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(19) AUSTRALIAN PATENT OFFICE **(10)** Patent No. **699802**

(54) Title
Novel imidazoline-2,4-diones with an ortho-substituted ar(alk)yl radical in position 1, having an anti-convulsive effect, and process for their production

(51)[6] International Patent Classification(s)
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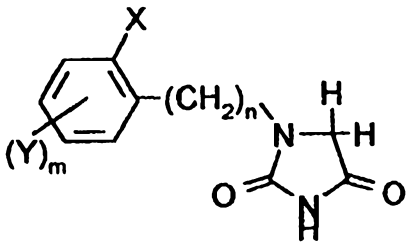
Veröffentlicht
Mit internationalem Recherchenbericht.

(54) Title: NOVEL IMIDAZOLINE-2,4-DIONES WITH AN ORTHO-SUBSTITUTED AR(ALK)YL RADICAL IN POSITION 1, HAVING AN ANTI-CONVULSIVE EFFECT, AND PROCESS FOR THEIR PRODUCTION

(54) Bezeichnung: NEUE, ANTIKONVULSIV WIRKENDE IMIDAZOLIN-2,4-DIONE, DIE IN 1-STELLUNG EINEN ORTHOSUBSTITUIERTEN AR(ALK)YL-REST ENTHALTEN, UND VERFAHREN ZU DEREN HERSTELLUNG



n = 0, 1
m = 0, 1, 2, 3, 4 (1)

(57) Abstract

Anti-convulsive compounds of general formula (1) in which X is C_1-C_4 alkyl, trifluoromethyl, halogen; and Y = hydrogen, halogen.

(57) Zusammenfassung

Antikonvulsiv wirkende Verbindungen der allgemeinen Formel (1), worin X = C_1-C_4-Alkyl, Trifluormethyl, Halogen und Y = Wasserstoff, Halogen bedeuten.

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

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.

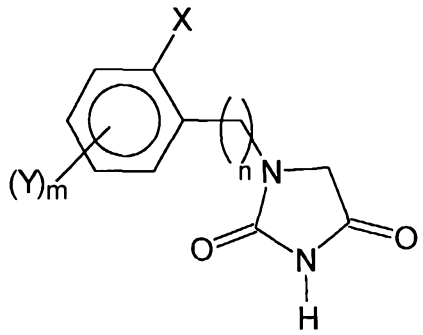
Imidazoline-2,4-diones having an ortho-substituted phenyl radical in the 1-position have not been described until now.

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)).

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

The invention is thus based on the object of making available novel compounds having favourable pharmacological properties which can be employed, for example, as medicaments having antiepileptic activity.

According to the present invention, these novel compounds are 1-ar(alk)ylimidazoline-2,4-diones of the general formula 1



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

in which

X = C_1-C_4-alkyl, trifluoromethyl and, when n = 1, also halogen

Y = hydrogen or halogen.

with the exception of 1-(2-methylphenyl)imidazolin-2,4-one.

The number of CH_2 groups is either 0 (1-arylimidazoline-2,4-diones) or 1 (1-aralkylimidazoline-2,4-diones).

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

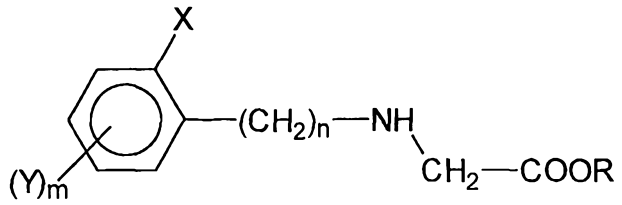
1-(4-chloro-2-methylphenyl)imidazoline-2,4-dione

1-(2-chlorobenzyl)imidazoline-2,4-dione

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

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

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



n = 0, 1; m = 0, 1, 2, 3, 4; R = H, Alkyl

in which

X = C_1-C_4alkyl, trifluoromethyl or halogen

Y = hydrogen or halogen,

with chlorosulfonyl isocyanate.

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 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 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 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	log 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

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

2) Octanol/water partition coefficient

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

4) in mg/kg

5) in % of the protected animals

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

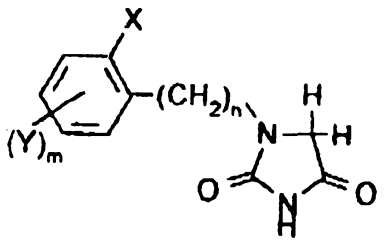
Analogously to J. het. Chem. 11 (1974), 0.2 mol of N-aralkylglycine ester of the general formula **2** are dissolved in 40 ml of 33 percent hydrochloric acid. 0.25 ml of potassium cyanate, dissolved in 50 ml of water, is slowly added dropwise at room temperature. After 8 hours, the reaction material 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 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**



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

in which

X = C_1-C_4-alkyl, trifluoromethyl and, when n = 1, also halogen
Y = hydrogen or halogen,

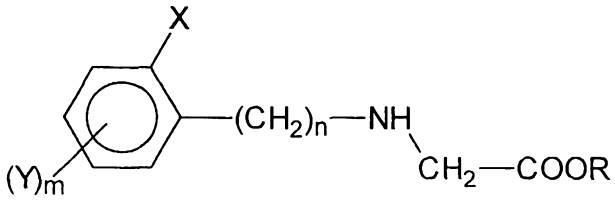
with the exception of 1-(2-methylphenyl)imidazolin-2,4-one.

2. Compounds according to claim 1,

1-(4-chloro-2-methylphenyl)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. An imidazoline-2,4-dione derivative ortho substituted with an ar(alk)yl group, substantially as hereinbefore described with reference to any one of the Examples according to Table 2.

4. Process for the preparation of the compounds of the general formula 1, characterised in that compounds of the general formula 2



n = 0, 1; m = 0, 1, 2, 3, 4; R = H, Alkyl

in which

X = C_1-C_4alkyl, trifluoromethyl or halogen

Y = hydrogen or halogen,

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

5. A process for the preparation of an imidazoline-2,4-dione derivative ortho substituted with an ar(alk)yl group, substantially as hereinbefore described with reference to any one of the examples.

6. Pharmaceutical preparations characterised in that, as active substance, they contain at least one compound of claims 1 to 3 together with a suitable excipient, adjuvant or carrier.

7. Pharmaceutical preparations according to claim 6 characterised in that, as active substance, they contain at least one of the compounds according to claim 2 or claim 3.

8. A method for the treatment or prophylaxis of epileptic disorders in a mammal requiring said treatment or prophylaxis, which method includes or consists of administering to said mammal an effective amount of at least one compound according to any one of claims 1 to 3, or of a composition according to claim 5 or claim 6.

9. Use of the compounds of any one of claims 1 to 3 for the production of medicaments for the treatment of epileptic disorders.

10. A compound according to any one of claims 1 to 3 when used for the treatment of epileptic disorders.

Dated 26 October 1998
ARZNEIMITTELWERK DRESDEN GMBH

Patent Attorneys for the Applicant/Nominated Person
SPRUSON&FERGUSON

INTERNATIONAL SEARCH REPORT

In ional Application No
PCT/EP 96/03296

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D233/72 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	CHEMICAL ABSTRACTS, vol. 124, no. 1, 1 January 1996 Columbus, Ohio, US; abstract no. 8821t, K. ITOH ET AL.: "Preparation of azole compounds as antifungal agents." page 935; column 1; XP002019524 siehe die Zusammenfassung; und Chemical Abstracts, CHEMICAL SUBSTANCE INDEX, vol. 124, 1996, Seite 8339CS, 2.Spalte, die Verbindung mit der RN: [170910-60-8]	1
X	& CA 2 132 791 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 25 March 1995 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
26 November 1996	03. 12. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Fink, D

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INTERNATIONAL SEARCH REPORT

Ir. tional Application No
PCT/EP 96/03296

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 85, no. 25, 20 December 1976 Columbus, Ohio, US; abstract no. 191674k, S. ICLI ET AL.: "A carbon-13 NMR study of some 1-aryl hydantoins." page 469; column 1; XP002019525 siehe die Zusammenfassung; und Chemical Abstracts, CHEMICAL SUBSTANCES, 9th Collective Index, vol. 76-85, 1972-1976, Seite 19413CS, 3.Spalte, die Verbindung mit der RN: [60984-45-4] & MIDDLE EAST TECH. UNIV. J. PURE APPL. SCI., vol. 9, no. 1, 1976, pages 39-50, ---	1
A	GB 997 037 A (IMPERIAL CHEMICAL INDUSTRIES LIMITED) 30 June 1965 see page 1, column 1, line 9 - line 23 see page 2, column 2; example 1 -----	1-7

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int onal Application No
PCT/EP 96/03296

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-997037		NONE	

INTERNATIONALER RECHERCHENBERICHT

In ...ionales Aktenzeichen
PCT/EP 96/03296

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 C07D233/72 A61K31/415

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 C07D

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
P,X	CHEMICAL ABSTRACTS, vol. 124, no. 1, 1.Januar 1996 Columbus, Ohio, US; abstract no. 8821t, K. ITOH ET AL.: "Preparation of azole compounds as antifungal agents." Seite 935; Spalte 1; XP002019524 siehe die Zusammenfassung; und Chemical Abstracts, CHEMICAL SUBSTANCE INDEX, vol. 124, 1996, Seite 8339CS, 2.Spalte, die Verbindung mit der RN: [170910-60-8]	1
X	& CA 2 132 791 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 25.März 1995 --- -/--	1

[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

° Besondere Kategorien von angegebenen Veröffentlichungen :
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1

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
26.November 1996	03. 12. 96

Name und Postanschrift der Internationale Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Fink, D

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INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 96/03296

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	CHEMICAL ABSTRACTS, vol. 85, no. 25, 20.Dezember 1976 Columbus, Ohio, US; abstract no. 191674k, S. ICLI ET AL.: "A carbon-13 NMR study of some 1-aryl hydantoins." Seite 469; Spalte 1; XP002019525 siehe die Zusammenfassung; und Chemical Abstracts, CHEMICAL SUBSTANCES, 9th Collective Index, vol. 76-85, 1972-1976, Seite 19413CS, 3.Spalte, die Verbindung mit der RN: [60984-45-4] & MIDDLE EAST TECH. UNIV. J. PURE APPL. SCI., Bd. 9, Nr. 1, 1976, Seiten 39-50, ---	1
A	GB 997 037 A (IMPERIAL CHEMICAL INDUSTRIES LIMITED) 30.Juni 1965 siehe Seite 1, Spalte 1, Zeile 9 - Zeile 23 siehe Seite 2, Spalte 2; Beispiel 1 -----	1-7

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

In ionales Aktenzeichen
PCT/EP 96/03296

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
GB-A-997037		KEINE	