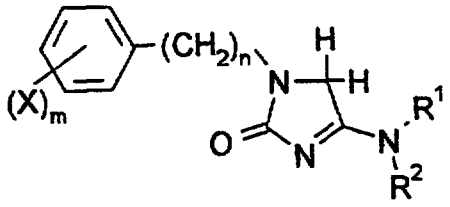
Use of 1-ar(alk)ylimidazolin-2-ones for the treatment of anxiety and tension states

The invention relates tc the use of 1-ar(alk)yl-imidazolin-2-ones of the general formula I or their pharmaceutically utilisable salts for the treatment of anxiety and tension states.

The compounds of the general formula I



n = 0, 1
m = 0, 1, 2, 3, 4, 5

in which
X = hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, trifluoromethyl, halogen,
R^1 and R^2 = C_1-C_4-alkyl, cycloalkyl, heteroalkyl
or
R^1 and R^2 together are an alkylene group having 2-6 carbon atoms in which one $-CH_2-$ group can be replaced by oxygen, nitrogen or sulphur,
and the number of the CH_2 groups is either 0 (1-aryl-imidazolin-2-ones) or 1(1-aralkylimidazolin-2-ones) are described in German Patent Application 195 32 668.7.

Pharmacological results show that the compounds of the general formula I are suitable for the treatment of various types of epileptic disorders.

Anxiety and tension states of differing cause and intensity even today cannot be treated satisfactorily in all cases. Since approximately 1960, benzodiazepine derivatives have been employed as a matter of priority for the treatment of anxiety and tension states. Substances having such a profile in general have a calming and emotion-damping action. In the short term,

these medicaments are a great help, but even in therapeutic doses side effects such as sedation, drowsiness and decreased responsiveness occur.

There can be a negative effect on mental processes due to sedation. Partly, ataxia and coordination disorders are to be observed, which affect the functional capacity. On continuous use, these benzodiazopine compounds lead to habituation effects, so-called tolerance. The efficacy of the preparation becomes lower and the dose has to be increased. A psychological dependence, moreover even a physiological dependence, can develop. Complicated withdrawal phenomena therefore occur in withdrawal trials.

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 mg/ml [sic] 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 high 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-relaxant phenomena.

All three medicaments potentiate the action of numerous centrally active pharmaceuticals and of alcohol. In this case, effects can occur which are barely noticeable after administration of the individual substances.

Until now, there has been no success in achieving a satisfactory therapeutic standard in the case of relatively long-lasting anxiety states. A therapy-outlasting action of anxiolytic medicaments is presently also not adequately guaranteed.

The object of the present invention is therefore to make available medicaments for the treatment of different anxiety and tension states and which have a great therapeutic breadth.

Surprisingly, it has been found that compounds of the general formula I have significant anxiolytic actions in animal experiments without sedating effects.

Pharmacological investigations

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

Investigation of the inhibition of anxiety in the Vogel conflict test

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 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. Avoidance reactions result, which can be suppressed by

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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 experimental results obtained as in Table 1 are shown graphically in Figure 1.

Table 1

Anxiolytic action of substances in the Vogel Conflict Test/rat

X ± SEM; *p< 0.05, **p<0.01

Substance	**mg/kg p.o.**	**Impulses**	**Changed number of impulses to the control in %**
Control	-	51.4 ± 7.73	
Example 1	1	61.3 ± 8.72	19.3
	3	83.2 ± 7.19**	61.9
	10	80.1 ± 9.23**	55.8
Control	-	39.6 ± 7.20	
	30	126.0 ± 15.7**	218.0
	-	62.3 ± 7.07	
	0.1	58.4 ± 6.47	-6.3
Control	0.3	70.9 ± 6.85	13.8
Diazepam	1.0	92.1 ± 3.22**	47.8
	3.0	104.4 ± 11.9**	67.6
Control	-	63.9 ± 6.63	
Clonazepam	0.1	77.7 ± 8.54	21.6
	0.3	81.8 ± 7.81	28.0
	1.0	110.3 ± 13.5*	72.6
Control	-	54.6 ± 7.89	
Medazepam	0.3	54.8 ± 8.85	0.4
	1.0	71.3 ± 10.0	30.6
	3.0	42.7 ± 4.54	-21.8

For the compound as in Example 1, even from 3 mg/kg p.o. an anxiolytic action was detected which is not increased on increasing the dose to 10 mg/kg p.o.
After increasing the dose to 30 mg/kg p.o., it was possible to measure a potentiation of action.
Equieffective doses of diazepam and clonazepam are 1 to 3 mg/kg p.o. and 1 mg/kg p.o.
For medazepam it was not possible to detect an action in the dose range from 0.3 to 3 mg/kg p.o.

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

It is therefore to be expected that the compound [sic] of the general formula I. cause an inhibition of anxiety, particularly in conflict situations.

Investigation of the inhibition of anxiety in the elevated maze

In this model, rats 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 attempt the closed passages. The inhibition of anxiety is measured by the number of entries into the open arms and by the length of stay in the open arms as a percentage of the total entries or of the total length

of stay. Treatments with the compounds of the general formula I increase the entries and the length of stay in the open arms as a percentage, as can be seen from Figure 2. The proportion of the entries into the open arms and the time of stay in the open arms is significantly increased after intraperitoneal administration of 10 or 30 mg/kg of the compound as in Example 1.

In the pharmacological experiment, the compounds of the general formula I showed a strong separation between the anxiolytic action and the sedating effects.
It is evident from Figure 3 that, for example, the compound as in Example 1 exhibits a significantly lower sedation compared with the comparison substance diazepam.

The centrally sedating action of the compounds of the general formula I was investigated in mice. The animals were administered an amount of alcohol which did not cause any mice to lie on their sides. It was checked to what extent the hypnotic effect of alcohol is potentiated and the animals can be induced to lie on their sides by additional administration of compounds of the general formula I. Doses, for example, of the compound as in Example 1 which are 15 to 66-fold the anxiolytic dose induce only a low and non-dose-dependent potentiation of the action of alcohol. Diazepam and clonazepam, in contrast, were investigated in the anxiolytic dose range. For both standard compounds, it was possible to measure a strong and dose-dependent potentiation of the action of alcohol (Figure 3).

The compounds of the general formula I have a very low neurotoxicity compared with the comparison substances diazepam and clonazepam.

The minimum neurotoxic dose of the compound as in Example 1 was determined in the rotorod test as 998 mg/kg p.o.

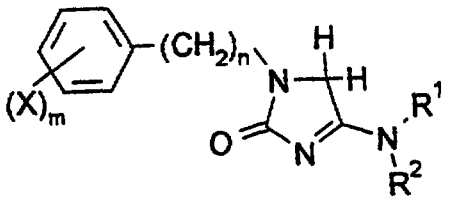
The therapeutic index, calculated as the quotient of the minimum neurotoxic dose in the rotorod test and the anxiolytic dose, is very high with the value 333 and points to a great therapeutic breadth, as can be seen from Figure 4.

The therapeutic breadth of a substance as an important pharmacological characteristic quantity is a measure of the safety between therapeutic and toxic action.
It was therefore all the more surprising that compounds of the general formula I have a significantly higher therapeutic breadth compared with anxiolytically active substances on the market.
As a result, the treatment of patients with anxiety and tension states, in particular even over a relatively long period of time, is markedly improved.

The compounds of the general formula I and their pharmaceutically utilizable salts can be converted in a known manner into pharmaceutical formulations such as tablets, capsules, coated tablets, granules, emulsions, suspensions or solutions.
The customary pharmaceutical excipients and auxiliaries can be used for the production of these preparations.
In this case, the daily dose should preferably be 3 - 30 mg/day.

Patent Claims

1. Use of compounds of the general formula I



n = 0, 1
m = 0, 1, 2, 3, 4, 5

in which
X = hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, trifluoromethyl, halogen,
R^1 and R^2 = C_1-C_4-alkyl, cycloalkyl, heteroalkyl
or
R^1 and R^2 together are an alkylene group having 2-6 carbon atoms in which one $-CH_2-$ group can be replaced by oxygen, nitrogen or sulphur,
and the number of the CH_2 groups is either 0 (1-aryl-imidazolin-2-ones) or 1(1-aralkylimidazolin-2-ones)
and their pharmaceutically utilisable salts for the production of a medicament for the treatment of anxiety and tension states.

2. Use of the compounds of the general formula I according to Claim 1 for the treatment of conflict-related anxiety states.

3. Medicaments having anxiolytic action comprising at least one compound of the general formula I or its pharmaceutically utilisable salts and, if appropriate, excipients and/or auxiliaries.

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