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Novel 4-amino-1-arylpyridin-2-ones having anticonvulsive activity and processes for their preparation

The invention relates to novel 4-amino-1-arylpyridin-2-ones, processes for their preparation, and their use as medicaments, in particular for the treatment of various forms of epilepsy.

4-Aminopyridin-2-ones unsubstituted in the 1-position are obtained, according to the prior art, by reaction of 4-hydroxy-1H-pyridin-2-ones with amine derivatives [Synthesis; 9 (1984); 765-766)]. A further arylation in the 1-position to give compounds of the general formula **1** is not possible, so that the compounds according to the invention cannot be prepared according to this process.

Another process describes the synthesis of 1-aryl-4-amino-3-cyano-5-alkoxycarbonylpyridin-2-ones [Chem. Ber. **114(11)**; (1981); 3471-3484]. Since dimeric cyanoacetic acid esters are used as starting materials in this process, substituents are necessary in the 3- and 5-positions on the pyridin-2-one, so that the compounds according to the invention can likewise not be obtained according to this process.

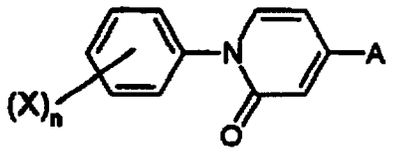
4-Amino-1-arylpyridin-2-ones of the general formula **1** have not previously been described.

A large number of compounds having anticonvulsive activity are known. However, there is a still a great need for novel anticonvulsants, since even today still not all epileptic disorders can be treated satisfactorily.

The invention is based on the object of making available novel compounds having favourable pharmacological properties, which can be employed, in

particular, as medicaments having antiepileptic activity.

According to the present invention, these novel compounds are 4-amino-1-arylpyridin-2-ones of the general formula **1**



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

in which

X = hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, trifluoromethyl, trifluoromethoxy or halogen and

A = amino, C_1-C_4-alkylamino, C_1-C_4-dialkylamino, morpholino, piperidino or pyrrolidino.

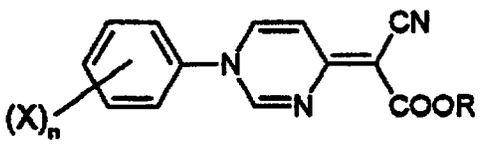
Examples of compounds of the general formula **1** which may be mentioned are:

4-amino-1-phenylpyridin-2-one
4-amino-1-(2-chlorophenyl)pyridin-2-one
4-amino-1-(4-chlorophenyl)pyridin-2-one
4-amino-1-(2-methylphenyl)pyridin-2-one
4-amino-1-(3-methylphenyl)pyridin-2-one
4-amino-1-(4-methylphenyl)pyridin-2-one
4-amino-1-(4-methoxyphenyl)pyridin-2-one
4-amino-1-(4-trifluoromethoxyphenyl)pyridin-2-one
4-amino-1-(2,6-dichlorophenyl)pyridin-2-one
4-amino-1-(2-fluorophenyl)pyridin-2-one
4-amino-1-(4-fluorophenyl)pyridin-2-one
4-amino-1-(2,6-difluorophenyl)pyridin-2-one
4-amino-1-(2-chloro-4-fluorophenyl)pyridin-2-one
1-(2-chlorophenyl)-4-dimethylaminopyridin-2-one
1-(2-chlorophenyl)-4-(4-morpholino)pyridin-2-one

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



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

in which

X = hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, trifluoromethyl, trifluoromethoxy or halogen and

R = C_1-C_4-alkyl.

Pyrimidine derivatives of the general formula **2** can be synthesized in a simple manner (Chem. Heterocycl. Compd.; **24(8)**; (1988); 914-919; Khim. Geterotsikl. Soedin.; **8**; (1988); 1109-1114).

The compounds of the general formula **1** are prepared in two process stages, pyrimidine derivatives of the general formula **2** being heated at 50°C to 150°C in an alkaline medium, preferably in 5 to 50 per cent sodium hydroxide solution, for 0.1 to 10 hours, preferably one hour. The mixture is then heated at 100°C to 200°C with strong acids, preferably 50 to 98 per cent sulphuric acid, for 10 to 30 minutes. The primary amino group can be mono- or dialkylated according to known processes. Alkylation is preferably carried out using dimethyl sulphate, methyl iodide, 1,4-dibromobutane, 1,5-dibromopentane or di(2-chloroethyl) ether.

The compounds of the general formula **1** according to the invention are suitable for the production of pharmaceutical compositions. These pharmaceutical

compositions contain at least one of the compounds of the general formula **1** according to the invention.
The customary pharmaceutical excipients and auxiliaries can be used for the production of the pharmaceutical preparations.

The medicaments can be administered, for example, parentally (for example intravenously, intramuscularly, subcutaneously) or alternatively orally.
The appropriate administration forms are prepared according to processes which are generally known and customary in pharmaceutical practice.

Investigations on the compounds according to the invention show that these have strong anticonvulsive actions.
The compounds according to the invention were tested for their anticonvulsive action in vivo after i.p. administration to mice or after (p.o. administration) to rats according to the internationally customary standard (Pharmac. Weekblad. Sc.Ed. **14**, 132 (1992) and Antiepileptic Drugs, Third Ed., Raven Press, New York 1989).

For example, for the compound 4-amino-1-phenylpyridin-2-one (Example 1) in the rat, the ED_{50} (p.o.) was determined to be 3.1 mg/kg for the maximal electroshock and the ED_{50} = 200 mg/kg for the rotorod. In comparison with this, known antiepileptics either only react at relatively high doses in the maximal electroshock model or have relatively strong, undesired (neurotoxic) side effects.

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Table 1

Compound according to the examples	X	A	Test[1]	Dose[2]	Action[3]
1	H	NH_2	MES Rotorod	10 100	30 40
2	4-Cl	NH_2	MES Rotorod	100 300	30 0
3	4-CH_3	NH_2	MES Rotorod	30 30	100 0
4	2-CH_3	NH_2	MES Rotorod	30 100	70 0
5	4-CH_3-O	NH_2	MES Rotorod	30 300	30 0
6	4-CF_3-O	NH_2	MES Rotorod	100 300	70 0
7	3-CH_3	NH_2	MES Rotorod	30 30	100 0
8	3-Cl	NH_2	MES Rotorod	100 100	50 15
9	2-Cl, 6-Cl	NH_2	MES Rotorod	100 300	70 0
10	4-F	NH_2	MES Rotorod	10 100	30 0
11	2-Cl, 3-Cl	NH_2	MES Rotorod	30 100	30 30
12	2-F	NH_2	MES Rotorod	30 100	100 15
13	2-Cl	NH_2	MES Rotorod	10 30	70 15
14	2-F, 6-F	NH_2	MES Rotorod	30 30	100 0
15	2-Cl, 4-F	NH_2	MES Rotorod	10 100	100 30
16	2-Cl	$N(CH_3)_2$	MES Rotorod	30 30	30 0
17	2-Cl	$N(CH_2CH_2)O$	MES Rotorod	30 30	100 0
Comparison substance					
Carbamazepine			MES Rotorod	100 100	100 60
Valproate			MES Rotorod	100 100	10 0

Footnotes to Table 1:

1) Mouse i.p.: MES = maximal electroshock
Rotorod = neurotoxicity

2) in mg/kg

3) in % of the protected animals or % animals having a visible neurotoxic action

The anticonvulsive activity found and the low side effect potential of the claimed compounds make possible the preparation of novel medicaments for the treatment of epilepsies of various forms.

Working examples

The preparation of the compounds according to the invention is explained in greater detail with the aid of the following examples.

This is an exemplary enumeration, which is not a restriction of the present invention.

General procedure for the preparation of the compounds of the formula **1** according to Table 1, Examples 1-15

General synthesis procedure

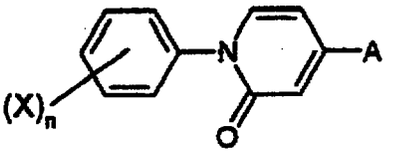
0.05 mol of pyrimidine derivative of the general formula **2** is heated under reflux for one hour in 100 ml of 10 per cent sodium hydroxide solution. After cooling, the reaction mixture is filtered and the filter residue is washed twice with 50 ml of water each time. The solid is treated with 100 ml of 75 per cent sulphuric acid and heated to 180°C in a preheated oil bath. After a few minutes (reaction time according to Table 2), the reaction mixture is rapidly cooled, diluted with 200 ml of water and rendered alkaline using ammonia solution. The precipitate is separated off and recrystallized.

General procedure for the preparation of the compounds of the formula **1** according to Table 1, Examples 16 and 17

A 4-aminopyridin-2-one (Examples 1-15) prepared according to the general synthesis procedure is alkylated using a suitable alkylating agent such as dimethyl sulphate or di(2-chloroethyl) ether in the presence of sodium methoxide. The reaction mixture is introduced into water. The precipitate is separated off and recrystallized.

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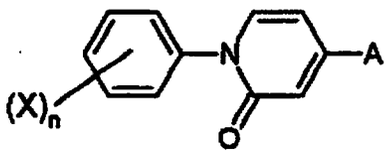
Table 2



Example No.	X	A	Reaction time (min)	Recrystallized from:	m.p. (°C)	Yield (%)
1	H	NH_2	15	Ethanol	288	67
2	4-Cl	NH_2	15	Methanol	312	71
3	4-CH_3	NH_2	15	Ethanol	283	38
4	2-CH_3	NH_2	30	Methanol	267	31
5	4-CH_3-O	NH_2	15	Isopropanol	298	21
6	4-CF_3-O	NH_2	10	Methanol	296	44
7	3-CH_3	NH_2	20	Isopropanol	243	40
8	3-Cl	NH_2	15	Methanol	285	62
9	2-Cl, 6-Cl	NH_2	20	Isopropanol	282	46
10	4-F	NH_2	15	Isopropanol	283	58
11	2-Cl, 3-Cl	NH_2	11	Isopropanol	270	32
12	2-F	NH_2	15	Ethanol	270	55
13	2-Cl	NH_2	15	Ethanol	259	64
14	2-F, 6-F	NH_2	15	Isopropanol	216	51
15	2-Cl, 4-F	NH_2	20	Isopropanol	255	66
16	2-Cl	$N(CH_3)_2$	15	Isopropanol	185	68
17	2-Cl	$N(CH_2CH_2)O$	15	Isopropanol	183	52

Patent Claims

1. Novel compounds of the general formula **1**



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

in which

X = hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, trifluoromethyl, trifluoromethoxy or halogen and

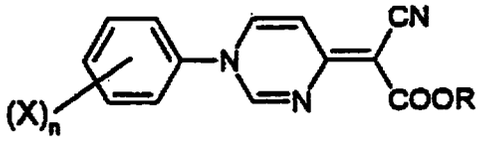
A = amino, C_1-C_4-alkylamino, C_1-C_4-dialkylamino, morpholino, piperidino or pyrrolidino.

2. Compounds according to Claim 1:

4-amino-1-phenylpyridin-2-one
4-amino-1-(2-chlorophenyl)pyridin-2-one
4-amino-1-(4-chlorophenyl)pyridin-2-one
4-amino-1-(2-methylphenyl)pyridin-2-one
4-amino-1-(3-methylphenyl)pyridin-2-one
4-amino-1-(4-methylphenyl)pyridin-2-one
4-amino-1-(4-methoxyphenyl)pyridin-2-one
4-amino-1-(4-trifluoromethoxyphenyl)pyridin-2-one
4-amino-1-(2,6-dichlorophenyl)pyridin-2-one
4-amino-1-(2-fluorophenyl)pyridin-2-one
4-amino-1-(4-fluorophenyl)pyridin-2-one
4-amino-1-(2,6-difluorophenyl)pyridin-2-one
4-amino-1-(2-chloro-4-fluorophenyl)pyridin-2-one
1-(2-chlorophenyl)-4-dimethylaminopyridin-2-one
1-(2-chlorophenyl)-4-(4-morpholino)pyridin-2-one

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

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

in which

X = hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, trifluoromethyl, trifluoromethoxy or halogen and

R = C_1-C_4-alkyl,

is heated at 50°C to 150°C in an alkaline medium for 0.1 to 10 hours and is then heated at 100°C to 200°C with strong acids for 10 to 30 minutes.

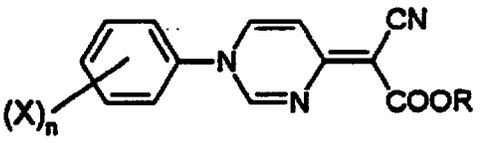
4. Process for the preparation of the compounds of the general formula **1** according to Claim 3, characterized in that preferably 5 to 50 per cent sodium hydroxide solution is employed.

5. Process for the preparation of the compounds of the general formula **1** according to Claim 3, characterized in that the heating is carried out preferably within one hour in an alkaline medium.

6. Process for the preparation of the compounds of the general formula **1** according to Claim 3, characterized in that preferably 50 to 98 per cent sulphuric acid is employed.

7. Process for the preparation of the compounds of the general formula **1** where A = C_1-C_4-alkylamino, C_1-C_4-dialkylamino, morpholino, piperidino or pyrrolidino, characterized in that a compound of the general formula **2**

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

in which
X = hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, trifluoromethyl, trifluoromethoxy or halogen and
R = C_1-C_4-alkyl,

is heated at 50°C to 150°C in an alkaline medium for 0.1 to 10 hours, then heated at 100°C to 200°C with strong acids for 10 to 30 minutes and then alkylated in an alkaline medium.

8. Process for the preparation of the compounds of the general formula **1** according to Claim 7, characterized in that the alkylation is preferably carried out using dimethyl sulphate, methyl iodide, 1,4-dibromobutane, 1,5-dibromopentane or di(2-chloroethyl) ether.

9. 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.

10. Pharmaceutical preparations according to Claim 9, characterized in that as active substance they contain at least one of the compounds according to Claim 2.

11. Use of the compounds of the general formula **1** for the production of medicaments for the treatment of epileptic disorders of various forms.

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12. Use of the compounds according to Claim 2 for the production of medicaments for the treatment of epileptic disorders of various forms.