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4-amino-1-aryl-1,5-dihydropyrrol-2-ones having anticonvulsant and anxiolytic activity and processes for their preparation

5 The invention relates to 1,5-dihydropyrrol-2-ones which contain a secondary amine radical in the 4-position and an aryl radical in the 1-position, to processes for their preparation and to their use as medicaments, specifically for the treatment of epilepsies of various
10 forms and for the treatment of states of anxiety and tension.

Unsubstituted 1-phenyl-1,5-dihydropyrrol-2-one was described in 1981 by a Japanese group [K. Tabei et al.,
15 Heterocycles 1981, 16, 795]. 1,5-dihydropyrrol-2-ones having aryl substituents in the 1-position and primary amines as substituents in the 4-position have been claimed by Lonza AG (DE 22 14 488). A biological activity of the compounds described therein has not
20 been mentioned or suggested.

Compounds which are alkoxy-substituted in the 4-position, such as, for example, 4-ethoxy-1-phenyl-1,5-dihydropyrrol-2-one, are known [T. Nishio et al., J. Chem. Soc. Perkin Trans. 1, 1992, 899]. For these
25 compounds, too, no biological action has been shown.

1,5-dihydropyrrol-2-ones having a secondary amine radical in the 4-position and an aryl radical in the 1-position have hitherto not been described in the
30 literature.

Epilepsy is a behavioral change in the form of convulsions. The cause is short-term, extremely strong neuronal discharges of the brain. Altogether, about 5%
35 of all people suffer an epileptic attack in their life; 1% suffer from epilepsy.



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Fundamentally, two factors are to be considered for the genesis of convulsions, pathological discharges in groups of nerve cells and/or absent stimulus limitation which makes possible a spread of the pathological stimulation, i.e. there is an increased instability of the cell membrane potential with a tendency for spontaneous electrical discharges.

Only about 60-80% of patients currently become attack-free under medicinal treatment. Certain forms of epilepsy, however, can still not be treated adequately.

In addition, undesired side effects, such as neurotoxicity and idiosyncrasy, can occur through the administration of anticonvulsants found on the market.

The invention is therefore based on the object of making available compounds having favorable pharmacological properties, which can be employed as medicaments, in particular for the treatment of epilepsy.

Neither can states of anxiety and tension of differing etiology and intensity currently be treated satisfactorily in all cases. Since approximately 1960, benzodiazepine derivatives have been employed as a matter of priority for the treatment of states of anxiety and tension. Substances having such a profile in general have a calming and emotion-dampening action. In the short term, these medicaments are a great help, but even in therapeutic doses side effects such as sedation, drowsiness and decreases responsiveness occur.

There can be an adverse effect on mental processes due to sedation. In some cases, ataxia and co-ordination disorders are to be observed, which affect performance.

On continuous use, these benzodiazepine compounds lead to habituation effects, so-called tolerance. The efficacy of the preparation decreases and the dose has to be increased. A psychological dependence, moreover even a physiological dependence, may develop. Complicated withdrawal phenomena therefore occur when withdrawal is attempted.

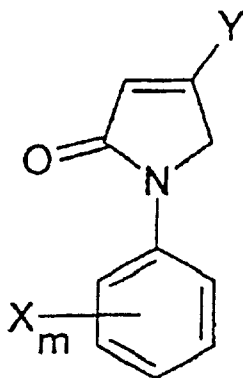
The most important representatives of the anxiolytics introduced onto the market are the active compounds diazepam, clonazepam and medazepam.

In order to achieve an anxiolytic action of diazepam, plasma concentrations of 300 to 400 ng/ml are necessary. The side effects mentioned, such as sedation and psychomotor disorders, which are manifested in daytime sedation, drowsiness and restricted attentiveness and responsiveness, also occur, however, at the same concentrations. On account of the long half-life of diazepam and clonazepam, severe "hang-over" effects occur, which are likewise associated with drowsiness, impairment of intellectual and motor capacities, and prolonged reaction time. The anxiolytic action of clonazepam is masked by the sedating or hypnotic action. High doses of medazepam are also associated with hypnotic, muscle-relaxing phenomena. All three medicaments potentiate the action of numerous centrally acting pharmaceuticals and of alcohol. In these cases, effects can occur which are barely noticeable after administration of the individual substances.

Until now, attempts to achieve a satisfactory therapeutic standard in the case of relatively long-lasting states of anxiety have been unsuccessful. A therapy-outlasting action of anxiolytic medicaments is presently also not adequately ensured.

Accordingly, it is a further object of the present invention to provide medicaments for the treatment of different states of anxiety and tension and which have a great therapeutic spectrum.

According to the present invention, these novel medicaments are 4-amino-1-aryl-1,5-dihydropyrrol-2-ones of the general formula 1



Formula 1

where

- 15 X = hydrogen, halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, trifluoromethyl or trifluoromethoxy, nitro, amine;
Y = secondary amine, such as, for example, morpholine, piperidine, 2-methylpiperidine, 3-methylpiperidine, 4-methylpiperidine, pyrrolidine, 4-methylpiperazine,
20 azepam, diethylamino, bis(methoxyethyl)amine and
m = 1 to 3.

Examples of compounds of the general formula 1 which may be mentioned are:

- 25 1-(2-chlorophenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one
1-(3-methylphenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one

- 1-(4-fluorophenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one
- 1-(4-chlorophenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one
- 5 1-(4-bromophenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one
- 1-(4-methylphenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one
- 1-(4-methoxyphenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one
- 10 4-morpholin-4-yl-1-(4-trifluoromethylphenyl)-1,5-dihydropyrrol-2-one
- 4-morpholin-4-yl-1-(4-trifluoromethoxyphenyl)-1,5-dihydropyrrol-2-one
- 15 1-(3-chloro-4-fluorophenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one
- 4-morpholin-4-yl-1-(3,4,5-trimethoxyphenyl)-1,5-dihydropyrrol-2-one
- 1-(3-methylphenyl)-4-piperidin-1-yl-1,5-dihydropyrrol-2-one
- 20 1-(4-fluorophenyl)-4-piperidin-1-yl-1,5-dihydropyrrol-2-one
- 1-(4-chlorophenyl)-4-piperidin-1-yl-1,5-dihydropyrrol-2-one
- 25 1-(4-methylphenyl)-4-piperidin-1-yl-1,5-dihydropyrrol-2-one
- 1-(3-chloro-4-fluorophenyl)-4-piperidin-1-yl-1,5-dihydropyrrol-2-one
- 1-(4-chlorophenyl)-4-pyrrolidin-1-yl-1,5-dihydropyrrol-2-one
- 30 1-(4-chlorophenyl)-4-(4-methylpiperidin-1-yl)-1,5-dihydropyrrol-2-one
- 1-(4-chlorophenyl)-4-(3-methylpiperidin-1-yl)-1,5-dihydropyrrol-2-one
- 35 1-(4-chlorophenyl)-4-(2-methylpiperidin-1-yl)-1,5-dihydropyrrol-2-one

1-(4-chlorophenyl)-4-(4-methylpiperazin-1-yl)-1,5-dihydropyrrol-2-one

1-(4-chlorophenyl)-4-azepam-1-yl-1,5-dihydropyrrol-2-one

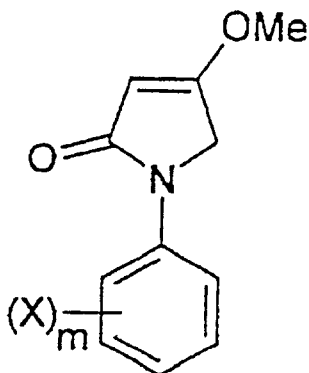
5 1-(4-chlorophenyl)-4-(diethylamino)-1,5-dihydropyrrol-2-one

1-(4-chlorophenyl)-4-(bis(methoxyethyl)amino)-1,5-dihydropyrrol-2-one

4-morpholin-4-yl-1-phenyl-1,5-dihydropyrrol-2-one.

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The process for preparing compounds of the formula 1 is based on the substitution of compounds of the general formula 2 by the corresponding amines.



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Formula 2

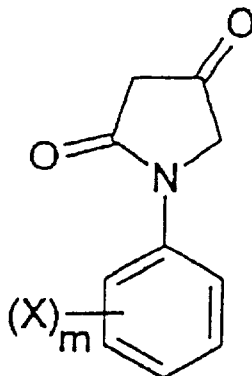
where

X = hydrogen, halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy,
20 trifluoromethyl or trifluoromethoxy, nitro, amine;
m = 1 to 3.

Compounds of the formula 2 are obtained by heating 4-(arylamino)-3-methoxybut-2-enoic esters in an organic
25 solvent, preferably acetic acid, at the boil for 1-6 hours.

According to the prior art, 4-(arylamino)-3-methoxybut-2-enoic esters can be obtained from 4-haloacetoacetic
30 esters.

Alternatively, compounds of the general formula 3 can be condensed with the corresponding amines.



Formula 3

where

X = hydrogen, halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy,
10 trifluoromethyl or trifluoromethoxy, nitro, amine;
m = 1 to 3.

The compounds of the formula 3 are synthesized starting from known N-aryl-substituted glycine esters,
15 analogously to the literature [Mulholland, T. P.C.; Foster, R.; Haydock, D.B.; J. Chem. Soc., Perkin Trans. 1 1972, 17, 2121-8].

The compounds according to the invention are suitable
20 for preparing pharmaceutical compositions. The pharmaceutical compositions comprise at least one of the compounds of the general formula 1.

The medicaments can be administered, for example, parenterally (for example intravenously,
25 intramuscularly or subcutaneously) or orally.

The administration forms can be prepared by processes which are customary and generally known in the pharmaceutical practice, using customary pharmaceutical
30 vehicles and excipients.

The compounds according to the invention have strong pharmacological actions.

5 Anticonvulsive activity

Compounds according to the invention were tested in vivo for their anticonvulsive action (table 1) in mice (i.p. administration) or rats (p.o. administration) according to the internationally customary standard (Pharmac. Weekblad, Sc.Ed. 14, 132 (1992) and Antiepileptic Drugs, Third Ed., Raven Press, New York 1989).

15 Analogous results were obtained for oral action. For example, for the compound 1-(4-chlorophenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one, in the rat in maximal electroshock the ED₅₀ (p.o.) was determined to be 19 mg/kg, in the pentetrazol convulsion model, the ED₅₀ (p.o.) was determined to be 11 mg/kg and for the neurotoxicity, the NT₅₀ was determined to be > 500 mg/kg.

25 Table 1: Anticonvulsive action of selected 1,5-dihydropyrrol-2-ones of the formula 1

Compound ¹⁾	log P ²⁾	Test ³⁾	Dose ⁴⁾	Action ⁵⁾
1	n	MES	100	0
		PTZ	100	0
2	1.46	MES	100	33
		PTZ	300	100
3	n	MES	100	50
		PTZ	100	33
4	1.91	MES	300	0
		PTZ	30	100

Table 1 continued:

5	2.16	MES	100	33
		PTZ	100	100
6	1.42	MES	300	100
		PTZ	100	100
7	0.74	MES	300	0
		PTZ	300	80
8	n	MES	100	66
		PTZ	100	100
9	2.45	MES	100	100
		PTZ	10	50
10	2.19	MES	100	100
		PTZ	100	100
11	n	MES	300	0
		PTZ	300	66
12	2.66	MES	300	0
		PTZ	300	0
13	2.35	MES	300	0
		PTZ	300	0
14	3.06	MES	100	100
		PTZ	100	100
15	2.62	MES	100	100
		PTZ	100	100
16	n	MES	300	100
		PTZ	300	0
17	2.60	MES	300	66
		PTZ	300	0
18	n	MES	100	66
		PTZ	100	66
19	3.58	MES	300	0
		PTZ	100	40
20	n	MES	300	66
		PTZ	100	40

Table 1 continued:

21	n	MES	100	66
		PTZ	100	100
22	3.40	MES	300	100
		PTZ	300	100
23	n	MES	300	50
		PTZ	300	66
24	n	MES	300	33
		PTZ	300	66
25	n	MES	100	40
		PTZ	100	66
Comparison substances Carbamazepin		MES	100	100
		PTZ	100	0
Valproate		MES	100	0
		PTZ	100	30

- 1) Numbering of the compounds corresponding to the
5 examples in Table 3
- 2) Octanol/water partition coefficient, n = not
measured
- 3) Mouse i.p.: MES = maximal electroshock, PTZ = s.c.
pentetrazole
- 10 4) in mg/kg
- 5) in % of the protected animals

It can be seen from Table 1 that the compounds
according to the invention have anticonvulsive action
15 and exhibit little if any neurotoxicity.

Surprisingly, it has also been found that the compounds
of the general formula 1 have considerable anxiolytic
actions in the animal experiment, without any sedating
20 effects.

Anxiolytic activity

It is the aim of the investigations with compounds of
5 the general formula 1 to estimate the possible effects
in models for the investigation of the action against
states of anxiety. To this end, the animals were
exposed to different conflict situations and an effect,
for example by the compound 1-(4-chlorophenyl)-4-
10 morpholine-4-yl-1,5-dihydropyrrol-2-one (Example 4),
was measured.

Investigation of the inhibition of anxiety in the Vogel conflict test

15 In this model, continuous access to drinking water is
withheld from rats for a certain time. After this
period, free access is given to drinking water, but is
coupled with a mild electrical stimulation. The
20 conflict for the animals is of accepting the electrical
stimulation or doing without drinking.

The reactions to a conflict situation of this type are
similar to the secondary phenomena of anxiety in man.
25 Avoidance reactions result, which can be suppressed by
anxiolytic substances. As a measure of the anxiolytic
action, the number of tolerated current pulses of the
animals treated with substance is assessed in
comparison to the vehicle-treated control group. The
30 experimental results obtained are shown in Table 2.

Table 2: Anxiolytic action of substances in the Vogel
Conflict Test/rat

$\bar{x} \pm \text{SEM}$; * $p < 0.05$, ** $p < 0.01$

Substance	mg/kg p.o.	Changed number of impulses to the control in %
Control	-	100
Compound 4	3	102
	10	174
Control	-	100
Diazepam	-0.1	94
	0.3	114
	1.0	148
	3.0	167
Control	-	100
Clonazepam	0.1	122
	0.3	128
	1.0	173
Control	-	100
Medazepam	0.3	100
	1.0	131
	3.0	78

For the compound of Example 4, even from 10 mg/kg p.o. an anxiolytic action was detected.

5

Equieffective doses of diazepam and clonazepam are 1 to 3 mg/kg p.o. and 1 mg/kg p.o., respectively.

10 For medazepam it was not possible to detect an action in the dose range from 0.3 to 3 mg/kg p.o.

15 Untreated animals drink significantly less, which means that they are more anxious than animals which are treated with anxiety-inhibiting substances. The compound of Example 1 increases the number of electrical stimulations tolerated significantly from a dose of 3 mg/kg orally. This effect confirms the good anxiolytic action of the compounds of the general formula 1.

It is therefore to be expected that the compounds of the general formula 1 cause an inhibition of anxiety, particularly in conflict situations.

5 Investigation of the inhibition of anxiety in the elevated maze

In this model, mice are placed in an elevated passage system with open and closed arms (Pellow, S., Chopin, P., File S. E., Briley, M.: Validation of open: closed arm entries in an elevated plus-maze as a measure of anxiety in rats. J. of Neuroscience Methods 14: 149-167, 1985; Hogg, S.: A review of the validity and variability of the elevated plus-maze as an animal model of anxiety. Pharmacology Biochemistry and Behavior: 21-30, 1996).

Untreated animals repeatedly try the closed passages. The inhibition of anxiety is measured by the length of stay in the open arms as a percentage of the total length of stay. Treatments with the compounds of the general formula 1 increase the length of stay in the open arms as a percentage, as can be seen from Table 3.

Table 3: Anxiolytic action of substances in the elevated maze test/mouse

Treatment		Activity in %
Control:		100
Compound 4:	1 mg/kg	128 (p < 0.05)
	3 mg/kg	110
Control:		100
Compound 4:	10 mg/kg	158 (p < 0.05)
	30 mg/kg	129

Following intraperitoneal administration of the compound of Example 4, the proportionate length of stay in the open arms is increased significantly.

Compared to customary anxiolytics, compounds of the general formula 1 have a considerably wider therapeutic spectrum.

5 In the Vogel Conflict Test and in the elevated maze test, for example, the therapeutic index for compound 4 > 50. In contrast, the therapeutic index of diazepam in the Vogel Conflict Test is 13.

10 The examples below serve to illustrate the invention in more detail, without limiting it.

General procedure for preparing the compounds of the formula 1 and their tautomers according to Table 2, Examples 1 - 22

15

30.0 mmol of the compound 2 (Process A) or the compound 3 (Process B) are dissolved in the appropriate amine, preferably in 5-10 ml per g of Compound 2, and admixed with the appropriate amine hydrochloride, preferably 1-20 3 g, and the mixture is heated. After 4-12 hours at 100-150°C, the reaction solution is cooled and the crystalline product is filtered off. Amine-hydrochloride can be removed by washing with water, and the resulting crude product is recrystallized from a 25 suitable organic solvent, preferably acetic acid and isopropanol.

Alternatively, the crude product can also be purified by chromatography.

30 Table 4: 4-amino-1-aryl-1,5-dihydropyrrol-2-ones,
Examples 1 - 24

Compound	X	Y	Process/ Yield in (%)	m.p. (°C)	Recrystal- lization from:
1	2-Cl	morpholine	B 22	154-156	Isopropanol
2	3-Me	morpholine	A 18	121-123	Chromatography

Table 4 continued:

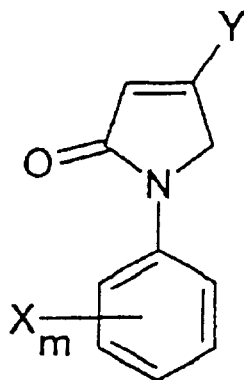
3	4-F	morpholine	B 37	226-229	Isopropanol
4	4-Cl	morpholine	A 84	238-241	Acetic acid
5	4-Br	morpholine	A 36	230-233	Toluene
6	4-Me	morpholine	A 50	214-217	Without recrystal- lization
7	4-OMe	morpholine	A 37	198-202	Isopropanol
8	4-CF ₃	morpholine	A 54	205-207	Acetic acid
9	4-OCF ₃	morpholine	A 49	148-153	Without recrystal- lization
10	3-Cl- 4-F	morpholine	A 51	162-166	Without recrystal- lization
11	3,4,5 - (OMe) ₃	morpholine	A 54	179-182	Isopropanol
12	3-Me	piperidine	B 15	117-123	Without recrystal- lization
13	4-F	piperidine	B 14	214-216	Chromatography
14	4-Cl	piperidine	A 60	20-212	Without recrystal- lization
15	4-Me	piperidine	A 68	174-177	Without recrystal- lization
16	3-Cl- 4-F	piperidine	A 63	195-196	Chromatography
17	4-Cl	pyrrolidine	A 51	223-227	Without recrystal- lization
18	4-Cl	4-Me- piperidine	A 57	194-196	Acetic acid
19	4-Cl	3-Me- piperidine	B 19	188-189	Isopropanol
20	4-Cl	2-Me- piperidine	B 5	181-185	Chromatography
21	4-Cl	4-methyl- piperazine	A 42	194-197	Chromatography
22	4-Cl	Azepam	B 30	182-185	Isopropanol

Table 4 continued:

23	4-Cl	Diethyl- amine	A 55	165-168	Acetic acid
24	4-Cl	Bis (methoxy ethyl) amine	B 6	189-195	Chromatography
25	H	morpholine	B 25	161-164	Chromatography

Patent Claims

1. Novel compounds of the general formula 1



Formula 1

where

x is hydrogen, halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, trifluoromethyl or trifluoromethoxy, nitro, amine;

Y is a secondary amine, such as morpholine, piperidine, 2-methylpiperidine, 3-methylpiperidine, 4-methylpiperidine, pyrrolidine, 4-methylpiperazine, azepam, diethylamino, bis(methoxyethyl)amine and

m is 1 to 3.

2. Compounds of the general formula 1:

1-(2-chlorophenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one

1-(3-methylphenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one

1-(4-fluorophenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one

1-(4-chlorophenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one

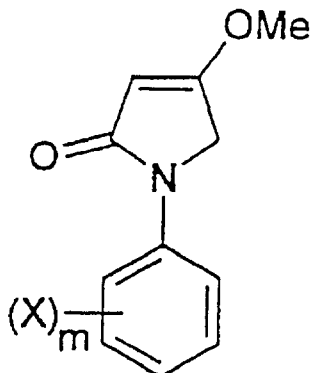
1-(4-bromophenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one

- 1-(4-methylphenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one
- 1-(4-methoxyphenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one
- 5 4-morpholin-4-yl-1-(4-trifluoromethylphenyl)-1,5-dihydropyrrol-2-one
- 4-morpholin-4-yl-1-(4-trifluoromethoxyphenyl)-1,5-dihydropyrrol-2-one
- 10 1-(3-chloro-4-fluorophenyl)-4-morpholin-4-yl-1,5-dihydropyrrol-2-one
- 4-morpholin-4-yl-1-(3,4,5-trimethoxyphenyl)-1,5-dihydropyrrol-2-one
- 1-(3-methylphenyl)-4-piperidin-1-yl-1,5-dihydropyrrol-2-one
- 15 1-(4-fluorophenyl)-4-piperidin-1-yl-1,5-dihydropyrrol-2-one
- 1-(4-chlorophenyl)-4-piperidin-1-yl-1,5-dihydropyrrol-2-one
- 1-(4-methylphenyl)-4-piperidin-1-yl-1,5-dihydropyrrol-2-one
- 20 1-(3-chloro-4-fluorophenyl)-4-piperidin-1-yl-1,5-dihydropyrrol-2-one
- 1-(4-chlorophenyl)-4-pyrrolidin-1-yl-1,5-dihydropyrrol-2-one
- 25 1-(4-chlorophenyl)-4-(4-methylpiperidin-1-yl)-1,5-dihydropyrrol-2-one
- 1-(4-chlorophenyl)-4-(3-methylpiperidin-1-yl)-1,5-dihydropyrrol-2-one
- 1-(4-chlorophenyl)-4-(2-methylpiperidin-1-yl)-1,5-dihydropyrrol-2-one
- 30 1-(4-chlorophenyl)-4-(4-methylpiperazin-1-yl)-1,5-dihydropyrrol-2-one
- 1-(4-chlorophenyl)-4-azepam-1-yl-1,5-dihydropyrrol-2-one
- 35 1-(4-chlorophenyl)-4-(diethylamino)-1,5-dihydropyrrol-2-one

1-(4-chlorophenyl)-4-(bis(methoxyethyl)amino)-1,5-dihydropyrrol-2-one

4-morpholin-4-yl-1-phenyl-1,5-dihydropyrrol-2-one.

- 5 3. Process for preparing compounds of the general formula 1, characterized in that a compound of the general formula 2



Formula 2

10

where

X is hydrogen, halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, trifluoromethyl or trifluoromethoxy, nitro, amine and

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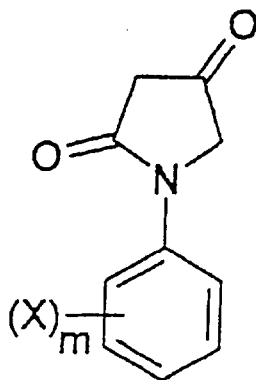
m is 1 to 3

is reacted with secondary amines, such as morpholine, piperidine, 2-methylpiperidine, 3-methylpiperidine, 4-methylpiperidine, pyrrolidine, 4-methylpiperazine, azepam, diethylamino, bis(methoxyethyl)amine and the corresponding amine hydrochlorides.

20

4. Process for preparing compounds of the general formula 1, characterized in that a compound of the general formula 3

25



Formula 3

where

X is hydrogen, halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, trifluoromethyl or trifluoromethoxy, nitro, amine and

m is 1 to 3

is reacted with secondary amines, for example, morpholine, piperidine, 2-methylpiperidine, 3-methylpiperidine, 4-methylpiperidine, pyrrolidine, 4-methylpiperazine, azepam, diethylamino, bis(methoxyethyl)amine and the corresponding amine hydrochlorides.

5. Pharmaceutical compositions, characterized in that they comprise, as active substance, at least one compound of the general formula 1 and, if appropriate, physiologically acceptable excipients and/or vehicles.

6. Pharmaceutical compositions, characterized in that they comprise, as active substance, at least one of the compounds according to Claim 2 and, if appropriate, physiologically acceptable excipients and/or vehicles.

7. Use of 1,5-dihydropyrrol-2-ones of the formula 1 for the treatment of various forms of epilepsy.

8. Use of the compounds of the general formula 1 for the treatment of states of anxiety and tension.
- 5 9. Use of the compounds according to claim 2 for the treatment of epileptic disorders.
10. Use of the compounds according to claim 2 for the treatment of states of anxiety and tension.
- 10 11. Process for preparing medicaments comprising the compounds according to claims 1 and 2, characterized in that at least one compound according to claims 1 and 2 is mixed with
15 physiologically acceptable excipients and/or vehicles and formulated as a medicament.