kg.

The comparison of the EEG of rats treated with compound No. 6 and with medazepam indicates that the two compounds have a qualitatively similar tranquillizing action, but the former is about three times more active: in fact a dose of 10 mg/kg of compound No. 6 gives place to the same effect caused by a dose of 30 mg/kg of medazepam. Moreover, the effect of the compound No. 6 is already detectable 30 minutes after the administration and is still present after 120 minutes.

9. Anticonvulsant effect with respect to convulsions induced in the mouse either by strychnine and by cardiazol. The Tables 6 and 7 show the results of these tests which indicate that the compound No. 6 has effects similar to those of the other known benzodiazepinic compounds.

TABLE NO. 6

Substance	Effect on the convulsions induced by strychnine in the mouse.	
	LD ₅₀ * (mg/kg/os) against Strychnine (0.75 mg/kg/i.v.)	
Compound No. 6	20	
Medazepam	30	
Diazepam	20	

Doses (mg/kg) by which the 50% of the mice is protected from the tonic extension of the hindlegs.

TABLE NO. 7

Substance	Effect on the convulsions induced by cardiazol in the mouse.	
	LD ₅₀ * (mg/kg/os) against cardiazol (40 mg/kg/i.v.)	
Compound No. 6	5,8	
Medazepam	5	
Diazepam	1,55	
Chlordiazepoxide	10	
Temazepam	6,4	

Doses (mg/kg) by which the 50% of the mice is protected from the tonic extension of the hindlegs.

Besides these tests, aiming to gather information about the claimed products, and particularly about the compound No. 6 in view of the foreseen therapeutical use, extensive toxicological tests have been carried out, namely:

Acute toxicity in mice, rats and guinea-pigs.

Chronic toxicity in rats and dogs.

Teratological tests.

All these tests gave favourable results, thus excluding any objectionable side or toxic effects, which would raise doubts about the foreseen therapeutical use. Of particular interest are the data relating to the acute toxicity, and from the Table 8 it is clearly evident that the compound No. 6 has a lower toxicity than other drugs of the 1,4-benzodiazepine class; in fact the LD₅₀ of the compound No. 6 are 1.700 mg/kg (24 hours), 1.200 mg/kg (48 hours) and 970 mg/kg (72 hours) whereas the corresponding values for medazepam are 630, 495 and 476 mg/kg respectively, and diazepam shows an acute toxicity of 720 mg/kg (24 hours).

TABLE NO. 8

Substance	Doses mg/kg/os	Acute Toxicity					
		Deaths observed after		LD ₅₀ mg/kg			
		24 h	LD ₅₀ mg/kg	48 h	LD ₅₀ mg/kg	72 h	LD ₅₀ mg/kg
Compound No. 6	250	0/10		0/10		0/10	
	500	0/10		1/10		3/10	
	750	1/10	1700 (1307-2221)	3/10	1200 (895-1608)	3/10	970 (688-1406)
	1000	2/10		4/10		6/10	
	2000	7/10		8/10		8/10	
Medazepam	250	0/10		0/10		0/10	
	500	3/10		5/10		6/10	
	750	6/10	630 (525-756)	10/10	495 (430-569)	10/10	475 (394-549)
	1000	10/10		10/10		10/10	
Diazepam			DL ₅₀ mg/kg				
	500	1/10		8/10		10/10	
	750	67/10	720 (626-828)	8/10		10/10	
	1000	8/10		10/10		10/10	

Another interesting pharmacological characteristic of the compound No. 6, is that the heart contractility is not affected, i.e., depressed.

In this connection a test has been carried out on awake dogs, according to which, before and after administering the compounds being tested, the left ventricular pressure and its first derivative with respect to time were determined, by means of a cannula, previously inserted by a surgical operation within the said left ventricular cavity (Covell et al., *Circulation Research*, 19 364 (1966)).

The compound No. 6 and the chlordiazepoxide have been intravenously injected as a solution in a mixture of water-propylen glycol at the doses of 1-5 mg/kg. The measured parameters are indicative of the efficacy of the heart contractility: more particularly, the left ventricular pressure (pvs) is representative of the force generated by the ventricle during the contraction, whereas its derivative (d_p/dt) is representative of the myocardial velocity of contraction. In the enclosed figures 3 and 4, it can be seen that the ventricular pressure and its derivative are already depressed by 30 percent by a dose of 1 mg/kg of chlordiazepoxide, such a depression becoming more marked and prolonged at a dose of 5 mg/kg of chlordiazepoxide, whereas the same parameters are practically unaffected by 1 to 5 mg/kg of compound No. 6.

This characteristic of the compound No. 6 is of particular importance in view of a possible use of this substance for the treatment of anxious states in patients suffering from cardiac insufficiency.

Some clinical trials have been carried out with compound No. 6 in a 10 mg oral dosage form and other clinical investigations are in progress.

In some experiments, in order to assess, under controlled conditions, its effectiveness in the treatment of anxiety, the compound was investigated by the double blind method in comparison with one of the previously mentioned known 1,4-benzodiazepines, e.g., chlordiazepoxide or temazepam.

For the evaluation of the anxiety symptoms and of their modification by the treatment, the patients to which 3 tablets each containing 10 mg of the active ingredient together with a suitable excipient were administered each day, before and during the treatment, had to answer to a predetermined series of questions concerning their physical and psychical conditions and their attitude toward the external factors and toward the treatment itself.

The questions asked during the interview were derived from the model suggested by W. K. Zung (*Rassogna Medica e Culturale*, 4, 63 (1,966)). The answers given by the patients were appropriately scored and statistically processed. The results thus obtained can be summarized as follows:

1. The improvement of the anxious symptomatology in the patients treated with compound No. 6 was greater than that obtained either with temazepam and chlordiazepoxide; the difference between compound No. 6 and the comparison drugs was statistically significant.

2. Drowsiness, asthenia and fatigue, were not observed in the patients treated with compound No. 6, whilst these side effects occurred with the usual incidence in the patients treated with the comparison drugs.

3. A peculiar characteristic of compound No. 6 emerged from this investigation: it is able to improve the mood of the patients, to support a more optimistic attitude and to improve the food appetite; this antidepressant effect differentiates the compound No. 6 from the known 1,4-benzodiazepines; the latter exhibiting an exceeding sedation and depression.

The above characteristics of compound No. 6 and the lack of cardiodepressant effect have proved of particular interest; the administration of anti-anxiety drugs, in fact, in some cases, reduces the incidence of anginal attacks in these patients.

In this connection a double blind clinical trial of compound No. 6 in comparison with temazepam, in which three tablets/day containing 10 mg of active compound were orally administered to the patients, has shown a statistically significant superiority of compound No. 6, as measured by the reduced intake of pills of nitroglycerine, a drug giving relief from anginal attacks.

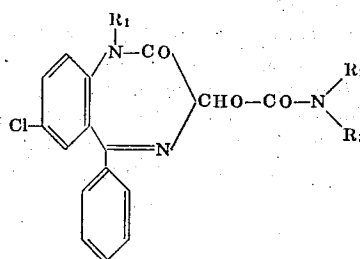
Furthermore the lack of side effects and the improvement of the mood previously observed was evident also in this group of patients receiving the compound No. 6.

These clinical trials have completely confirmed the indications given by the pharmacological tests and for this reason also other compounds of the present invention are liable to exhibit like favourable results from the therapeutical point of view.

The pharmaceutical composition of this invention may be administered alone or in combination with another anti-anginal drug.

What is claimed is:

1. A tranquilizing and anti-anxiety pharmaceutical composition including a carrier, and an effective amount of an active ingredient comprising a 1,4-benzodiazepin derivative containing a carbamic ester group having the general formula:



(I)

wherein R_1 is selected from the group consisting of hydrogen, and lower alkyls having 1 to 4 carbon atoms, and R_2 and R_3 are, each hydrogen, lower alkyl having from 1 to 4 carbon atoms, cyclohexyl or amino lower alkyl or hydroxy lower alkyl or when R_2 and R_3 are taken together with the attached nitrogen nitrogen atom to form a heterocyclic ring selected from the group consisting of pyrrolidino, piperidino, morpholino and piperazino.

2. A pharmaceutical composition according to claim 1, wherein said active ingredient is 3-N,N-dimethylcarbamoyloxy-1-methyl-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one.

3. A pharmaceutical composition according to claim 1, wherein said active ingredient is 3-carbamoyloxy-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one.

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4. A pharmaceutical composition according to claim 1, wherein said active ingredient is 3-carbamoyloxy-1-methyl-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one.

5. A pharmaceutical composition according to claim 1, wherein said active ingredient is 3-N-methylcarbamoyloxy-1-methyl-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one.

6. A pharmaceutical composition according to claim 1, wherein said active ingredient is 3-N,N-dimethylcarbamoyloxy-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one.

7. A pharmaceutical composition according to claim 1, wherein said active ingredient is 3-N,N-dimethylcarbamoyloxy-1-methyl-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one.

8. A pharmaceutical composition according to claim 1, wherein said active ingredient is 3-N-(beta-hydroxyethyl)carbamoyloxy-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one.

9. A pharmaceutical composition according to claim 1, wherein the dosage of said active ingredient is 10 milligrams.

10. A method for the treatment of patients suffering from anxious states comprising the administering of a pharmaceutical composition, according to claim 1.

11. A method for the treatment of a patient suffering from anxious states, comprising the administering of a pharmaceutical composition according to claim 2.

12. A method for the treatment of a patient suffering from anginal attacks, comprising the administering of a pharmaceutical composition according to claim 2.

13. A method for the treatment of a patient suffering from anxious states comprising administering a pharmaceutical composition according to claim 1 at a daily dose level of 5 to 90 mg of said active ingredient.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,867,529 Dated February 18, 1975

Inventor(s) GIORGIO FERRARI and CESARE CASAGRANDE

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

On the first page, beneath the inventors names the name of the Assignee should be inserted as follows:

--Assignee: SIPHAR S.A., Lugano, Switzerland--; and following the Foreign Application Priority Data, the Swiss Patent No. reading "126620/70" should read --12620/70--.

Signed and Sealed this

twenty-seventh Day of *April* 1976

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks