

SPECIFICATION

Pharmaceutical compositions containing immunestimulating N-substituted aziridine-2-carboxylic acid derivatives

5 The present invention is concerned with pharmaceutical compositions containing N-substituted aziridine-2-carboxylic acid derivatives, some of which are new, and with the preparation of such N-substituted aziridine-2-carboxylic acid derivatives.

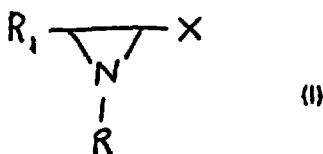
It is known that aziridines, because of their structure and properties, belong to the alkylating-acting compounds, for example cyclophosphamide and N-lost compounds, which play an important part in the 10 therapy of cancer. Unfortunately, the alkylating action does not take place selectively with the components of the cancer cells so that these compounds can also act cancerogenically on normal cells. However, substitution with a cyano group in the 2-position of the aziridine rings showed that the ability to alkylate and thus also the toxicity was lost.

German Democratic Republic Patent Specification No. 110,492 describes 1-carbamoyl-2-cyanoaziridine 15 which, when administered intravenously to rats, bring about a very marked increase of the leukocytes and lymphocytes, whereas the number of erythrocytes remains almost unchanged. Furthermore, a considerably multiplication of the antibody-forming spleen cells was observed. Therefore, this compound can be used as an immunestimulating therapeutic in cases of bacterial and viral infections (see Federal Republic of Germany Patent Specification No. 25 28 460.0). However, the low stability of this compound in solution and 20 the complete ineffectiveness when administered orally proved to be serious disadvantages of this compound.

Therefore, the problem exists of finding immunestimulating therapeutic compounds which, with the same or increased effectiveness and low toxicity, do not display any noteworthy side effects, are more stable and can be more simply administered, preferably orally.

25 We have now found that this problem is solved by a class of aziridine-2-carboxylic acid derivatives which are substituted on the ring nitrogen atom by alkyl or aryl radicals.

Thus, according to the present invention, there are provided pharmaceutical compositions containing at least one aziridine-2-carboxylic acid derivative which is substituted on the ring nitrogen atom and which have the general formula:-



wherein X is a carboxyl or nitrile group or an alkoxy-carbonyl radical or an unsubstituted or substituted carbamoyl group; R is a straight-chained or branched, saturated or mono- or poly-unsaturated aliphatic hydrocarbon radical which is optionally substituted one or more times by halogen, alkoxy, hydroxyl, 40 dialkylamino, cycloalkylamino, acylamino, acyl, nitro, alkylthio, alkylsulphinyl, alkylsulphonyl, nitrile, carbalkoxy or carbamoyl radicals or by cycloalkyl radicals optionally substituted by alkyl, alkoxy or carbalkoxy, or by cycloalkenyl radicals, which can optionally be bridged, or by an aliphatic or aromatic heterocyclic radical, by aryl, aryloxy, arylthio, acyloxy, alkoxy-carbonyl-amino or ureido groups, or R is a cycloalkyl or cycloalkenyl radical containing 3 to 10 carbon atoms which is optionally substituted by alkyl, 45 alkoxy, alkoxy-carbonyl or oxo groups and is also optionally interrupted by hetero atoms and optionally bridged by 1 to 3 carbon atoms, or R is an aryl or hetaryl radical, the aryl and hetaryl radicals being optionally substituted by halogen, alkoxy, alkyl, hydroxyl, carbalkoxy, carbamoyl, dialkylamino, cycloalkylamino, acylamino, nitro, cyano, acyl, alkylthio, alkylsulphinyl, alkylsulphonyl, sulphamoyl, phenyl, trifluoromethyl, aryloxy, acyloxy or methylenedioxy; and R₁ is a hydrogen atom or a saturated straight-chained or branched 50 alkyl radical containing up to 4 carbon atoms or a phenyl radical; and/or at least one pharmacologically-acceptable salt thereof, in admixture with a solid or liquid pharmaceutical diluent or carrier.

The immune stimulation of these compounds of general formula (I) was demonstrated by:

1. an increase of the leukocytes and lymphocytes after oral and intravenous administration thereof;
2. an increase of the lymphocyte transformation, measured with the use of the incorporation of 55 radioactively-marked thymidine into human lymphocytes after incubation with the above-mentioned compounds (see K. Resch in "Praxis der Immunologie", ed. K.O. Vorlaender, pub. Thieme-Verlag, Stuttgart, 1976);
3. the use of animal experimental infection in mice in which it was possible to show that the additional administration of the above-mentioned compounds to known bacteriostatically-acting chemotherapeutic 60 compounds, for example chloramphenicol, produced a clearly improved therapeutic effect in comparison with the sole administration of the bacteriostatic chemotherapeutic, for example, chloramphenicol.

Consequently, the present invention also provides pharmaceutical compositions which, in addition also provides pharmaceutical compositions which, in addition to containing at least one compound of general 65 formula (I) and an appropriate carrier, also contain at least one known chemotherapeutic agent.

A chemotherapeutic agent is generally to be understood to be a substance with an antimicrobial action, for example a penicillin or cephalosporin compound, as well as a compound of the nitrofuran group.

The synergistic effect is shown, for example, in the case of a pharmaceutical combination which contains an immune stimulant compound of general formula (I) and the bacteriostatically-acting chemotherapeutic compound chloramphenicol.

The present invention includes within its scope all stereoisomeric compounds of general formula (I) which, for example, exist because of asymmetric carbon atoms or of *cis-trans* isomerism, the separation of which into the stereoisomeric forms can be carried out by known processes.

The term "alkyl", if not stated otherwise, is to be understood to mean, alone or in combination, for example in alkoxy, alkoxycarbonyl, N-alkylamino, alkylthio, alkylsulphinyl and alkylsulphonyl radicals, a straight-chained or branched chain containing up to 8 carbon atoms. Preferred alkyl radicals methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *neo*-pentyl and *n*-hexyl radicals. The alkyl chain can optionally be substituted by, for example, halogen, such as chlorine, or by hydroxyl, nitro or cyano. Further substituents which can be present include amino groups, preferably dimethylamino and 2-cyanoaziridin-1-yl radicals, acylamino radicals, for example, formamido, acetamido and benzamido radicals, and carbamoyl, carbalkoxy and alkoxy radicals.

The mono- and poly-unsaturated aliphatic hydrocarbon radicals are to be understood to be radicals which contain 3 to 8 and preferably 3 to 5 carbon atoms, with at least one double and/or triple bond in any desired position of the unsaturated chain, preferred radicals of this type including the vinyl, allyl, methallyl, crotyl, 2-methylpropenyl, propargyl, but-2-ynyl, but-3-ynyl and pent-3-enyl radicals.

The cycloalkyl and cycloalkenyl radicals are to be understood to be those containing 3 to 10 carbon atoms, especially the cyclopropyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptenyl and 3,6-dioxo-1,4-cyclohexadienyl radicals, as well as cycloalkyl radicals bridged with 1 to 3 carbon atoms, for example the norbornyl and adamantyl radicals. The cycloalkyl and cycloalkenyl radicals interrupted by hetero atoms are preferably the tetrahydrofuryl, tetrahydropyranyl, thianyl, optionally substituted piperidinyl, morpholinyl and pyrrolidinyl radicals, as well as the N-methyl-3,4-dehydropiperidinyl and the N-methyl-piperazinyl radicals.

The aryl radicals, alone or in combination, for example in aryloxy and arylthio radicals, are aromatic carbocyclic radicals and preferably phenyl, naphthyl, anthracenyl, phenanthrenyl and fluorenyl radicals.

By hetaryl radicals, there are to be understood aromatic ring systems containing 5 or 6 members and one or more hetero atoms, for example, oxygen, sulphur or alkylated or acylated nitrogen, which can also be condensed with one or two benzene rings or with another heterocycle. Preferred radicals of this type include the pyridyl, quinolyl, furyl, thienyl, benzofuryl, imidazolyl, pyrazolyl, thiazolyl, pyrimidinyl, pyridazinyl, *s*-triazolyl, *s*-triazinyl and purinyl radicals.

The halogen atoms are to be understood to be fluorine, chlorine and bromine atoms.

By acyl radicals there are to be understood, alone or in combination, for example in acyloxy radicals, the acid residues of organic carboxylic and sulphonic acids, preferred radicals of this type including the formyl, acetyl, benzoyl, furoyl, tosyl and methanesulphonyl radicals.

In all cases, the aryl and hetaryl radicals can be substituted one or more times by the above-mentioned substituents.

When X is a carbomoyl group, it can be optionally substituted by lower alkyl, cycloalkyl, aryl and acyl radicals.

Some of the compounds of general formula (I), in which R₁ is a hydrogen atom or a methyl or phenyl radical and X is a cyano group or an alkoxycarbonyl radical, are known from the literature. Thus, for example, the lower N-alkyl-2-cyanoaziridines, the alkyl radical of which is unsubstituted, 1-benzyl-2-cyanoaziridine and the like, have been described by Gundermann aziridine and the like, have been described by Gundermann *et al.* (Chem. Ber., 105, 312-315). Other compounds have been described as intermediates without any mention of a pharmacological effectiveness so that it was surprising that these compounds also have an immune-stimulating action.

The new compounds which can also be used according to the present invention have the general formula:-



(I')

wherein X is a carboxy or nitrile group or an alkoxy-carbonyl radical or an unsubstituted or substituted carbamoyl group, R' is a straight-chained or branched, saturated or mono- or polyunsaturated aliphatic hydrocarbon radical which is optionally substituted one or more times by halogen, alkoxy, hydroxyl, dialkylamino, cycloalkylamino, acylamino, acyl, nitro, alkylthio, alkylsulphinyl, alkylsulphonyl, nitrile, carbalkoxy or carbamoyl radicals or by cycloalkyl radicals optionally substituted by alkyl, alkoxy or carbalkoxy, or by cycloalkenyl radicals, which can optionally be bridged, or by an aliphatic or aromatic heterocyclic radical, by aryl, aryloxy, arylthio, acyloxy, alkoxycarbonyl- amino or ureido groups, or R' is a

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cycloalkyl or cycloalkenyl radical containing 3 to 10 carbon atoms which is optionally substituted by alkyl, alkoxy, alkoxycarbonyl or oxo groups and is also optionally interrupted by hetero atoms and optionally bridged by 1 to 3 carbon atoms, or R' is an aryl or hetaryl radical, the aryl and hetaryl radicals being optionally substituted by halogen, alkoxy, alkyl, hydroxyl, carbalkoxy, carbamoyl, dialkyl-amino, cycloalkylamino, acylamino, nitro, cyano, acyl, alkylthio, alkylsulphinyl, alkylsulphonyl, sulphamoyl, phenyl, trifluoromethyl, aryloxy, acyloxy or methylenedioxy; and R₁ is a hydrogen atom or a saturated, straight-chained or branched alkyl radical containing up to 4 carbon atoms or a phenyl radical, with the proviso that when X is a cyano group or an alkoxycarbonyl radical and R₁ is a hydrogen atom, R' is not an unsubstituted alkyl radical or an alkyl radical substituted by hydroxyl, alkoxy, dialkylamino, phenyl, 4-chloro-phenyl or 4-methoxyphenyl or a vinyl radical substituted by a phenyl or methyl radical, or a cycloalkyl radical, a phenyl, a 4-chlorophenyl, a 4-methoxyphenyl, an *s*-triazinyl or a pyridinyl radical and with the proviso that when X is a carbamoyl group and R₁ is a hydrogen atom, R' is not an unsubstituted cyclohexyl, alkyl or benzyl radical and with the proviso that when X is a cyano group or an alkoxycarbonyl radical and R₁ is a phenyl radical, R' is not an isopropyl, cyclohexyl, phenyl, benzyl or *p*-chlorobenzyl radical and when R₁ is a methyl radical, is not a benzyl, *p*-chloro- or *p*-methoxybenzyl radical. These new compounds of general formula (I) are described and claimed in our co-pending British Patent Application No. 82.15159.

Preferred compounds of general formula I' which can be used according to the present invention include:

- 2-Cyano-1-(2-methylsulphinyloethyl)-aziridine
- 2-Cyano-1-(2-cyanoethyl)-aziridine
- 20 1-(3-Chloropropyl)-2-cyanoaziridine 20
- 1-(2-Acetamidoethyl)-2-cyanoaziridine
- 1-(2-Benzamidoethyl)-2-cyanoaziridine
- 2-Cyano-1-(2-carbamoyloethyl)-aziridine
- 2-Cyano-1-(but-2-ynyl)-aziridine
- 25 2-Cyano-1-(4-hydroxy-3-methoxybenzyl)-aziridine 25
- 2-Cyano-1-(cyclohept-2-enylmethyl)-aziridine
- 2-Cyano-1-(cyclohept-3-enyl)-aziridine
- 1-(1-Acetylpiperidin-4-yl)-2-cyanoaziridine
- 2-Cyano-1-(thian-3-yl)-aziridine
- 30 2-Cyano-1-(2,2,2-trichloroethyl)-aziridine 30
- 2-Cyano-1-(3,4-methylenedioxybenzyl)-aziridine
- 2-Cyano-1-(2,2,2-trifluoroethyl)-aziridine
- 2-Cyano-1-(2-nitroethyl)-aziridine
- 2-Cyano-1-(1-naphthylmethyl)-aziridine
- 35 1-Benzyl-aziridine-2-carboxylic acid 35
- 1-Allyl-2-cyano-3-phenyl-aziridine
- 2-Cyano-1-(pent-3-enyl)-aziridine
- 2-Cyano-1-(4-cyanobenzyl)-aziridine
- 2-Cyano-1-(2-methylcyclohexyl)-aziridine
- 40 2-Cyano-1-(4-methoxycyclohexyl)-aziridine 40
- 2-Cyano-1-(pyrimidin-2-yl)-aziridine
- 2-Cyano-1-(4-phenylbenzyl)-aziridine
- 2-Cyano-1-(2-methylsulphinylobenzyl)-aziridine
- 2-Cyano-1-(2-methylsulphonylobenzyl)-aziridine
- 45 2-Cyano-1-(4-sulphamoylobenzyl)-aziridine 45
- 2-Cyano-1-(3-carbamoylobenzyl)-aziridine
- 1-(4-Acetylobenzyl)-2-cyanoaziridine
- 1-(2-Acetamido-5-methylbenzyl)-2-cyanoaziridine
- 2-Cyano-1-(3,4,5-trimethoxybenzyl)-aziridine
- 50 2-Cyano-1-(naphth-1-yl)-aziridine 50
- 2-Cyano-1-(thiazol-2-yl)-aziridine
- Methyl 2-cyano-1-aziridine-propionate
- 1-Allyl-2-cyanoaziridine
- 2-Cyano-1-(3-morpholinopropyl)-aziridine
- 55 2-Cyano-1-(2-pyrrolidinoethyl)-aziridine 55
- 2-Cyano-1-[3-(2-methylpiperidino)-propyl]-aziridine
- 2-Cyano-1-(2- α -furoylaminoethyl)-aziridine
- 2-Cyano-1-(4-methylsulphonamidobenzyl)-aziridine
- 2-Cyano-1-(4-phenoxybenzyl)-aziridine
- 60 Ethyl 3-(2-cyanoaziridin-1-yl)-propionate 60
- 2-Cyano-1-(4-hydroxybenzyl)-aziridine
- 2-Cyano-1-(cyclohex-1-enylmethyl)-aziridine
- 2-Cyano-1-(2-thenyl)-aziridine
- 2-Cyano-1-(2-furylmethyl)-aziridine
- 65 2-Cyano-1-(2-methylallyl)-aziridine 65

- 1-(1-Adamantyl)-2-cyanoaziridine
Ethyl 2-cyano-1-aziridine-acetate
3-(2-Cyano-aziridin-1-yl)-acrolein
Dimethyl 3-(2-cyanoaziridin-1-yl)-fumerate
5 Ethyl 3-(2-cyanoaziridin-1-yl)-acrylate 5
1-Phenyl-1-(2-cyanoaziridin-1-yl)-2-cyanoethylene
1-(2-Carbamoylaziridin-1-yl)-1-(*p*-methoxycarbonylphenyl)-
1-Phenyl-1-(2-carbamoylaziridin-1-yl)-ethylene
1-Phenyl-1-(2-carbamoylaziridin-1-yl)-2-cyanoethylene
10 1-(2-Carbamoyl-aziridine-1-yl)-2-carbethoxy-cyclohex-1-ene 10
4-(2-Carbamoylaziridin-1-yl)-1-methyl-3,4-dehydropiperidine
1-Allyl-2-cyano-3-methylaziridine
Ethyl 1-allylaziridine-2-carboxylate
2-Cyano-1-(2-methylthiobenzyl)-aziridine
15 2-Cyano-1-(3,4-dimethoxybenzyl)-aziridine 15
2-Cyano-1-(4-methylbenzyl)-aziridine
1-(2-Cyanoaziridin-1-yl)-2-carbethoxy-cyclohex-1-ene;
and the pharmacologically-acceptable salts thereof, as well as all the stereoisomeric forms of these compounds.
- 20 The preparation of the compounds of general formula (I') is also described and claimed in our copending 20
British Patent Application No.
- For the production of pharmaceutical compositions with immune-stimulating action, the compounds of general formula (I) are mixed in conventional manner with appropriate pharmaceutical carrier materials, optionally granulated and pressed, for example, into tablets or dragee cores. The mixture can also be filled
25 into hard gelatine capsules. With the addition of appropriate adjuvants, there can also be produced a 25
solution or suspension in water, an oil, for example olive oil, or high molecular weight polymer, for example polyethylene glycol, which can then be worked up to give injection solutions, soft gelatine capsules, syrups or drops.
- Since the active materials are acid labile, the compositions are either provided with a coating which only
30 dissolves in the alkaline medium of the small intestine or an adjuvant, such as antacid, for example 30
magnesium oxide, which is able to neutralise the gastric juices to a pH value above 6, is incorporated into the formulation.
- Examples of solid carrier materials which can be used include starch, starch derivatives, sugar, sugar alcohols, celluloses and cellulose derivatives, tensides, talc, highly-dispersed silicic acids, high molecular
35 weight fatty acids and the salts thereof, gelatine, agaragar, calcium phosphate, animal and vegetable fats 35
and waxes and solid high molecular weight polymers, for example polyethylene glycols or polyvinylpyrrolidones. If liquid active materials are to be worked up to give tablets or hard gelatine capsules, in addition to highly-dispersed silicic acid, there can also be used carriers, such as phosphates, carbonates and oxides. Compositions suitable for oral administration can, if desired, contain flavouring and/or sweetening agents.
- 40 For pharmaceutical combinations in which compounds of general formula (I) are present together with a 40
chemotherapeutic agent, in general there are used the same galenical forms of composition as are described above for the individual substances. The two active materials, i.e. the immune stimulant and the chemotherapeutic agent, are usually present in the composition in a weight ratio of 10:1 to 1:10, it having proved to be advantageous to use an equimolar ratio of the two components.
- 45 A preferred composition comprises 100 mg. of chloramphenicol as chemotherapeutic agent and 33.3 mg. 45
of 1-allyl-2-cyanoaziridine, together with appropriate carrier materials, such as starch, and can be produced in the form of a 250 mg. tablet which, as a rule, are taken orally twice a day.
- For the demonstration of the immune-stimulating action, there is employed, as already mentioned, on the one hand the influencing of an acute infection with *Escherichia coli* (108) in mice by an immune stimulant
50 selected from compounds of general formula (I), for example 1-allyl-2-cyanoaziridine (B), with the 50
simultaneous administration of a subtherapeutic dose of chloramphenicol (A).

Experimental protocol

Groups of 20 female adult NMRI mice (body weight 25 to 30 g.) were, on 0 day, infected with 1.0×10^7
55 micro-organisms/animal (*Escherichia coli*) intraperitoneally. Treatment was carried out as follows: 55

- 1st Group: 40 mg./kg. A, oral, dissolved in 0.5 % tylose solution
2nd Group: 13.4 mg./kg. B, oral, dissolved in 0.5% tylose solution
3rd Group: 40 mg./kg. A + 13.4 mg./kg. B, oral dissolved in 0.5% tylose solution
60 4th Group: 10 mg./kg. A, oral, dissolved in 0.5% tylose solution 60
5th Group: 3.3 mg./kg. B, oral, dissolved in 0.5% tylose solution
6th Group: 10 mg./kg. A + 3.3 mg./kg. B, oral, dissolved in 0.5% tylose solution
7th Group: control: tylose solution.

Results.**% Survival**

5 A	B	1st	2nd	3rd	4th	5th	6th	5
mg/kg.	mg/kg.	day	day	day	day	day	day	
40	-	70	70	65	65	65	65	
10 -	13.4	0	0	0	0	0	0	10
40 +	13.4	100	100	100	100	100	100	
10	-	15	15	15	15	15	15	
15 -	3.3	10	10	10	10	10	10	15
10 +	3.3	65	55	50	50	50	50	
20 Control		0	0	0	0	0	0	20

On the other hand, in a leukocyte screening test, the increase of the leukocytes after oral administration of compounds of general formula (I) was determined.

25 Experimental protocol.

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Groups of 10 female, adult Sprague-Dawley rats were fasted and then blood was sampled from the retro-orbital=venous complex and the leukocytes counted with the help of a Coulter counter. Subsequently, the compounds to be investigated were administered orally in a dosage of 200 mg./kg., dissolved or suspended in 0.5% tylose solution. 4 days later, again after fasting overnight, blood was taken from the

30 retro-orbital venous complex and the leukocytes counted in a Coulter counter and the average values, with standard deviations from the average value, were calculated. ("Coulter" is a Registered Trade Mark).

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Results:

Substance		0 day	4th day	Example	
5	B	8.5	17.1	1	5
	C	8.93	12.84	1 a)	
	D	8.0	13.5	1 b)	
	E	8.0	14.3	1 f)	10
	F	6.7	16.2	5	
15	G	7.55	10.4	5 b)	15
	H	7.37	8.5	7 b)	
	I	6.5	11.2	1 c)	
	J	6.5	9.6	1 n)	20
	K	8.9	12.0	1 p)	
25	L	7.1	11.3	11 f)	25
	M	7.1	12.3	13 o)	
	N	7.4	11.3	16 a)	
	O	7.0	13.7	13 a)	30
	P	6.6	10.6	13 c)	
35	Q	6.3	11.9	13 d)	35
	R	7.9	12.3	13 x)	
	S	7.5	13.5	13 v)	
	T	7.0	13.2	13 e)	40
	U	8.0	11.9	6 b)	
45	V	7.8	11.9	6 c)	45
	W	6.9	10.6	6 d)	
	X	5.8	11.9	13 w)	
	Z	6.7	9.8	13 i)	50
	A	=	Chloroamphenicol		
55	B	=	1-Allyl-2-cyanoaziridine		55
	C	=	Cyano-1-methylaziridine		
	D	=	2-Cyano-1- <i>n</i> -propylaziridine		
	E	=	1-Benzyl-2-cyanoaziridine		60
	F	=	3-(2-Cyanoaziridin-1-yl)-acrolein		
65	G	=	Ethyl 3-(2-Cyanoaziridin-1-yl)-acrylate		65

H	=	1-Phenyl-1-(2-carbamoylaziridin-1-yl)-2-cyanoethylene.	
I	=	2-Cyano-1-isopropylaziridine	
5 J	=	2-Cyano-1-(2-thenyl)-aziridine	5
K	=	2-Cyano-1-(2-methylallyl)-aziridine	
L	=	1-(2-Chlorethyl)-2-cyanoaziridine	
10 M	=	2-cyano-1-(3-trifluoremethylbenzyl)-aziridine	10
N	=	2-Cyano-1-(5-carboxy-2-furfuryl)-aziridine	
15 O	=	2-Cyano-1-(5-methoxycarbonyl-2-thenyl)-aziridine	15
P	=	2-Cyano-1-(2,2-dichloroethyl)-aziridine	
Q	=	1-(But-2-enyl)-2-cyanoaziridine	
20 R	=	2-Cyano-1-(5-methyl-2-nitrobenzyl)-aziridine	20
S	=	1-(2-Chlorobenzyl)-2-cyanoaziridine	
25 T	=	2-Cyano-1-(5-methylpyrimidin-4-ylmethyl)-aziridine	25
U	=	L-(-)-2-Cyano-(L-(-)-phenylethyl)-aziridine	
V	=	D-(+)-2-Cyano-1-(L-(-)-Phenylethyl)-aziridine	
30 W	=	L-(-)-2-Cyano-1-(D-(+)-phenylethyl)-aziridine	30
X	=	2-Cyano-1-(pyrimidin-2-ylmethyl)-aziridine	
35 Z	=	2-Cyano-1-[(2-methoxy-6-methylpyridin-3-yl)-methyl]-aziridine	35

Furthermore, the 2-cyanoaziridines in which the nitrogen atom is substituted by alkyl radicals show only insignificant secondary effects. Thus, in contradistinction to known aziridines, the compounds of the present invention possess no or only small mutagenic effects, as demonstrated by the Ames-Test.

Apart from the compounds mentioned in the following Examples, preferred compounds according to the present invention for the preparation of pharmaceutical compositions with immune-stimulating action include the following compounds:

45	2-Cyano-1-(2-dimethylaminoethyl)-aziridine	45
	2-Cyano-1-(2-methylsulphinylethyl)-aziridine	
	2-Cyano-1-(2-cyanoethyl)-aziridine	
	1-(3-Chloropropyl)-2-cyanoaziridine	
50	1-(2-Acetamidoethyl)-2-cyanoaziridine	50
	1-(2-Benzamidoethyl)-2-cyanoaziridine	
	2-Cyano-1-(2-carbamoylethyl)-aziridine	
	2-Cyano-1-(prop-1-enyl)-aziridine	
	2-Cyano-1-(but-2-ynyl)-aziridine	
55	2-Cyano-1-(4-hydroxy-3-methoxybenzyl)-aziridine	55
	2-Cyano-1-(cyclohept-2-enylmethyl)-aziridine	
	2-Cyano-1-(cyclohept-3-enyl)-aziridine	
	1-(1-Acetylpiperidin-4-yl)-2-cyanoaziridine	
	2-Cyano-1-(thian-3-yl)-aziridine	
60	2-Cyano-1-(2,2,2-trichloroethyl)-aziridine	60
	2-Cyano-1-(3,4-methylenedioxybenzyl)-aziridine	
	2-Cyano-1-(2,2,2-trifluoroethyl)-aziridine	
	2-Cyano-1-(2-nitroethyl)-aziridine	
	2-Cyano-1-(1-napthylemethyl)-aziridine	
65	1-Benzyl-aziridine-2-carboxylic acid	65

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- 1-Allyl-2-cyano-3-phenyl-aziridine
 2-Cyano-1-(pent-3-enyl)-aziridine
 2-Cyano-1-(4-cyanobenzyl)-aziridine
 2-Cyano-1-(2-methylcyclohexyl)-aziridine
 5 2-Cyano-1-(4-methoxycyclohexyl)-aziridine 5
 2-Cyano-1-(pyrimidin-2-yl)-aziridine
 2-Cyano-1-(4-phenylbenzyl)-aziridine
 2-Cyano-1-(2-methylsulphinyl-benzyl)-aziridine
 2-Cyano-1-(2-methylsulphonyl-benzyl)-aziridine
 10 2-Cyano-1-(4-sulphamoylbenzyl)-aziridine 10
 2-Cyano-1-(3-carbamoylbenzyl)-aziridine
 1-(4-Acetylbenzyl)-2-cyanoaziridine
 1-(2-Acetamido-5-methylbenzyl)-2-cyanoaziridine
 2-Cyano-1-(3,4,5-trimethoxybenzyl)-aziridine
 15 2-Cyano-1-(naphth-1-yl)-aziridine 15
 2-Cyano-1-(thiazol-2-yl)-aziridine
 Methyl S-2[(-)-2-cyano-1-aziridine]-propionate
 Methyl R-2[(+)-2-cyano-1-aziridine]-propionate
 (+)-1-Allyl-2-cyanoaziridine
 20 (-)-1-Allyl-2-cyanoaziridine 20
 2-Cyano-1-(3-morpholinopropyl)-aziridine
 2-Cyano-1-(2-pyrrolidinoethyl)-aziridine
 2-Cyano-1-[3-(2-methylpiperidino)-propyl]-aziridine
 2-Cyano-1-(2- α -furoylaminoethyl)-aziridine
 25 2-Cyano-1-(4-methylsulphonamidobenzyl)-aziridine 25
 2-Cyano-1-(4-phenoxybenzyl)-aziridine.

The following Examples 1 to 17 which are given for the purpose of illustrating the preparation of some of the compounds used according to the present invention, show some of numerous process variants which can be used for the synthesis of these compounds. The structures of all of the compounds described in the following Examples 1 to 17 have been confirmed by micro-combustion analyses, NMR spectra and mass spectra. Example 18 is given for the purpose of illustrating the present invention.

Example 1.

1-Allyl-2-cyanoaziridine.

- 35 A solution of 28.5 g. allylamine and 51 g. triethylamine in 250 ml. toluene is added dropwise, with stirring, 35
 at 0°C. to a solution of 66 g. 2-bromoacrylonitrile in 250 ml. toluene. The reaction mixture is subsequently stirred for 3 days at ambient temperature and then filtered with suction. The filtrate is evaporated and the residue is taken up in diethyl ether, extracted once with ice-cold, dilute hydrochloric acid and washed neutral with ice water. This solution is then passed over 400 g. of deactivated aluminium oxide. After evaporation,
 40 the residue is distilled twice. There are obtained 28.6 g. (about 53% of theory) 1-allyl-2-cyano-aziridine; 40
 b.p._{0.2}: 53 - 55°C.

In an analogous manner, by the reaction of 2-bromo-acrylonitrile with the appropriate amines, there are obtained the following compounds, which are known from the literature:

- a) 2-cyano-1-methylaziridine (b.p.₁₁: 53 - 54°C.)
 45 b) 2-cyano-1-*n*-propylaziridine (b.p.₁₅: 80 - 82°C.) 45
 c) 2-cyano-1-isopropylaziridine (b.p.₁₅: 53 - 55°C.)
 d) 2-cyano-1-*n*-pentylaziridine (b.p._{0.3}: 50 - 52°C.)
 e) 1,6-bis-(2-cyanoaziridin-1-yl)-hexane (m.p.: 64 - 66°C.)
 f) 1-benzyl-2-cyanoaziridine (b.p._{0.05}: 103 - 105°C.)
 50 g) 2-cyano-1-cyclohexylaziridine (b.p._{0.1}: 93 - 94°C.) 50

Compounds a) to f) have been described by Gundermann *et al.* (Chem. Ber., 105, 312/1972) and compound g) has been described by Wagner-Jauregg (helv. Chim. Acta, 44, 1237/1961).

- In an analogous manner, by the reaction of 2-bromoacrylonitrile with the appropriate amines and subsequent purification by means of a silica gel and/or deactivated aluminium oxide column, there are
 55 obtained the following compounds: 55

h) 2-Cyano-1-(2-hydroxyethyl)-aziridine

oily product; yield: 31.1% of theory

- 60 i) Ethyl 3-(2-cyanoaziridin-1-yl)-propionate 60

b.p._{0.15}: 105°C.; yield: 33% of theory

- 65 (dioxan used as solvent) 65

k) 2-Cyano-1-(4-hydroxybenzyl)-aziridine

m.p.: 112 - 114°C.; yield: 37% of theory

5 (ethanol used as solvent)

5

l) Methyl S-2-[(+)-2-cyano-1-aziridine]-propionate

m.p. 88 - 91°C. recrystallised from diisopropyl ether;

10

$[\alpha]_D^{20} = +99.4^\circ \text{ c} = 1$ (methanol)

10

m) 2-Cyano-1-(cyclohex-1-enylmethyl)-aziridine

15 b.p._{0.01}: 103 - 105°C; yield: 42.9% of theory

15

n) 2-Cyano-1-(2-thenyl)-aziridine

b.p._{0.1}: 90 - 92°C.; yield 20% of theory

20

(reaction time 10 days)

20

o) 2-Cyano-1-(2-furylmethyl)-aziridine

25 b.p._{0.1}: 100 - 101°C; yield: 8.1% of theory

25

(reaction time 10 days)

p) 2-Cyano-1-(2-methylallyl)-aziridine

30

b.p._{0.1}: 36 - 38°C.; yield: 16.4% of theory

30

q) 1-(1-Adamantyl)-2-cyanoaziridine

m.p. 62 - 64°C.; yield: 51.8% of theory

35

(dioxan used as solvent)

35

Example 2.

1-tert.-Butyl-2-cyanoaziridine

40 6.0 g. 2-Bromo-3-tert-butylaminopropionitrile hydrobromide (prepared by reacting 2,3-dibromopropionitrile with tert.-butylamine; m.p. 188 - 190°C.) are dissolved in 50 ml. methanol and heated under reflux for 4 hours with 25 ml. triethanolamine. The solution is then evaporated, neutralised with 2N sulphuric acid and extracted with diethyl ether and the collected ethereal fractions are dried and evaporated, the residue obtained being subsequently distilled. There is obtained 1.2 g. (about 39.5% of theory)

40

45 1-tert.-butyl-2-cyanoaziridine; b.p._{0.2}: 52 - 54°C.; m.p. 53 - 54°C.

45

The following compounds are obtained in an analogous manner:

a) reaction of 2-bromo-3-n-pentylaminopropionitrile hydrochloride (prepared by reacting 2,3-dibromopropionitrile with n-pentylamine; m.p. 133 - 135°C.) with triethanolamine gives 2-cyano-n-pentylaziridine;

50 b.p._{0.3}: 50 - 52°C.; yield 43% of theory;

50

b) reaction of 2-bromo-3-(carbethoxymethylamino)-propionitrile hydrochloride (prepared by reacting 2,3-dibromo-propionitrile with glycine ethyl ester; m.p. 70 - 75°C.) with triethanolamine gives ethyl 2-cyano-1-aziridine-acetate; b.p._{0.1}: 88 - 90°C.; yield 34% of theory;

55 c) reaction of 2-bromo-3-[(1-carbomethoxyethyl)-amino]-propionitrile (prepared by reacting 2,3-dibromopropionitrile with L-alanine methyl ester; oily substance) with triethylamine gives methyl S-2-[(+)-2-cyano-1-aziridine]-propionate; m.p. 88 - 91°C. (recrystallised from diisopropyl ether); $[\alpha]_D^{20} = +99.4^\circ$ (c = 1 in methanol).

55

Example 3.

60 1-Allyl-2-cyanoaziridine.

60

4.2 g. Sodium bicarbonate are dissolved in 30 ml. ethanol/15 ml. water, 3.4 g. 2-cyanoaziridine are added thereto and 8.4 g. freshly distilled allyl iodide are added dropwise, whereafter the reaction mixture is stirred for 72 hours at ambient temperature. The solution is then evaporated on a rotary evaporator and the residue is taken up in water and extracted several times with diethyl ether. After drying, the diethyl ether is stripped off and the residue separated with the use of a silica gel column (elution agent: diethyl ether/ligroin 2:1 v/v).

65

The crude 1-allyl-2-cyanoaziridine thus obtained is subsequently distilled. The yield is 1.24 g. (23% of theory) b.p._{0.2}: 53 - 55°C.

Example 4.

5 2-Cyano-1-phenylaziridine.

A mixture of 11.65 g. phenyl azide and 18 g. acrylonitrile is left to stand in the dark for 9 days at ambient temperature. Excess acrylonitrile is then stripped off in a vacuum and the 4-cyano-1-phenyl-triazole-(2) obtained as an intermediate (a sample thereof was crystallised with cyclohexane; m.p. 87 - 91°C.) is dissolved in 80 ml. toluene and heated to 100°C. for 40 minutes, nitrogen thereby being evolved. The toluene is stripped off in a vacuum and the residue distilled. There are obtained 5.9 g. (42% of theory) 2-cyano-1-phenylaziridine; b.p._{0.1}: 109-111°C. 10

Example 5.

3-(2-Cyanoaziridin-1-yl)-acrolein.

15 5.78 g. 2-Cyanoaziridine are added dropwise, with cooling, to 4.6 g. propargyl aldehyde. The reaction mixture is stirred overnight at 208°C., the dark oil obtained is taken up in 500 ml. ethanol and the solution is treated with active charcoal, filtered and concentrated to 50 ml. Upon cooling with ice, the desired product precipitates out and is washed with ethanol/diethyl ether. There are obtained 4.2 g. (41% of theory) 3-(2-cyano-aziridin-1-yl)-acrolein; m.p. 57 - 58°C. 15

20 The following compounds are obtained in an analogous manner by reacting 2-cyanoaziridine with: 20

a) dimethyl acetylene-dicarboxylate:

dimethyl 3-(2-cyanoaziridin-1-yl)-fumarate; m.p. 127 - 128°C. (recrystallised from ethanol); yield 11% of theory;

b) ethyl propiolate:

25 ethyl 3-(2-cyanoaziridin-1-yl)-acrylate; oily substance, purified with a silica gel column; yield 24% of theory. 25

Example 6.

1-Phenyl-1-(2-cyanoaziridin-1-yl)-2-cyanoethylene.

2.7 g. 1-Phenyl-1-(2-carbamoylaziridin-1-yl)-2-cyanoethylene and 5.0 g. triphenyl phosphine are dissolved in a mixture of 400 ml. anhydrous methylene chloride, 1.76 g. triethylamine and 1.2 ml. anhydrous carbon tetrachloride and the reaction mixture then stirred under reflux, the dehydration reaction being monitored by thin layer chromatography. The reaction mixture is then evaporated and the residue purified on a silica gel column with the elution mixture chloroform/acetone/cyclohexane (5:5:1 v/v/v). The desired fraction is caused to crystallise with ligroin. There is obtained 0.7 g. (23.5% of theory) 1-phenyl-1-(2-cyanoaziridin-1-yl)-2-cyanoethylene; m.p. 95°C. (recrystallised from diethyl ether). 30 35

The following compounds are obtained in an analogous manner from the indicated starting materials:

a) 1-(2-Carbamoylaziridin-1-yl)-2-carebethoxy-cyclohex-1-ene

40 1-(2-Cyanoaziridin-1-yl)-2-carebethoxy-cyclohex-1-ene m.p.: 101 - 104°C.; yield: 54.5% of theory 40

b) L(-)-1-(L(-)-Phenylethyl)-aziridine-2-carboxamide (see Example 14)

L(-)-2-Cyano-1-(L(-)-phenylethyl)-aziridine

m.p.: 44 - 48°C.; yield: 45% of theory

45 $[\alpha]_D^{20}$: -129.4° (c = 1 in methanol) 45

c) D-(+)-1-(L(-)-Phenylethyl)-aziridine-2-carboxamide (see Example 14a)

D-(+)-2-Cyano-1-(L(-)-phenylethyl)-aziridine

oily substance; yield: 51% of theory

50 $[\alpha]_D^{20}$: +58.8° (c = 1 in methanol) 50

d) L(-)-1-(D-(+)-Phenylethyl)-aziridine-2-carboxamide (see Example 14b)

L(-)-2-Cyano-1-(D-(+)-phenylethyl)-aziridine

oily substance; yield: 74% of theory

55 $[\alpha]_D^{20}$: -53.5° (c = 1 in methanol) 55

e) D-(+)-1-(D-(+)-Phenylethyl)-aziridine-2-carboxamide (see Example 14c)

D-(+)-2-Cyano-1-(D-(+)-phenylethyl)-aziridine

m.p. 45 - 48°C.; yield: 62% of theory

60 $[\alpha]_D^{20}$: +128.1° (c = 1 in methanol) 60

Example 7.

1-(2-Carbamoylaziridin-1-yl)-1-(p-methoxycarbonylphenyl)-ethylene.

2.7 g. p-Methoxycarbonylacetophenone and 1.03 g. 2-cyanoaziridine are mixed and, after the addition of 1.05 ml. triethylamine, stirred for 3 hours at 60°C. After cooling, the reaction mixture is stirred with diethyl 65 65

ether. The residue is brought to crystallisation with a mixture of chloroform and methanol (9:1 v/v). There is obtained 0.9 g. (24% of theory) 1-(2-carbamoyl-aziridin-1-yl)-1-(*p*-methoxycarbonylphenyl)-ethylene; m.p. 140 - 141°C. (decomp.).

The following compounds are obtained in an analogous manner by reacting 2-cyanoaziridine with

- 5 a) acetophenone: 1-phenyl-1-(2-carbamoylaziridin-1-yl)ethylene; m.p. 93 - 96°C.; yield 16% of theory 5
- b) ω -cyanoacetophenone: 1-phenyl-1-(2-carbamoylaziridin-1-yl)-2-cyanoethylene; m.p. 164 - 167°C. (recrystallised from ethyl acetate); yield 84.5% of theory 10
- c) ethyl cyclohexanone-2-carboxylate: 1-(2-carbamoylaziridin-1-yl)-2-carboethoxycyclohex-1-ene; m.p. 168 - 170°C.; yield 17% of theory (reaction time 70 hours; crystallised by trituration with ethyl acetate) 15
- 15 d) 1-methylpiperidinone-(4): 4-(2-carbamoylaziridin-1-yl)-1-methyl-3,4-dehydro-piperidine; m.p. 149 - 150°C.; yield 12% of theory (reaction time 24 hours, crystallised by trituration with isopropanol). 15

Example 8.

- 20 1-Allyl-2-cyano-3-methylaziridine 20
- 13.4 g. Crotonitrile are mixed at ambient temperature, within the course of 2 hours, with 32 g. bromine and the solution then heated to 30°C. until decolorised. The reaction mixture is diluted with 100 ml. diethyl ether and cooled to 0°C. A solution of 20.2 g. triethylamine in 50 ml. diethyl ether is added dropwise thereto and the reaction mixture further stirred for 1 hour at 0°C. To the suspension obtained is added at 0°C. a mixture of 25 20.2 g. triethylamine and 11.4 g. allylamine in 100 ml. diethyl ether and the reaction mixture stirred for 4 days at ambient temperature. The precipitate obtained is filtered off with suction, washed with diethyl ether and the ethereal solution, after drying, passed over 250 g. deactivated aluminium oxide. The eluate is subsequently evaporated and fractionated. There are obtained 10.3 g. (42.2% of theory) 1-allyl-2-cyano-3-methylaziridine; b.p._{0.1}: 55 - 57°C. 25

Example 9.

Ethyl 1-benzylaziridine-2-carboxylate.

- 55.3 ml. Triethylamine are added, with stirring, at 0°C. to 52 g. ethyl 2,3-dibromopropionate in 250 ml. toluene and, after 2 hours, a solution of 21.4 g. benzylamine in 250 ml. toluene added thereto. The reaction mixture is subsequently further stirred for 3 days at ambient temperature. The suspension is then shaken out several times with water and the organic phase is dried and evaporated and the residue is taken up in diethyl ether. The ethereal solution is passed over 400 g. deactivated aluminium oxide and the eluate is evaporated and fractionated. There are obtained 30.7 g. (about 75 % of theory) ethyl 1-benzylaziridine-2-carboxylate; b.p._{0.03}: 98 - 101°C. 35
- 40 The following compounds are obtained in an analogous manner by reacting ethyl 2,3-dibromopropionate with: 40
- a) methylamine: ethyl 1-methylaziridine-2-carboxylate; b.p.₁₆: 70 - 72°C; yield 40% of theory 45
- 45 b) allylamine: ethyl 1-allylaziridine-2-carboxylate; b.p.₁₂: 91 - 92°C; yield 24% of theory. 45

Example 10.

- 50 2-Cyano-1-methylaziridine. 50
- 5.0 g. 1-(2-Cyanoethyl)-1-methyl-2,2,2-trimethyl-hydrazinium iodide (m.p. 125 - 130°C.) are heated to 40°C. for 12 hours in a solution of 0.2 g. sodium methylate in 30 ml. methanol, trimethylamine being liberated during the reaction. Subsequently, the reaction mixture is evaporated, the residue is passed over a silica gel column (elution agent: acetone/toluene 1:1 v/v) and the crude product so obtained is distilled twice. There is 55 obtained 0.35 g. (about 23% of theory) 2-cyano-1-methylaziridine; b.p.₁₁: 53 - 54°C. 55

Example 11

In a manner analogous to that described in Example 1, the following compounds are obtained by reacting 2-bromoacrylonitrile with:

- 60 a) 2-methylthiobenzylamine: 2-cyano-1-(2-methylthiobenzyl)-aziridine; oily product; yield 54% of theory 60
- b) 3,4-dimethoxybenzylamine: 2-cyano-1-(3,4-dimethoxybenzyl)-aziridine; oily product; yield 25% of theory 65

- c) 4-methylbenzylamine:
2-cyano-1-(4-methylbenzyl)-aziridine; b.p._{0.05}: 113 - 115°C.; yield 23% of theory
- d) cyclopropylamine:
2-cyano-1-cyclopropylaziridine; b.p._{1.5}: 70°C.; yield 22% of theory
- 5 e) 2-methyl-3-carbethoxybenzylamine: 5
2-cyano-1-(2-methyl-3-carbethoxybenzyl)-aziridine;
b.p._{0.01}: 168 - 170°C.; m.p. 40 - 43°C.; yield 20% of theory
- f) 2-chloroethylamine hydrochloride:
- 10 l-(2-chloroethyl)-2-cyanoaziridine (using dioxan as solvent); b.p._{0.1}: 74°C.; yield 5.1% of theory 10
g) 4-aminotetrahydropyran:
l-(4-tetrahydropyranyl)-2-cyanoaziridine (using dioxan as solvent); m.p. 74 - 76°C.; yield 13.2% of theory
- h) 2-methoxyethylamine:
2-cyano-1-(2-methoxyethyl)-aziridine; b.p._{0.2}: 80°C;
15 yield 17.5% of theory 15
i) 2-phenoxyethylamine:
2-cyano-1-(2-phenoxyethyl)-aziridine; b.p._{0.05}: 115°C;
yield 38.8% of theory.
- 20 **Example 12.** 20
1-Benzylaziridine-2-carboxamide.
0.7 g. Ethyl 1-benzylaziridine-2-carboxylate is stirred for 16 hours at ambient temperature with 10 ml. concentrated aqueous ammonia solution. The precipitated crystals are filtered off with suction and washed with a little water. There is obtained 0.45 g. (about 75% of theory) 1-benzylaziridine-2-carboxamide; m.p. 114
25 - 116°C. 25
- Example 13**
Analogously to Example 1, by the reaction of 2-bromoacrylonitrile with the indicated starting materials, there are obtained the following compounds:
- 30 a) 5-Methoxycarbonyl-2-thenylamine: 30
2-Cyano-1-(5-methoxycarbonyl-2-thenyl)-aziridine
m.p.: 51 - 54°C.; yield: 49% of theory
- b) 5-Methoxycarbonyl-2-furfurylamine:
2-Cyano-1-(5-methoxycarbonyl-2-furfuryl)-aziridine
35 m.p.: 86 - 89°C.; yield: 46% of theory 35
- c) 2,2-Dichloroethylamine:
2-Cyano-1-(2,2-dichloroethyl)-aziridine
m.p.: 94 - 95°C.; yield: 16% of theory
- d) But-2-enylamine:
40 1-(But-2-enyl-2-cyanoaziridine 40
b.p._{0.1}: 60 - 61°C.; yield: 70% of theory
- e) 5-Methylpyrimidin-4-ylmethylamine:
2-Cyano-1-(5-methylpyrimidin-4-ylmethyl)-aziridine
m.p.: 88-92°C. (recrystallised from isopropanol); yield:
45 56% of theory 45
- f) 2-Hydroxy-6-methylpyridin-3-ylmethylamine:
2-Cyano-1-[(2-hydroxy-6-methylpyrimidin-3-yl)-methyl]-aziridine
m.p.: 187 - 190°C. (recrystallied from water); yield
47% of theory
- 50 g) Aminoacetaldehyde dimethyl acetal: 50
2-Cyano-1-(2,2-dimethoxy-1-ethyl)-aziridine
b.p._{0.1}: 90 - 92°C.; yield: 70% of theory
- h) 1,6-Dimethyl-2-oxo-pyridin-3-ylmethylamine:
2-Cyano-1-[(1,6-dimethyl-2-oxo-pyridin-3-yl)-methyl]-aziridine
55 m.p.: 82 - 84°C.; yield: 78% of theory 55
- i) 2-Methoxy-6-methylpyridin-3-ylmethylamine:
2-Cyano-1-[(2-methoxy-6-methylpyridin-3-yl)-methyl]-aziridine
m.p.: 70 - 73°C. (recrystallised from isopropanol);
yield: 69% of theory
- 60 k) 2,5-Dimethyl-pyrimidin-4-ylmethylamine: 60
2-cyano-1-[(2,5-dimethyl-pyrimidin-4-yl)-methyl]-aziridine
m.p.: 88 - 92°C. (recrystallised from isopropanol);
yield: 82% of theory

- 1) 4-Methylthiazol-2-ylmethylamine:
2-Cyano-1-(4-methylthiazol-2-ylmethyl)-aziridine
 m.p.: 73 - 75°C.; yield: 21% of theory
- m) Prop-2-ynylamine:
 5 *2-Cyano-1-(prop-2-ynyl)-aziridine* 5
 b.p._{0.1}: 48°C.; yield: 28% of theory
- n) Tetrahydrofurfurylamine:
2-Cyano-1-tetrahydrofurfuryl-aziridine
 b.p._{0.1}: 95°C.; yield: 20% of theory
- 10 o) 3-Trifluoromethyl-benzylamine: 10
2-Cyano-1-(3-trifluoromethylbenzyl)-aziridine
 b.p._{0.15}: 92°C.; yield: 31% of theory
- p) 3-Methylthiopropylamine:
2-Cyano-1-(3-methylthiopropyl)-aziridine
 15 b.p._{0.05}: 110°C.; yield: 18% of theory 15
- q) 2-Methylsulphonylethylamine:
2-Cyano-1-(2-methylsulphonylethyl)-aziridine
 oily substance; yield: 47% of theory
- r) Phenethylamine:
 20 *2-Cyano-1-phenethyl-aziridine* 20
 b.p._{0.05}: 122 - 124°C.; yield: 18% of theory
- s) Cinnamylamine:
1-Cinnamyl-2-cyanoaziridine
 b.p._{0.05}: 138 - 140°C.; yield: 13% of theory
- 25 t) But-3-ynylamine: 25
1-(But-3-ynyl)-2-cyanoaziridine
 b.p._{0.1}: 70 - 71°C.; yield: 68% of theory
- u) 2-Norbornylamine:
2-Cyano-1-(2-norbornyl)-aziridine
 30 b.p._{0.05}: 84 - 85°C.; yield: 20% of theory 30
- v) 2-Chlorobenzylamine:
1-(2-Chlorobenzyl)-2-cyanoaziridine
 m.p.: 55 - 57°C. (recrystallised from isopropanol);
 yield: 36% of theory
- 35 w) Pyrimidin-2-ylmethylamine: 35
2-Cyano-1-(pyrimidin-2-ylmethyl)-aziridine
 m.p.: 72 - 76°C. (recrystallised from isopropanol);
 yield: 33% of theory
- x) 5-Methyl-2-nitrobenzylamine:
 40 *2-Cyano-1-(5-methyl-2-nitrobenzyl)-aziridine* 40
 m.p.: 95 - 96°C. (recrystallised from isopropanol);
 yield: 41% of theory
- y) R-(-)Alanine methyl ester:
Methyl-R-(-)-2-(1-2-Cyano-1-aziridin)-propionate
 45 m.p.: 90 - 91°C. (recrystallised from isopropyl ether); 45
 yield: 12% of theory; $[\alpha]_D^{20}$: -99.1° (c = 1 in methanol).

Example 14.

L-(-)-1-(L-(-)-Phenylethyl)-aziridine-2-carboxamide

- 50 5.6 g. Ethyl L-(-)-1-(L-(-)-phenylethyl)-aziridine-2-carboxylate (see Example 15) are dissolved in 55 ml. 50
 concentrated aqueous ammonia solution and 55 ml. ethanol and left to stand for 72 hours at ambient
 temperature. The solution is then evaporated and the residue triturated with diethyl ether. The white
 precipitate is filtered off with suction and then washed with diethyl ether. There are obtained 3.7 g. (about
 79% of theory) L-(-)-1-(L-(-)-phenylethyl)-aziridine-2-carboxamide; m.p. 108 - 111°C.; $[\alpha]_D^{20}$: -116.5° (c = 1 in
 55 methanol). 55
- The following compounds are obtained in an analogous manner from:
- a) ethyl D-(+)-1-(L-(-)-phenylethyl)-aziridine-2-carboxylate (see Example 15):
 D-(p)-1-(L-(-)-phenylethyl)-aziridine-2-carboxamide;
 m.p. 95 - 98°C.; yield 70% of theory; $[\alpha]_D^{20}$: +40.5°
- 60 (c = 1 in methanol) 60
- b) ethyl L-(-)-1-(D-(+)-phenylethyl)-aziridine-2-carboxylate (see Example 15a):
 L-(-)-1-(D-(+)-phenylethyl)-aziridine-2-carboxamide;
 m.p. 94 - 97°C.; yield 76% of theory; $[\alpha]_D^{20}$: -38.8.048
 (c = 1 in methanol)
- 65 c) ethyl D-(+)-1-(D-(+)-phenylethyl)-aziridine-2-carboxylate (see Example 15b): 65

D-(+)-1-(d-(+)-phenylethyl)-aziridine-2-carboxamide;
m.p. 102 - 104°C.; yield: 77% of theory; $[\alpha]_D^{20}$: +115°
(c = 1 in methanol).

5 Example 15.

Ethyl L-(-)-1-(L-(-)-phenylethyl)-aziridine-2-carboxylate and ethyl D-(+)-1-(L-(-)-phenylethyl)-aziridine-2-carboxylate.

15 g. Triethanolamine in 20 ml. ethanol are added, with stirring, to 26 g. ethyl 2,3-dibromopropionate in 60 ml. ethanol and, after 1 hour, there are simultaneously added a solution of 12.1 g. L-(-)-phenylethylamine in 10 20 ml. ethanol and a solution of 15 g. triethanolamine in 20 ml. ethanol. The suspension is stirred for 12 hours at ambient temperature and filtered off with suction. The filtrate is evaporated and the residue is separated over a silica gel column into the diastereomers using, as elution agent, diethyl ether/ligroin 2:1 v/v).

Yield of L,L-isomer: 39% of theory;

15 oily substance; $[\alpha]_D^{20}$: -90° (c = 1 in ethanol)

yield of D,L-isomer: 47% of theory

oily substance; $[\alpha]_D^{20}$: +53.2° (c = 1 in ethanol)

In an analogous manner, by the reaction of ethyl 2,3-dibromopropionate with D-(+)-phenylethylamine, there are obtained the following compounds:

20 a) ethyl L-(-)-1-(D-(+)-phenylethyl)-aziridine-2-carboxylate; oily substance; yield 39% of theory;

$[\alpha]_D^{20}$: 57.9° (c = in ethanol); and

b) ethyl D-(+)-1-(D-(+)-phenylethyl)-aziridine-2-carboxylate; oily substance; yield 39% of theory;

$[\alpha]_D^{20}$: +89.7° (c = 1 in ethanol).

25 Example 16

2-Cyano-1-(5-carboxy-2-thenyl)-aziridine

95 ml. 0.1N Aqueous sodium hydroxide solution are added dropwise, with stirring, to 2.1 g.

2-cyano-1-(5-methoxycarbonyl-2-thenyl)-aziridine (see Example 13a) in 21 ml. acetone. When no more ester can be detected by thin layer chromatography, the reaction mixture is evaporated in a vacuum, acidified with 30 dilute hydrochloric acid and extracted with ethyl acetate. The evaporation residue is crystallised with diethyl ether. There is obtained 1.2 g. (61% of theory) 2-cyano-1-(5-carboxy-2-thenyl)-aziridine; m.p. 108 - 111°C. The sodium salt melts with decomposition at 238 - 243°C.

a) In an analogous manner, from 2-cyano-1-(5-methoxy-carbonyl-2-furfuryl)-aziridine (see Example 13b), there is obtained 2-cyano-1-(5-carboxy-2-furfuryl)-aziridine;

35 m.p. 108 - 111°C.; yield 44% of theory.

Example 17

1-Benzyl-2-cyanoaziridine.

2.74 g. 3-Benzyl-4-cyano-2-oxazolidione (m.p. 81 - 83°C.; prepared by reacting 4-cyano-2-oxazolidone (m.p. 40 95 - 96°C.) with benzyl bromide in the presence of sodium hydride) are heated under reflux for 3 hours in 20 ml. o-dichlorobenzene, with the addition of 1.5 g. triethanolamine. After cooling, the reaction mixture is extracted with ice-cold 1N hydrochloric acid, washed neutral with water, dried and the organic phase fractionated. There are obtained 0.47 g. (about 31% of theory) 1-benzyl-2-cyanoaziridine; b.p._{0.05}: 103 - 105°C.

45 Example 18.

The following Examples illustrate the pharmaceutical compositions according to the present invention.

Example A (tablets)

50	active material	X mg. X = up to 40.0 mg.	50
	lactose	ad 60.0 mg.	
	polyvinylpyrrolidone	2.0 mg.	
55	microcrystalline		55
	cellulose	8.0 mg.	
60	sodium carboxymethyl-amylopectin	4.0 mg.	60
	silicic acid, highly dispersed	0.5 mg.	
65			65

	talc	5.0 mg.	
	magnesium stearate	0.5 mg.	
5	end weight	<u>80.0 mg.</u>	5
	For liquid active materials in disages of up to about		
	40 mg.:		
10	active material	X mg. X = up to 40.0 mg.	10
	silicic acid, highly dispersed	ad 100.0 mg.	
15	lactose	135.0 mg.	15
	polyvinylpyrrolidone	10.0 mg.	
20	microcrystalline cellulose	25.0 mg.	20
	sodium carboxymethyl-amylopectin	10.0 mg.	
25	silicic acid, highly dispersed	2.0 mg.	25
	talc	15.0 mg.	
30	magnesium stearate	3.0 mg.	30
	end weight	<u>300.0 mg.</u>	
35	The active materials and adjuvants are mixed, optionally granulated and pressed into dragee cores using conventional machines. The dragee cores are then coated in the usual manner with a film which is resistant to gastric juices but is soluble in intestinal juice (for example an anionic polymer of methacrylic acid and methyl methacrylate).		
40	active material	X mg. X = up to 40.0 mg.	40
	lactose	ad 60.0 mg.	
	magnesium oxide	100.0 mg.	
45	polyvinylpyrrolidone	2.0 mg.	45
	microcrystalline cellulose	8.0 mg.	
50	sodium carboxymethyl-amylopectin	4.0 mg.	50
	silicic acid, highly dispersed	0.5 mg.	
55	talc	5.0 mg.	55
	magnesium stearate	0.5 mg.	
60	end weight	<u>180.0 mg.</u>	60

The active material and adjuvants are mixed, optionally granulated and pressed into tablets.

Example B (injection solution)

65 As preparations suitable for injection, which contain 1-allyl-2-cyanoaziridine, there can be mentioned 65

aqueous solutions of polyethylene glycol 400, ethylene glycol monoethyl ether and ethanol, as well as a solution of the active material in "Miglyol" 812 neutral oil, the latter adjuvant only being used for intramuscular administration. ("Miglyol" is a Registered Trade Mark). The compositions are formulated in such a manner that the pH value, buffer capacity and titration basicity do not deviate very much from the physiological values. These injection compositions withstand sterilisation in an autoclave for 20 minutes at 121°C. without any chemical change taking place.

Example.

10	1-allyl-2-cyanoaziridine	40 mg.	40 mg.	40 mg.	40 mg.	10
	polyethylene glycol 400	1 mg.				
	water	3 mg.	3 mg.	4 mg.		
15	ethylene glycol mono-ethyl ether		2 mg.	1 mg.		15
	"Miglyol" 812 neutral oil				3 mg.	
20	ethanol	1 mg.				20

The solvents are mixed together with the active material in a kettle. The solution thus obtained is sterilised by filtration through filter layers of Fibrifix AF. ("Fibrifix" is a Registered Trade Mark). The first 15 litres are pre-runnings which are recycled to the batch. The membrane filtration is carried out directly on a filling machine via a Sartorius membrane filter of 0.2 µm. pore size. ("Sartorius" is a Registered Trade Mark). The solution is subsequently filled in 5 ml. ampoules and then sterilised in an autoclave for 20 minutes at 121°C.

Example C (soft gelatine capsules)

The active material is soluble in organic compounds, such as "Miglyol" 812 (triglyceride of saturated fatty acids with a chain length of C = 30), mixtures of ethanol in water, polyethylene glycol 400 in water and ethylene glycol monoethyl ether in water and can, in such solutions, be worked up to give soft gelatine capsules. The active material can also be worked up in admixture with wax, soya bean oil, lecithine and hydrogenated fats to give a conventional soft gelatine formulation.

35	<i>Example.</i>						35
	1-Allyl-2-cyanoaziridine	40 mg.	40 mg.	40 mg.	40 mg.	40 mg.	
	bees' wax	20 mg.					
40	hydrogenated soya bean oil	140 mg.					40
	soya lecithine	70 mg.					
45	polyethylene glycol 400		210 mg.			180 mg.	45
	"Miglyol" 812		100 mg.	100 mg.	200 mg.	35 mg.	
50	ethylene glycol mono-ethyl ether			210 mg.	50 mg.		50
	ethyl acetate				43 mg.	85 mg.	

The active material can be mixed with the appropriate amounts of the above-mentioned adjuvants and worked up on a special machine to give soft gelatine capsules of various sizes and dosages.

Example D (drops and syrups)

60	a) 1-allyl-2-cyanoaziridine	2.5 ml.	2.5 ml.	2.5 ml.	2.5 ml.	2.5 ml.	2.5 ml.	60
	polyethylene glycol 400	-	9.5 ml.	10.5 ml.	7.5 ml.	-	7.5 ml.	
65	ethyl acetate	-	8.0 ml.	5.0 ml.	-	2.5 ml.	-	65

	ethylene glycol monomethyl ether	12.0ml.	-	-	9.0 ml.	3.0 ml.	3.0 ml.	
5	"Miglyol" 812	5.5 ml.	-	2.0 ml.	1.0 ml.	12.0 ml.		5
	water						7.0 ml.	
		ml.	ml.	ml.	ml.			
10 b)	1-allyl-2-cyanoaziridine	2.5	2.5	2.5	2.5			10
15	polyethylene glycol 400	-	-	12.0	-			15
	ethylene glycol monoethyl ether	2.0	-	-	52.0			
20	"Miglyol" 812	-	154.0	-	80.0			20
	water	134.0		143.0				

The active material is mixed with appropriate amounts of the above-mentioned adjuvants. The mixture is sterilised by means of filter layers of Fibrafix AF and also filtered through membrane filters with a pore size of 0.2 $\mu\text{m.}$, followed by filling into 20 ml. drop bottles or into 200 ml. syrup bottles.

CLAIMS

1. Pharmaceutical compositions containing at least one aziridine-2-carboxylic acid derivative which is substituted on the ring nitrogen atom and which have the general formula:-



wherein X is a carboxyl or nitrile group or an alkoxy carbonyl radical or an unsubstituted or substituted carbamoyl group; R is a straight-chained or branched, saturated or mono- or polyunsaturated aliphatic hydrocarbon radical which is optionally substituted one or more times by halogen, alkoxy, hydroxyl, dialkylamino, cycloalkylamino, acylamino, acyl, nitro, alkylthio, alkylsulphinyl, alkylsulphonyl, nitrile, carbalkoxy or carbamoyl radicals or by cycloalkyl radicals optionally substituted by alkyl, alkoxy or carbalkoxy, or by cycloalkenyl radicals, which can optionally be bridged, or by an aliphatic or aromatic heterocyclic radical, by aryl, aryloxy, arylthio, acyloxy, alkoxy-carbonylamino or ureido groups, or R is a cycloalkyl or cycloalkenyl radical containing 3 to 10 carbon atoms which is optionally substituted by alkyl, alkoxy, alkoxy-carbonyl or oxo groups and is also optionally interrupted by hetero atoms and optionally bridged by 1 to 3 carbon atoms, or R is an aryl or hetaryl radical, aryl and hetaryl radicals being optionally substituted by halogen, alkoxy, alkyl, hydroxyl, carbalkoxy, carbamoyl, dialkylamino, cycloalkylamino, acylamino, nitro, cyano, acyl, alkylthio, alkylsulphinyl, alkylsulphonyl, sulphamoyl, phenyl, trifluoromethyl, aryloxy, acyloxy or methylene-dioxy; and R_1 is a hydrogen atom or a saturated, straight-chained or branched alkyl radical containing up to 4 carbon atoms or a phenyl radical; and/or at least one pharmacologically acceptable salt thereof in admixture with a solid or liquid pharmaceutical diluent or carrier.

2. Pharmaceutical compositions according to claim 1 which additionally contain at least one known chemotherapeutic agent.

3. Pharmaceutical compositions according to claim 2, wherein the chemotherapeutic compound is a penicillin, a cephalosporin, a nitrofurantoin or chloramphenicol.

4. Pharmaceutical compositions according to claim 2, wherein the chemotherapeutic compound is a penicillin, a cephalosporin, a nitrofurantoin or chloramphenicol.

5. Pharmaceutical composition according to any of the preceding claims, wherein the aziridine-2-carboxylic acid derivative is 1-allyl-2-cyanoaziridine.

6. Pharmaceutical compositions according to any of the preceding claims, substantially as hereinbefore described and exemplified.



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	ethylene glycol monomethyl ether	12.0ml.	-	-	9.0 ml.	3.0 ml.	3.0 ml.	
5	"Miglyol" 812	5.5 ml.	-	2.0 ml.	1.0 ml.	12.0 ml.		5
	water						7.0 ml.	
		ml.	ml.	ml.	ml.			
10 b)	1-allyl-2-cyano-aziridine	2.5	2.5	2.5	2.5			10
	polyethylene glycol 400	-	-	12.0	-			
15	ethylene glycol monoethyl ether	2.0	-	-	52.0			15
	"Miglyol" 812	-	154.0	-	80.0			
20	water	134.0		143.0				20

The active material is mixed with appropriate amounts of the above-mentioned adjuvants. The mixture is sterilised by means of filter layers of Fibrifix AF and also filtered through membrane filters with a pore size of 0.2 μ m., followed by filling into 20 ml. drop bottles or into 200 ml. syrup bottles.

CLAIMS

1. Pharmaceutical compositions containing at least one aziridine-2-carboxylic acid derivative which is substituted on the ring nitrogen atom and which have the general formula:-



wherein X is a carboxyl or nitrile group or an alkoxy carbonyl radical or an unsubstituted or substituted carbamoyl group; R is a straight-chained or branched, saturated or mono- or polyunsaturated aliphatic hydrocarbon radical which is optionally substituted one or more times by halogen, alkoxy, hydroxyl, dialkylamino, cycloalkylamino, acylamino, acyl, nitro, alkylthio, alkylsulphinyl, alkylsulphonyl, nitrile, carbalkoxy or carbamoyl radicals or by cycloalkyl radicals optionally substituted by alkyl, alkoxy or carbalkoxy, or by cycloalkenyl radicals, which can optionally be bridged, or by an aliphatic or aromatic heterocyclic radical, by aryl, aryloxy, arylthio, acyloxy, alkoxy-carbonylamino or ureido groups, or R is a cycloalkyl or cycloalkenyl radical containing 3 to 10 carbon atoms which is optionally substituted by alkyl, alkoxy, alkoxy-carbonyl or oxo groups and is also optionally interrupted by hetero atoms and optionally bridged by 1 to 3 carbon atoms, or R is an aryl or hetaryl radical, aryl and hetaryl radicals being optionally substituted by halogen, alkoxy, alkyl, hydroxyl, carbalkoxy, carbamoyl, dialkylamino, cycloalkylamino, acylamino, nitro, cyano, acyl, alkylthio, alkylsulphinyl, alkylsulphonyl, sulphamoyl, phenyl, trifluoromethyl, aryloxy, acyloxy or methylene-dioxy; and R₁ is a hydrogen atom or a saturated, straight-chained or branched alkyl radical containing up to 4 carbon atoms or a phenyl radical; and/or at least one pharmacologically acceptable salt thereof in admixture with a solid or liquid pharmaceutical diluent or carrier.

2. Pharmaceutical compositions according to claim 1 which additionally contain at least one known chemotherapeutic agent.

3. Pharmaceutical compositions according to claim 2, wherein the chemotherapeutic compound is a penicillin, a cephalosporin, a nitrofurantoin or chloramphenicol.

4. Pharmaceutical compositions according to claim 2, wherein the chemotherapeutic compound is a penicillin, a cephalosporin, a nitrofurantoin or chloramphenicol.

5. Pharmaceutical composition according to any of the preceding claims, wherein the aziridine-2-carboxylic acid derivative is 1-allyl-2-cyanoaziridine.

6. Pharmaceutical compositions according to any of the preceding claims, substantially as hereinbefore described and exemplified.