

Novel imidazoline-2,4-diones having anticonvulsive activity, which contain an ortho-substituted ar(alk)yl radical in the 1-position, and processes for their preparation

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The invention relates to imidazoline-2,4-diones which contain an ortho-substituted ar(alk)yl radical in the 1-position, processes for their preparation and their use as pharmaceutical agents for the treatment of disorders of the central nervous system, in particular of epilepsies of various forms.

1-Arylimidazoline-2,4-diones are known which can be prepared by reaction of arylglycines with urea (Ber. 10 2045 (1970); Khim. Geterosikl. Soed. 1978, 87), sodium cyanate (JP 05178802) or potassium cyanate (J. pr. Chem. 1926(113), 233) or by cyclization of N-acylurethanes (Drug Res. 1968, 1(1), 189).

The known processes exclude the preparation of imidazoline-2,4-diones which contain an ortho-substituted aryl radical in the 1-position.

Imidazoline-2,4-diones having an ortho-substituted phenyl radical in the 1-position have not been described until now.

Furthermore, a 1-aralkylimidazoline-2,4-dione which is ortho-substituted by a methoxy group on the benzyl radical is described (JP 05178802).

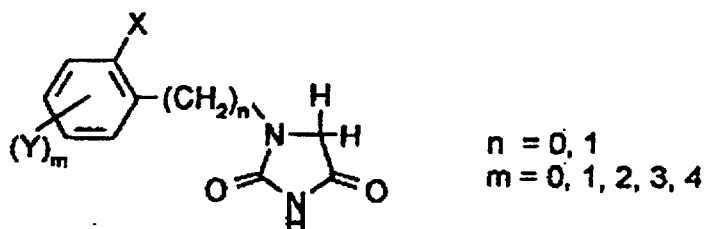
1-Aralkylimidazoline-2,4-diones can be obtained when appropriate aralkylglycines or aralkylglycine esters are reacted with potassium cyanate and then cyclized in glacial acetic acid containing hydrogen chloride (J. het. Chem. 11, (1974)).

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An anticonvulsive action is not mentioned or suggested for any of these compounds.

A multiplicity of compounds having anticonvulsive activity are known. However, even today not all epileptic disorders can be treated satisfactorily.

- 5 The invention is thus based on the object of making available novel compounds having favorable pharmacological properties which can be employed, for example, as medicaments having antiepileptic activity.
- 10 According to the present invention, these novel compounds are 1-ar(alk)ylimidazoline-2,4-diones of the general formula 1



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in which

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X = C₁-C₄-alkyl, trifluoromethyl or halogen and
Y = hydrogen or halogen.

The number of CH₂ groups is either 0 (1-arylimidazoline-2,4-diones) or 1 (1-aralkylimidazoline-2,4-diones).

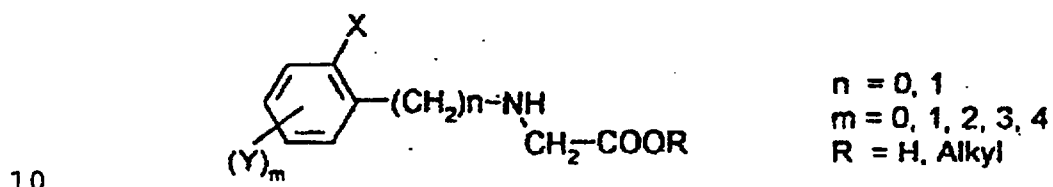
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Examples of compounds of the general formula I [sic] which may be mentioned are:

- 30 1-(2,3-dichlorophenyl)imidazoline-2,4-dione
1-(2,6-dichlorophenyl)imidazoline-2,4-dione
1-(2-chlorophenyl)imidazoline-2,4-dione
1-(4-chloro-2-methylphenyl)imidazoline-2,4-dione
1-(2-fluorophenyl)imidazoline-2,4-dione
35 1-(2-chlorobenzyl)imidazoline-2,4-dione

1-(2,6-difluorobenzyl)imidazoline-2,4-dione
 1-(2,6-dichlorobenzyl)imidazoline-2,4-dione

According to the present invention, the compounds of
 5 the general formula 1 can be prepared by a novel
 process by reaction of the compounds of the general
 formula 2



in which

15 X = C₁-C₄-alkyl, trifluoromethyl or halogen
 Y = hydrogen or halogen,

with chlorosulfonyl isocyanate.

20 Preferably, the reaction is carried out in a solvent at
 temperatures between -20°C and 120°C. Suitable solvents
 are preferably halogenated aliphatic hydrocarbons, for
 example methylene chloride, chloroform and carbon
 tetrachloride. Aromatic hydrocarbons such as benzene
 25 and toluene, as well as aliphatic ethers such as
 diethyl ether, tetrahydrofuran and 1,4-dioxane are also
 suitable solvents.

1-Aralkylimidazoline-2,4-diones can also be prepared
 30 analogously to J. het. Chem. 11 (1974).

The compounds according to the invention are suitable
 for the preparation of pharmaceutical compositions. The
 pharmaceutical compositions can contain one or more of
 35 the compounds according to the invention. The customary

pharmaceutical excipients and auxiliaries can be used to prepare the pharmaceutical preparations.

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

The administration forms can be prepared by processes which are generally known and customary in pharmaceutical practice.

The compounds according to the invention have strong anticonvulsive actions.

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

For example, for the compound 8 (1-(2,6-difluorobenzyl)imidazoline-2,4-dione) in the mouse the ED_{50} (i.p.) for the maximum electroshock was determined to be 36 mg/kg, the ED_{50} in the s.c. pentetrazole test was determined to be 50 mg/kg and the NT_{50} (i.p.) for the neurotoxicity was determined to be 123 mg/kg.

In comparison to this, known antiepileptics such as carbamazepine and calcium valproate are active either in the maximum electroshock model or in the pentetrazole test.

Table 1

Compound according to Examples	Iog P ²⁾	Test ³⁾	Dose ⁴⁾	Action ⁵⁾
1	0.49	MES	300	100
		PTZ	300	0
2	1.16	MES	100	100
		PTZ	100	100
3	0.69	MES	30	100
		PTZ	100	100
4		MES	100	100
		PTZ	100	100
5	0.86	MES	30	100
		PTZ	30	100
6	1.12	MES	30	100
		PTZ	30	100
7	1.44	MES	100	100
		PTZ	100	100
8	0.63	MES	100	100
		PTZ	100	100
9		MES	30	100
		PTZ	30	100

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Comparison substance	Test ³⁾	Dose ⁴⁾	Action ⁵⁾
Carbamazepine	MES	100	100
	PTZ	100	0
Valproate	MES	100	0
	PTZ	100	30

Notes for Table 1:

1) For numbering of the compounds see working examples

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2) Octanol/water partition coefficient

3) MES = maximum electroshock, PTZ = s.c. pentetrazole

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4) in mg/kg

5) in % of the protected animals

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The preparation of the novel compounds according to the invention will be illustrated with the aid of examples.

General procedure for the preparation of the compounds of the general formula 1 Examples 1-9, according to Table 2.

0.2 mol of N-arylglycine ester of the general formula 2 are dissolved in 250 ml of dichloromethane. 0.25 mol of chlorosulfonyl isocyanate is added dropwise at a temperature of -15 to -20°C. After a reaction time of two hours, precipitated sulfamoyl chloride is separated off (for polysubstituted aryl radical) or the methylene chloride is distilled off to dryness (monosubstituted aryl radical). The solid residue is stirred at 80°C for one hour with 300 ml of water. After cooling, the precipitate is separated off and then heated under reflux with 200 ml of 20 percent hydrochloric acid for two hours. The clear solution is cooled in an ice bath and the crystal magma obtained is recrystallized from ethanol.

General procedure for the preparation of the compounds of the general formula 1 Examples 6-9, according to Table 2

- 5 Analogously to J. het. Chem. 11 (1974), 0.2 mol of N-aralkylglycine ester of the general formula 2 are dissolved in 40 ml of 33 percent hydrochloric acid. 0.25 ml of potassium cyanate, dissolved in 50 ml of water, is slowly added dropwise at room temperature.
- 10 After 8 hours, the reaction material is extracted with chloroform, the organic phase is separated off and the chloroform is removed by distillation. The oily residue is then heated at 100°C for two hours with 100 ml of 25% strength hydrochloric acid. After cooling, the
- 15 solid product is separated off and recrystallized from ethanol.

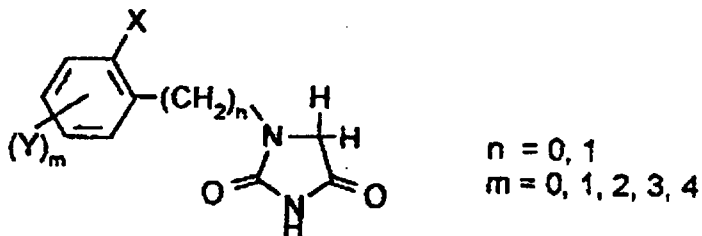
Table 2

Example No.	n	X	Y	m.p. (°C)	Yield (%)
1	0	Cl	H	186	65
2	0	Cl	3-Cl	155	55
3	0	Cl	6-Cl	182	43
4	0	F	H	159	66
5	0	CH ₃	4-Cl	202	61
6	1	Cl	H	155	72
7	1	Cl	6-Cl	164	67
8	1	F	6-F	138	69
9	1	CF ₃	H	165	66



Patent Claims

1. Novel compounds of the general formula 1



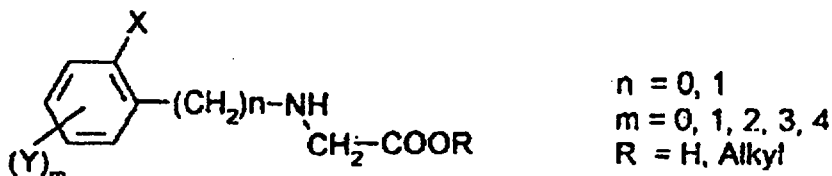
in which

X = C₁-C₄-alkyl, trifluoromethyl or halogen and
Y = hydrogen or halogen.

2. Compounds according to claim 1,

1-(2,3-dichlorophenyl)imidazoline-2,4-dione
1-(2,6-dichlorophenyl)imidazoline-2,4-dione
1-(2-chlorophenyl)imidazoline-2,4-dione
1-(4-chloro-2-methylphenyl)imidazoline-2,4-dione
1-(2-fluorophenyl)imidazoline-2,4-dione
1-(2-chlorobenzyl)imidazoline-2,4-dione
1-(2,6-difluorobenzyl)imidazoline-2,4-dione
1-(2,6-dichlorobenzyl)imidazoline-2,4-dione

3. Process for the preparation of the compounds of the general formula 1, characterized in that a [sic] compound of the general formula 2





in which

X = C₁-C₄-alkyl, trifluoromethyl or halogen and

Y = hydrogen or halogen,

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are reacted with chlorosulfonyl isocyanate in an organic solvent at temperatures between -20°C and 120°C.

10 4. Pharmaceutical preparations characterized in that, as active substance, they contain at least one compound of the general formula 1 and, if appropriate, pharmaceutical excipients and auxiliaries.

15 5. Pharmaceutical preparations according to claim 4 characterized in that, as active substance, they contain at least one of the compounds according to claim 2.

20 6. Use of the compounds of the general formula 1 for the production of medicaments for the treatment of epileptic disorders.

25 7. Use of the compounds according to claim 2 for the production of medicaments for the treatment of epileptic disorders.