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DE 2528460A
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US The Merck Index, 9th Edition (N), Monograph No. 8948: "Tetramin"
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A5B

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(54) Pharmaceutical compositions containing aziridine derivatives

(57) Pharmaceutical compositions having immunostimulating activity, comprise at least one aziridine-2-carboxylic acid derivative having the general formula:-

(I),

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 hydro-carbon radical which is optionally substituted, or a cycloaklyl or cycloalkenyl radical containing 3 to 10 carbon atoms which is optionally substituted and may be interrupted by hetero atoms and/or bridged by 1 to 3 carbon atoms, or an optionally substituted aryl or hetaryl radical; 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. The compositions may also contain anti-infective agents such as penicillins, cephalosporins, nitrofurans and chloramphenicol.

Many of the compounds of formula (I) above are said to be novel.

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SPECIFICATION

Immunestimulating N-substituted aziridine-2-carboxylic acid derivatives

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 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 which, when administered intravenously to rats, bring about a very marked increase of the leukocytes and lymphocytes, whereas the number of erthyrocytes 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 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.

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 whichhave the general formula:-

(I)

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, dialkylamino, cycloalkylamino, acylamino, acyl, nitro, alkylthio, alkysulphinyl, alkylsulohonyl, 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 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 aroms 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, alkylsulohonyl, sulphamoyl, phenyl, trifluoremethyl, aryloxy, acyloxy or methylenedioxy; 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.

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 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 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 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-cyanoziridin-l-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 carbocylic 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 of 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 R_1 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-cyano-aziridine 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 present invention also provides new compounds of 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, cycloalklamino, 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 ur ureido groups, or R' is a

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, trifluoremethyl, aryloxy, acyloxy or methylenedioxy; and R_1 is a hydrogen atom or a saturated, straight-chain 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 R_1 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-methoxyphenyl, an *s*-triazinyl or a pyridinyl radical and with the proviso that when X is a carbamoyl group and R_1 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 R_1 is a phenyl radical, R' is not an isopropyl, cyclohexyl, phenyl, benzyl or *p*-chlorobenzyl radical and when R_1 is a methyl radical, is not a benzyl, *p*-chloro- or *p*-methoxybenzyl radical.

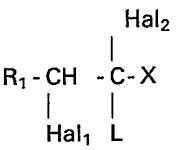
Preferred new compounds of general formula I' according to the present invention include:

2-Cyano-1-(2-methylsulphinylethyl)-aziridine
2-Cyano-1-(2-cyanoethyl)-aziridine
1-(3-Chloropropyl)-2-cyanoaziridine
1-(2-Acetamidoethyl)-2cyanoziridine
1-(2-Benzamidoethyl)-2-cyanoaziridine
2-Cyano-1-(2-carbamoylethyl)-aziridine
2-Cyano-1-(but-2-ynyl)-aziridine
2-Cyano-1-(4-hydroxy-3-methoxybenzyl)-aziridine
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
2-Cyano-1-(2,2,2-trichloroethyl)-aziridine
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
1-Benzyl-aziridine-2-carboxylic acid
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
2-Cyano-1-(4-methoxycyclohexyl)-aziridine
2-Cyano-1-(pyrimidin-2-yl)-aziridine
2-Cyano-1-(4-phenylbenzyl)-aziridine
2-Cyano-1-(2-methylsulphinylbenzyl)-aziridine
2-Cyano-1-(2-methylsulphonylbenzyl)-aziridine
2-Cyano-1-(4-sulphamoylbenzyl)-aziridine
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
2-Cyano-1-(naphth-1-yl)-aziridine
2-Cyano-1-(thiazol-2-yl)-aziridine
Methyl 2-cyano-1-aziridine-propionate
1-Allyl-2-cyanoaziridine
2-Cyano-1-(3-morpholinopropyl)-aziridine
2-Cyano-1-(2lpyrrolidinoethyl)-aziridine
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
Ethyl 3-(2-cyanoaziridin-1-yl)-propionate
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
2-Cyano-1-(2-methylallyl)-aziridine
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
Ethyl 3-(2-cyanoaziridin-1-yl)-acrylate
1-Phenyl-1-(2-cyanoaziridin-1-yl)-2-cyanoethylene
1-(2-Carbamoylaziridin-1-yl)-1-(*p*-methoxycarbonylphenyl)-
1-Phenyl-1-(2-carbomoylaziridin-1-yl)-ethylene
1-Phenyl-1-(2-carbamoylaziridin-1-yl)-2-cyanoethylene
1-(2-Carbamoyl-aziridine-1-yl)-2-carbethoxy-cyclohex-1-ene
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
2-Cyano-1-(3,4-dimethoxybenzyl)-aziridine
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.

The compounds of general formula (I') can be prepared in known manner and preferably by one of the following methods:

a) reaction of a compound of the general formula:-



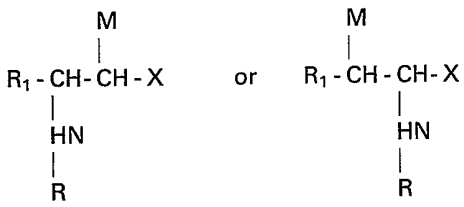
(II)

wherein R_1 and X have the same meanings as above, Hal_1 and Hal_2 are chlorine or bromine atoms, L is a hydrogen atom or Hal_1 and L can together represent a valency bond, with an amine of the general formula:-

$$R - NH_2 \qquad (III)$$

wherein r has the same meaning as above; or

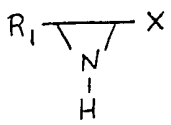
b) treatment of a compound of the general formula:-



(IV)

wherein X, R_1 and R have the same meanings as above and M is a chlorine or bromine atom or an A-Z grouping, A being an oxygen or sulphur atom and Z being a hydrogen atom or a grouping which, together with oxygen or sulphur, is easily eliminated, or of a salt thereof, with a reagent which splits off M-H; or

c) reaction of a compound of the general formula:-



(V)

wherein R_1 and X have the same meanings as above, with a compound of the general formula:-

$$R - Y \qquad (VI)$$

wherein R has the same meaning as above and Y is Hal or an $-O-SO_2-OR$ radical, Hal being a chlorine, bromine or iodine atom; or

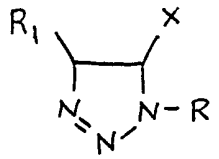
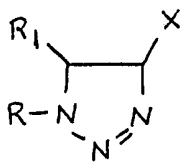
d) reaction of an azide of the general formula:-

$$R - N_3 \qquad (VII),$$

wherein R has the same meaning as above, with a compound of the general formula:-

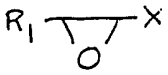
$$R_1\text{-}CH{=}CH\text{-}X \qquad \text{(VIII)}$$

wherein R_1 and X have the same meanings as above, to give a compound of general formula (I), whereby, as intermediate, there can be formed a triazoline of the general formula


or

(IX)

wherein R, R_1 and X have the same meanings as above, which, by thermolysis or photolysis, can be converted, with the splitting off of nitrogen, into a compound of general formula (I); or

e) reaction of an epoxide of the general formula:-


(X)

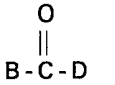
wherein R_1 and X have the same meanings, as above, with an amine of general formula (III); or

f) reaction of a compound of the general formula (V) with a compound of the general formula:-

$$T\text{-}C{=}C\text{-}U \qquad \text{(XI)},$$

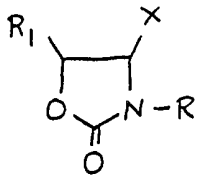
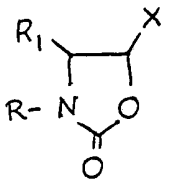
wherein T is a hydrogen atom or an alkyl or carboxylic acid ester group and U is an aldehyde or carboxylic acid ester group; or

g) reaction of a compound of the general formula (V) with a compound of the general formula:-


(XII),

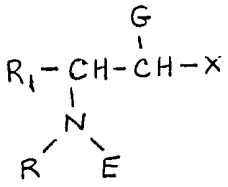
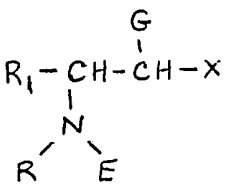
wherein B is an optionally substituted alkyl or phenyl radical, D is an optionally substituting alkyl radical or B and D together can represent a ring which is optionally interrupted by hetero atoms; or

h) subjection of an oxazolidinone of the general formula:-


or

(XIII),

wherein R, R_1 and X have the same meanings as above, to thermolysis; or

i) treatment of a compound of the general formula:-


or


wherein R, R_1 and X have the same meanings as above and G is a hydrogen atom or Hal and E is Hal or a trialkylamino or arylsulphonic acid ester radical, Hal being a chlorine or bromine atom, with a reagent splitting off E-G;

whereafter, if desired, a compound obtained of general formula (I) can subsequently be converted into another compound of general formula (I) and, if desired, a compound obtained of general formula (I) can be converted into a pharmacologically-acceptable salt.

Process a) for the preparation of aziridine derivatives of general formula (I) is known from the literature (see, for example, Gundermann *et al.*, Chem. Ber., *105*, 312/1972; and Wagner-Jauregg, Helv. Chim. Acta, *44*, 1237/1961/. It is preferably to use an inert solvent, for example, diethyl ether, dioxan, benzene, toluene or the like, but it is also possible to use a lower alcohol, for example methanol, ethanol or the like. The reaction

temperature can be from 0 to 80°C. and is preferably ambient temperature. The reaction period varies from 3 hours to 10 days.

In the case of process b), the reagent splitting off M-H is a base, especially a tertiary amine, for example, triethylamine, triethanlamine, dicyclohexyl-ethylamine or the like. In this case, too, an inert solvent can be used, for example, diethyl ether, dioxan, benzene or toluene, but also an alcohol, for example methanol or ethanol. Furthermore, in some cases, an alcoholate, for example sodium methylate or sodium ethylate, in the corresponding alcohol, can be used. Especially when the A-Z group is a hydroxyl group, as the agent for splitting off water, it has proved to be especially useful to use triphenylphosphine in the presence of carbon tetrachloride and triethylamine, in which case, as a rule, methylene chloride or chloroform is used as solvent. However, this splitting off of water can also be carried out with sulphuric acid. In the case of process b), the reaction time is from 3 to 24 hours.

The alkylation reaction in the case of process c) is preferably carried out in water, an alcohol, for example methanol or ethanol, or in an alcohol/water mixture in the presence of a base. Besides organic bases, there can also be used inorganic bases, for example, alkali metal carbonates or alkali metal bicarbonates, as acid acceptors. As a rule, the reaction is carried out at a temperature of from 20 to 60°C. In order to accelerate the reaction, it is also possible to add a phase transfer catalyst, for example, triethylbenzyl ammonium chloride.

The thermolysis of the triazolines in the case of process d) can be carried out at a temperature of from 80 to 150°c. and preferably of from 100 to 120°C. It is possible to work without the use of a solvent and to purify the resultant aziridine derivative by distillation or recrystallisation. However, it is also possible to use a solvent, an inert solvent, such as, for example, benzene, toluene and xylene, having proved to be especially useful. As a rule, photolysis is carried out at ambient temperature in solution, in which case it is especially preferred to use benzene, toluene or acetonitrile as solvent. The photolysis can be carried out with or without a sensitiser, for example, benzoquinine or acetophenone (see, for example J.A.C.S., *90*, 988/1968).

In the case of process e), an epoxide of general formula (X) can be reacted with an amine of the general formula (X) can be reacted with an amine of the general formula (III) and the aminoalcohol thereby obtained dehydrated, as described in process b), to give an aziridine derivative of general formula (I). However, for the conversion of the epoxide into an aziridine, use can also be made of compounds such as R-N-P(O)$(OAlk)_2^-$ or Ph_3P=N-R, wherein R has the same meaning as above, Ph is a phenyl radical and AlK is a lower alkyl radical, for example a methyl or ethyl radical (see Tetrahedron Letters, *1976*, 4003 and Chem. Ber. *109*, (814/1976).

In the case of processes f) and g), the reaction components are, as a rule, reacted without the use of a solvent at a temperature of from 0 to 60°C. The reaction products possibly have to be purified by column chromatography.

Oxazolidnones of general formula (XIII) are, as a rule, thermolysed without the use of a solvent in the presence of a base, for example, triethanolamine or dicyclohexylethylamine, the reaction product being removed by distillation during the thermolysis. The thermolysis temperature can be from 170 to 250°C.

In the case of process i), when G is a hydrogen atom, the reagent used for splitting off E-G is preferably an alcoholate, such as an alkali metal methylate or alkali metal ethylate, in the corresponding alcohol. However, it is also possible to use a tertiary amine for example, triethylamine, triethanolamine or dicyclohexylethylamine, in a solvent, for example, methanol, ethanol, benzene, toluene, diethyl ether or dioxan. When G and E are Hal, the splitting off reaction can be carried out with the use of a conventional dehalogenation agent and preferably with zinc or sodium.

The subsequent conversion of compounds of general formula (I) into other compounds of general formula (I) can be carried out, on the one hand, by conversion of the substituent X. In this case, for example, a compound in which X is an alkoxycarbonyl radical can be converted, by reaction with ammonia, into a compound in which X is a carbamoyl group which, in turn, can be converted with a dehydration agent into a compound in which X is a nitrile group.

Compounds of general formula (I) in which X is an alkoxycarbonyl of carbamoyl group can, therefore, also be used as intermediates for the preparation of compounds of general formula (I) in which X is a nitrile group.

The conversion of an ester group into an amide group can be carried out with gaseous ammonia in an organic solvent, preferably in methanol or ethanol, or with aqueous ammonia at a temperature of from 0 to 25°C. The desired amide either precipitates out or can be isolated from the reaction mixture by, for example, column chromatography.

A carbamoyl group can be converted into a nitrile group by using a dehydration agent known from the literature and preferably with a mixture of triphenylphosphine, carbon tetrachloride and triethylamine. The solvent usually employed is a halogenated hydrocarbon, for example methylene chloride or chloroform, but acetonitrile can also be used. As a rule, the desired nitrile is isolated from the reaction mixture by distillation.

The 2-alkoxycarbonyl-, 2-carbamoyl- and 2-cyano-aziridine derivatives are usually converted into 2-carboxyaxiridines by saponification processes which are known from the literature.

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 into hard gelatine capsules. With the addition of appropriate adjuvants, there can also be produced a 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 dissolves in the alkaline medium of the small intestine or an adjuvant, such as antacid, for example 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 weight fatty acids and the salts thereof, gelatine, agaragar, calcium phosphate, animal and vegetable fats 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.

For pharmaceutical combinations in which compounds of general formula (I) are present together with a 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.

A preferred composition comprises 100 mg. of chloramphenicol as chemotherapeutic agent and 33.3 mg. 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 selected from compounds of general formula (I), for example 1-allyl-2-cyanoaziridine (B), with the simultaneous administration of a subtherapeutic dose of chloramphenicol (A).

Experimental protocoll

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

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
4th Group: 10 mg./kg. A, oral, dissolved in 0.5% tylose solution
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*					
A mg/kg.	B mg/kg.	1st day	2nd day	3rd day	4th day	5th day	6th day
40	-	70	70	65	65	65	65
-	13.4	0	0	0	0	0	0
40 +	13.4	100	100	100	100	100	100
10	-	15	15	15	15	15	15
-	3.3	10	10	10	10	10	10
10 +	3.3	65	55	50	50	50	50
Control		0	0	0	0	0	0

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.

Experimental protocoll.

Groups of 10 female, adult Spraque-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 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.

Results:

Substance	0 day	4th day	Example
B	8.5	17.1	1
C	8.93	12.84	1 a)
D	8.0	13.5	1 b)
E	8.0	14.3	1 f)
F	6.7	16.2	5
G	7.55	10.4	5 b)
H	7.37	8.5	7 b)
I	6.5	11.2	1 c)
J	6.5	9.6	1 n)
K	8.9	12.0	1 p)
L	7.1	11.3	11 f)
M	7.1	12.3	13 o)
N	7.4	11.3	16 a)
O	7.0	13.7	13 a)
P	6.6	10.6	13 c)
Q	6.3	11.9	13 d)
R	7.9	12.3	13 x)
S	7.5	13.5	13 v)
T	7.0	13.2	13 e)
U	8.0	11.9	6 b)
V	7.8	11.9	6 c)
W	6.9	10.6	6 d)
X	5.8	11.9	13 w)
Z	6.7	9.8	13 i)

A = Chloroamphenicol

B = 1-Allyl-2-cyanoaziridine

C = Cyano-1-methylaziridine

D = 2-Cyano-1-*n*-propylaziridine

E = 1-Benzyl-2-cyanoaziridine

F = 3-(2-Cyanoaziridin-1-yl)-acrolein

G = Ethyl 3-(2-Cyanoaziridin-1-yl)-acrylate

H = 1-Phenyl-1-(2-carbamoylaziridin-1-yl)-2-cyanoethylene.

I = 2-Cyano-1-isopropylaziridine

J = 2-Cyano-1-(2-thenyl)-aziridine

K = 2-Cyano-1-(2-methylallyl)-aziridine

L = 1-(2-Chlorethyl)-2-cyanoaziridine

M = 2-cyano-1-(3-trifluoremethylbenzyl)-aziridine

N = 2-Cyano-1-(5-carboxy-2-furfuryl)-aziridine

O = 2-Cyano-1-(5-methoxycarbonyl-2-thenyl)-aziridine

P = 2-Cyano-1-(2,2-dichloroethyl)-aziridine

Q = 1-(But-2-enyl)-2-cyanoaziridine

R = 2-Cyano-1-(5-methyl-2-nitrobenzyl)-aziridine

S = 1-(2-Chlorobenzyl)-2-cyanoaziridine

T = 2-Cyano-1-(5-methylpyrimidin-4-ylmethyl)-aziridine

U = L-(-)-2-Cyano-(L-(-)-phenylethyl)-aziridine

V = D-(+)-2-Cyano-1-(L-(-)-Phenylethyl)-aziridine

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

X = 2-Cyano-1-(pyrimidin-2-ylmethyl)-aziridine

Z = 2-Cyano-1-[(2-methoxy-6-methylpyridin-3-yl)-methyl]-aziridine

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:

2-Cyano-1-(2-dimethylaminoethyl)-aziridine
2-Cyano-1-(2-methylsulphinylethyl)-aziridine
2-Cyano-1-(2-cyanoethyl)-aziridine
1-(3-Chloropropyl)-2-cyanoaziridine
1-(2-Acetamidoethyl)-2-cyanoaziridine
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
2-Cyano-1-(4-hydroxy-3-methoxybenzyl)-aziridine
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
2-Cyano-1-(2,2,2-trichlorethyl)-aziridine
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-naptheylemethyl)-aziridine
1-Benzyl-aziridine-2-carboxylic acid
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
2-Cyano-1-(4-methoxycyclohexyl)-aziridine
2-Cyano-1-(pyramidin-2-yl)-aziridine
2-Cyano-1-(4-phenylbenzyl)-aziridine
2-Cyano-1-(2-methylsulphinyl-benzyl)-aziridine
2-Cyano-1-(2-methylsulphonyl-benzyl)-aziridine
2-Cyano-1-(4-sulphamoylbenzyl)-aziridine
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
2-Cyano-1-(naphth-l-yl)-aziridine
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
(-)-l-Allyl-2-cyanoazridine
2-Cyano-1-(3-morpholinopropyl)-aziridine
2-Cyano-l-(2-pyrrolidinoethyl)-aziridine
2-Cyano-l-[3-(2-methylpiperidino)-propyl]-aziridine
2-Cyano-l-(2-α-furoylaminoethyl)-aziridine
2-Cyano-l-(4-methylsulphonamidobenzyl)-aziridine
2-Cyanò-l-(4-phenoxybenzyl)-aziridine.

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

Example 1.

1-Allyl-2-cyanoaziridine.

A solution of 28.5 g. allylamine and 51 g. triethylamine in 250 ml. toluene is added dropwise, with stirring, 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, the residue is distilled twice. There are obtained 28.6 g. (about 53% of theory) 1-allyl-2-cyano-aziridine; $b.p._{0.2}$: 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-l-methylaziridine ($b.p._{11}$: 53 - 54°C.)
b) 2-cyano-1-*n*-propylaziridine ($b.p._{15}$: 80 - 82°C.)
c) 2-cyano-l-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-l-yl)-hexane (m.p.: 64 - 66°C.)
f)1-benzyl-2-cyanoaziridine ($b.p._{0.05}$: 103 - 105°C.)
g) 2-cyano-l-cyclohexylaxiridine ($b.p._{0.1}$: 93 - 94°C.)

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-bromacrylonitrile with the appropriate amines and subsequent purification by means of a silica gel and/or deactivated aluminium oxide column, there are obtained the following compounds:

h) *2-Cyano-l-(2-hydroxyethyl)-aziridine*

oily product; yield: 31.1% of theory

i) *Ethyl 3-(2-cyanoaziridin-l-yl)-propionate*

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

(dioxan used as solvent)

k) *2-Cyano-l-(4-hydroxybenzyl)-aziridine*

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

(ethanol used as solvent)

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

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

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

m) *2-Cyano-l-(cyclohex-l-enylmethyl)-aziridine*

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

n) *2-Cyano-l-(2-thenyl)-aziridine*

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

(reaction time 10 days)

o) *2-Cyano-l-(2-furylmethyl)-aziridine*

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

(reaction time 10 days)

p) *2-Cyano-l-(2-methylallyl)-aziridine*

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

g) *l-(l-Adamantyl)-2-cyanoaziridine*

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

(dioxan used as solvent)

Example 2.

1-tert.-Butyl-2-cyanoaziridine

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) l-*tert.*-butyl-2-cyanoaziridine; $b.p._{0.2}$: 52 - 54°C.; m.p. 53 - 54°C.

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

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

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-l-aziridine]-propionate; m.p. 88 - 91°C. (recrystallised from diisopropyl ether); $[\alpha]^2{}_D{}^0 = +99.4°$ (c = 1 in methanol).

Example 3.

1-Allyl-2-cyanoaziridine.

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). The crude l-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.

2-Cyano-l-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-l-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-l-phenylaziridine; $b.p._{0.1}$: 109-111°C.

Example 5.

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

5.78 g. 2-Cyanoaziridine are added dropwise, with cooling, to 4.6 g. propargyl aldehyde. The reaction mixture is stirred overnight at 208C., 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-l-yl)-acrolein; m.p. 57 - 58°C.

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

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

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

Example 6.

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

2.7 g. l-Phenyl-l-(2-carbamoylaziridin-l-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-l-(2-cyanoaziridin-l-y-)-2-cyanoethylene; m.p. 95°C. (recrystallised from diethyl ether).

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

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

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

b) L)(-)-l-(L-(-)-Phenylethyl)-aziridine-2-carboxamide
(see Example 14)
L-(-)-2-Cyano-(l-(-)-phenylethyl)-aziridine
m.p.: 44 - 48°C.; yield: 45% of theory
$[\alpha]_D^{20}$: -129.4° (c = 1 in methanol)

c) D-(+)-l-(L-(-)-Phenylethyl)-aziridine-2-carboxamide
(see Example 14a)
D-(+)-2-Cyano l-(L-(-)-phenylethyl)-aziridine
oily substance; yield: 51% of theory
$[\alpha]_D^{20}$: +58.8° (c = 1 in methanol)

d) L-(-)-l-(D-(+)-Phenylethyl)-aziridine-2-carboxamide
(see Example 14b)
L-(-)-2-Cyano-l-(D-(+)lphenylethyl)-aziridine
oily substance; yield: 74% of theory
$[\alpha]_D^{20}$: -53.5° (c = l in methanol)

e) D-(+)-l-(D-(+)-Phenylethyl)-aziridine-2-carboxamide
(see Example 14c)
D-(+)-2-Cyano-l-(D-(+)-phenylethyl)-aziridine
m.p. 45 - 48°C.; yield: 62% of theory
$[\alpha]_D^{20}$: +128.1° (c = l in methanol)

Example 7.

1-(2-Carbamoylaziridin-l-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 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-l-yl)-l-(*p*-methoxycarbonylphenyl)-ethylene; m.p. 140 - 141°C. (decomp.).

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

a) acetophenone:
1-phenyl-l-(2-carbamoylaziridin-l-yl)ethylene; m.p. 93 - 96°C.; yield 16% of theory

b) ω-cyanoacetophonone:
1-phenyl-l-(2-carbamoylaziridin-l-yl)-2-cyanoethylene;
m.p. 164 - 167°C. (recrystallised from ethyl acetaté);
yield 84.5% of theory

c) ethyl cyclohexanone-2-carboxylate:
1-(2-carbamoylaziridin-l-yl)-2-carboethoxycyclohex-l-ene;
m.p. 168 - 170°C.; yield 17% of theory (reaction time 70 hours; crystallised by trituration with ethyl acetate)

d) 1-methylpiperidinone-(4):
4-(2-carbamoylaziridin-l-yl)-l-methyl-3,4-dehydro-piperidine; m.p. 149 - 150°C.; yield 12% of theory (reaction time 24 hours, crystallised by trituration with isopropanol).

Example 8.

1-Allyl-2-cyano-3-methylaziridine

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 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-methylziridine; $b.p._{0.1}$: 55 - 57°C.

Example 9.

Ethyl l-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 l-benzylaziridine-2-carboxylate; $b.p._{0.03}$: 98 - 101°C.

The following compounds are obtained in an analogous manner by reacting ethyl 2,3-dibromopropionate with:

a) methylamine:
ethyl 1-methylaziridine-2-carboxylate; $b.p._{18}$: 70 - 72°C;
yield 40% of theory

b) allylamine:
ethyl 1-allylaziridine-2-carboxylate; $b.p._{12}$: 91 - 92°C;
yield 24% of theory.

Example 10.

2-Cyano-1-methylaziridine.

5.0 g. 1-(2-Cyanoethyl)-l-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 obtained 0.35 g. (about 23% of theory) 2-cyano-l-methylaziridine; $b.p._{11}$: 53 - 54°C.

Example 11

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

a) 2-methylthiobenzylamine:
2-cyano-l-(2-methylthiobenzyl)-aziridine; oily product;
yield 54% of theory

b) 3,4-dimethoxybenzylamine:

2-cyano-l-(3,4-dimethoxybenzyl)-aziridine; oily product;
yield 25% of theory
c) 4-methylbenzylamine:
2-cyano-l-(4-methylbenzyl)-aziridine; $b.p._{0.05}$: 113 - 115°C.; yield 23% of theory
d) cyclopropylamine:
2-cyano-l-cyclopropylaziridine; $b.p._{1.5}$: 70°C.; yield
22% of theory
e) 2-methyl-3-carbethoxybenzylamine:
2-cyano-l-(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:
l-(2-chloroethyl)-2-cyanoaziridine (using dioxan as solvent); $b.p._{0.1}$: 74°C.; yield 5.1% of theory
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-l-(2-methoxyethyl)-aziridine; $b.p._{0.2}$: 80°C;
yield 17.5% of theory
i) 2-phenoxyethylamine:
2-cyano-l-(2-phenoxyethyl)-aziridine; $b.p._{0.05}$: 115°C;
yield 38.8% of theory.

Example 12.
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 - 116°C.

Example 13
Analogously to Example 1, by the reaction of 2-bromoacrylonitrile with the indicated starting materials, there are obtained the following compounds:
a) 5-Methoxycarbonyl-2-thenylamine:
2-Cyano-l-(5-methoxycarbonyl-2-thenyl)-aziridine
m.p.: 51 - 54°C.; yield: 49% of theory
b) 5-Methoxycarbonyl-2-furfurylamine:
2-Cyano-l-(5-methoxycarbonyl-2-furfuryl)-aziridine
m.p.: 86 - 89°C.; yield: 46% of theory
c) 2,2-Dichloroethylamine:
2-Cyano-l-(2,2-dichloroethyl)-aziridine
m.p.: 94 - 95°C.; yield: 16% of theory
d) But-2-enylamine:
1-(But-2-enyl-2-cyanoaziridine
$b.p._{0.1}$: 60 - 61°C.; yield: 70% of theory
e) 5-Methylpyrimidin-4-ylmethylamine:
2-Cyano-l-(5-methylpyrimidin-4-ylmethyl)-aziridine
m.p.: 88-92°C. (recrystallised from isopropanol); yield:
56% of theory
f) 2-Hydroxy-6-methylpyridin-3-ylmethylamine:
2-Cyano-l-[(2-hydroxy-6-methylpyrimidin-3-yl)-methyl]-aziridine
m.p.:187 - 190°C. (recrystallied from water); yield
47% of theory
g) Aminoacetaldehydr dimethyl acetal:
2-Cyano-l-(2,2-dimethoxy-l-ethyl)-aziridine
$b.p._{0.1}$: 90 - 92°C.; yield: 70% of theory
h) 1,6-Dimethyl-2-oxo-pyridin-3-ylmethylamine:
2-Cyano-l-[[(1,6-dimethyl-2-oxo-pyridin-3-yl)-methyl]-aziridine
m.p. : 82 - 84°C.; yield: 78% of theory
i) 2-Methoxy-6-methylpyridin-3-ylmethylamine:
2-Cyano-l-[(2-methoxy-6-methylpyridin-3-yl)-methyl]-aziridine
m.p.: 70 - 73°C. (recrystallised from isopropanol);
yield: 69% of theory
k) 2,5-Dimethyl-pyrimidin-4-ylmethylamine:
2-cyano-l-[(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-l-(4-methylthiazol-2-ylmethyl)-aziridine
m.p.: 73 - 75°C.; yield: 21% of theory
m) Prop-2-ynylamine:
2-Cyano-l-(prop-2-ynyl)-aziridine
$b.p._{0.1}$: 48°C.; yield: 28% of theory
n) Tetrahydrofurfurylamine:
2-Cyano-l-tetrahydrofurfuryl-aziridine
$b.p._{0.1}$: 95°C.; yield: 20% of theory
o) 3-Trifluoromethyl-benzylamine:
2-Cyano-l-(3-trifluoromethylbenzyl)-aziridine
$b.p._{0.15}$: 92°C.; yield: 31% of theory
p) 3-Methylthiopropylamine:
2-Cyano-l-(3-methylthiopropyl)-aziridine
$b.p._{0.05}$: 110°C.; yield: 18% of theory
q) 2-Methylsulphonylethylamine:
2-Cyano-l-(2-methylsulphonylethyl)-aziridine
oily substance; yield: 47% of theory
r) Phenethylamine:
2-Cyano-l-phenethyl-aziridine
$b.p._{0.05}$: 122 - 124°C.; yield: 18% of theory
s) Cinnamylamine:
1-Cinnamyl-2-cyanoaziridine
$b.p._{0.05}$: 138 - 140°C.; yield: 13% of theory
t) But-3-ynylamine:
1-(But-3-ynyl)-2-cyanoaziridine
$b.p._{0.1}$: 70 - 71°C.; yield: 68% of theory
u) 2-Norbornylamine:
2-Cyano-l-(2-norbornyl)-aziridine
$b.p._{0.05}$: 84 - 85°C.; yield: 20% of theory
v) 2-Chlorobenzylamine:
1-(2-Chlorobenzyl)-2-cyanoaziridine
m.p.: 55 - 57°C. (recrystallised from isopropanol);
yield: 36% of theory
w) Pyrimidin-2-ylmethylamine:
2-Cyano-l-(pyrimidin-2-ylmethyl)-aziridine
m.p.: 72 - 76°C. (recrystallised from isopropanol);
yield: 33% of theory
x) 5-Methyl-2-nitrobenzylamine:
2-Cyano-l-(5-methyl-2-nitrobenzyl)-aziridine
m.p.: 95 - 96°C. (recrystallised from isopropanol);
yield: 41% of theory
y) R-(-)Alanine methyl ester:
Methyl-R-(-)-2-[L-(-)-2-Cyano-l-aziridin]-propionate
m.p.: 90 - 91°C. (recrystallised from isopropyl ether);
yield: 12% of theory; $[\alpha]_D^{20}$: -99.1° (c = 1 in methanol).

Example 14.
L-(-)-l-(L-(-)-Phenylethyl)-aziridine-2-carboxamide

5.6 g. Ethyl L-(-)-l-(L-(-)-phenylethyl)-aziridine-2-carboxylate (see Example 15) are dissolved in 55 ml. 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-(-)-l-(L-(-)-phenylethyl)-aziridine-2-carboxamide; m.p. 108 - 111°C.; $[\alpha]_D^{20}$: -116.5° (c = 1 in methanol).

The following compounds are obtained in an analogous manner from:
a) ethyl D-(+)-l-(L-(-)-phenylethyl)-aziridine-2-carboxylate (see Example 15):
D-(p)-l-(L-(-)-phenylethyl)-aziridine-2-carboxamide;
m.p. 95 - 98°C.; yield 70% of theory; $[\alpha]_D^{20}$: +40.5°
(c = 1 in methanol)
b) ethyl L-(-)-l-(D-(+)-phenylethyl)-aziridine-2- carboxylate (see Example 15a):
L-(-)-l-(D-(+)-phenylthyl)-aziridine-2-carboxamide;
m.p. 94 - 97°C.; yield 76% of theory; $[\alpha]_D^{20}$: -38.8.048
(c = 1 in methanol)
c) ethyl D-(+)-l-(D-(+)-phenylethyl)-aziridine-2-carboxylate (see Example 15b):

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

Example 15.
Ethyl L-(-)-l-(L-(-)-phenylethyl)-aziridine-2-carboxylate and ethyl D-(+)-l-(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 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;
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:
a) ethyl L-(-)-l-(D-(+)-phenylethyl)-aziridine-2-carboxylate; oily substance; yield 39% of theory; $[\alpha]_D^{20}$: 57.9° (c = in ethanol); and
b) ethyl D-(+)-l-(D-(+)-phenylethyl)-aziridine-2-carboxylate; oily substance; yield 39% of theory; $[\alpha]_D^{20}$: +89.7° (c = 1 in ethanol).

Example 16
2-Cyano-l-(5-carboxy-2-thenyl)-aziridine

95 ml. 0.1n Aqueous sodium hydroxide solution are added dropwise, with stirring, to 2.1 g. 2-cyano-l-(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 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-l-(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-l-(5-carboxy-2-furfuryl)-aziridine;
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. 95 - 96°C.) with benzyl bromide in the presence of sodium hydride) ar 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.

Example 18.

The following Examples are concerned with pharmaceutical compositions which contain compounds of general formula (I) or salts thereof.

Example A (tablets)

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

talc	5.0 mg.
magnesium stearate	0.5 mg.
end weight	80.0 mg.

For liquid active materials in disages of up to about 40 mg.:

active material	X mg. X = up to 40.0 mg.
silicic acid, highly dispersed	ad 100.0 mg.
lactose	135.0 mg.
polyvinylpyrrolidone	10.0 mg.
microcrystalline cellulose	25.0 mg.
sodium carboxymethyl-amylopectin	10.0 mg.
silicic acid, highly dispersed	2.0 mg.
talc	15.0 mg.
magnesium stearate	3.0 mg.
end weight	300.0 mg.

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).

active material	X mg. X = up to 40.0 mg.
lactose	ad 60.0 mg.
magnesium oxide	100.0 mg.
polyvinylpyrrolidone	2.0 mg.
microcrystalline cellulose	8.0 mg.
sodium carboxymethyl-amylopectin	4.0 mg.
silicic acid, highly dispersed	0.5 mg.
talc	5.0 mg.
magnesium stearate	0.5 mg.
end weight	180.0 mg.

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

Example B (injection solution)

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

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. The compositions are formulated in such a manner that the pH value, buffer capacity and tritration 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.

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

The solvents are mixed together with the active material in a kettle. The solution thus obtained is sterilised by filtration through filter layers of Fibrafix AF. 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. 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 admixtue with wax, soya bean oil, lecithine and hydrogenated fats to give a conventional soft gelatine formulation.

Example.

1-Allyl-2-cyanoaziridine	40 mg.	40 mg.	40 mg.	40 mg.	40 mg.
bees' wax	20 mg.				
hydrogenated soya bean oil	140 mg.				
soya lecithine	70 mg.				
polyethylene glycol 400		210 mg.			180 mg.
"Miglyol" 812		100 mg.	100 mg.	200 mg.	35 mg
ethylene glycol mono-ethyl ether			210 mg.	50 mg.	
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)

a)	1-allyl-2-cyano aziridine	2.5 ml.	2.5 ml.	2.5 ml.	2.5 ml.	2.5 ml.	2.5 ml.
	polyethylene glycol 400	-	9.5 ml.	10.5 ml.	7.5 ml.	-	7.5 ml.
	ethyl acetate	-	8.0 ml.	5.0 ml.	-	2.5 ml.	-

	ethylene glycol monomethyl ether	12.0ml.	-	-	9.0 ml.	3.0 ml.	3.0 ml.
	"Miglyol" 812	5.5 ml.	-	2.0 ml.	1.0 ml.	12.0 ml.	
	water						7.0 ml.
		ml.	ml.	ml.	ml.		
b)	1-allyl-2-cyano-aziridine	2.5	2.5	2.5	2.5		
	polyethylene glycol 400	-	-	12.0	-		
	ethylene glycol monoethyl ether	2.0	-	-	52.0		
	"Miglyol" 812	-	154.0	-	80.0		
	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 witha pore size of 0.2 µm., 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 akyl, alkoxy or carbalkoxy, or by cycloalkenyl radicals, which can optionally be bridged, or by an aliphatic or aromatic hetercyclic 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, alkoxycarbonyl or oxo groups and is also optionally interrupted by heterto 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.

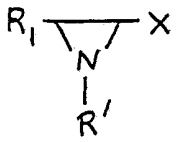
3. Pharmaceutical compositions according to claim 2, wherein the chemotherapeutic compound is a penicillin, a cephalosporin, a nitrofuran or chloramphenicol.

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

7. Compounds of the general formula:-

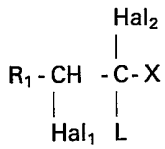


wherein X is a carboxyl or nitrile group or an alkoxy-carbonyl radical or an unsubstituted or substituted carbamoyl group, R is a straight-chained or branched, saturated or mono- or polyunsaturated aliphatic hydrocarbon radical which is optionally substituted one or more times by halogen, alkoxy, hydroxyl, 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 cyclo-alkenyl 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 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, the aryl and hetaryl radicals being optionally substituted by halogen, alkoxy, alkyl, hydroxyl, carbalkoxy, carbamoyl, dialkylamine, 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, with the proviso that when X is a cyano group or an alkoxycarbonyl radical and R_1 is a hydrogen atom, R′ is not an unsubstituted alkyl radical or an alkyl radical substituted by hydroxyl, alkoxy, dialkylamino, phenyl, 4-chlorophenyl 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 R_1 is a hydrogen atom, R′ is not an unsubsituted cyclohexyl, alkyl or benzyl radical and with the proviso that when X is a cyano group or an alkoxycarbonyl radical and R_1 is a phenyl radical, R′ is not an isopropyl, cyclohexyl, phenyl, benzyl or *p*-chlorobenzyl radical and when R_1 is a methyl radical, is not a benzyl, *p*-chloro- or *p*-methoxybenzyl radical.

8. 2-Cyano-l-(2-methylsulphinylethyl)-aziridine.
9. 2-Cyano-l-(2-cyanoethyl)-aziridine.
10. 1-(3-Chloropropyl)-2-cyanoaziridine.
11. 1-(2-Acetamidoethyl)-2-cyanoaziridine.
12. 1-(2-Benzamidoethyl)-2-cyanoaziridine.
13. 2-Cyano-l-(2-carbamoylethyl)-aziridine.
14. 2-Cyano-l-(but-2-ynyl)-aziridine.
15. 2-Cyano-l-(4-hydroxy-3-methoxybenzyl)-aziridine.
16. 2-Cyano-l-(cyclohept-2-enylenmethyl)-aziridine.
17. 2-Cyano-l-(cyclohept-3-enyl)-aziridine.
18. 1-(l-Acetylpiperidin-4-yl)-2-cyanoaziridine.
19. 2-Cyano-l-(thian-3-yl)-aziridine.
20. 2-Cyano-l-(2,2,2-trichloroethyl)-aziridine.
21. 2-Cyano-l-(3,4-methylenedioxybenzyl)-aziridine.
22. 2-Cyano-l-(2,2,2-trifluoroethyl)-aziridine.
23. 2-Cyano-l-(2-nitroethyl)-aziridine.
24. 2-Cyano-l-(1-napthylemethyl)-aziridine.
25. 1-Benzyl-aziridine-2-carboxylic acid.
26. 1-Allyl-2-cyano-3-phenyl-aziridine.
27. 2-Cyano-l-(pent-3-enyl)-aziridine.
28. 2-Cyano-l-(4-cyanobenzyl)-aziridine.
29. 2-Cyano-l-(2-methylcyclohexyl)-aziridine.
30. 2-Cyano-l-(4-methoxycyclohexyl)-aziridine.
31. 2-Cyano-l-(pyrimidin-2-yl)-aziridine.
32. 2-Cyano-l-(4-phenylbenzyl)-aziridine.
33. 2-Cyano-l-(2-methylsulphinyl-benzyl)-aziridine.
34. 2-Cyano-l-(2-methylsulphonyl-benzyl)-aziridine.
35. 2-Cyano-l-(4-sulphamoylbenzyl)-aziridine.
36. 2-Cyano-l-(3-carbamoylbenzyl)-aziridine.
37. 1-(4-Acetylbenzyl)-2-cyanoaziridine.
38. 1-(2-Acetamido-5-methylbenzyl)-2-cyanoaziridine.
39. 2-Cyano-l-(3,4,5-trimethoxybenzyl)-aziridine.
40. 2-Cyano-l-(naphth-l-yl)-aziridine.
41. 2-Cyano-l-(thiazol-2-yl)-aziridine.
42. Methyl 2-cyano-l-aziridine-propionate.
43. 1-Allyl-2-cyanoaziridine.
44. 2-Cyano-l-(3-morpholinopropyl)-aziridine.

45. 2-Cyano-l-(2-pyrrolidinoethyl)-aziridine.
46. 2-Cyano-l-[3-(2-methylpiperidino)-propyl]-aziridine.
47. 2-Cyano-l-(2-α-furoylaminoethyl)-aziridine.
48. 2-Cyano-l-(4-methylsulphonamidobenzyl)-aziridine.
49. 2-Cyano-l-(4-phenoxybenzyl)-aziridine.
50. Ethyl 3-(2-cyanoaziridin-l-yl)-propionate.
51. 2-Cyano-l-(4-hydroxybenzyl)-aziridine.
52. 2-Cyano-l-(cyclohex-l-enylmethyl)-aziridine.
53. 2-Cyano-l-(2-thenyl)-aziridine.
54. 2-Cyano-l-(2-furylemethyl)-aziridine.
55. 2-Cyano-l-(2-methylallyl)-aziridine.
56. 1-(l-Adamantyl)-2-cyanoaziridine.
57. Ethyl 2-cyano-l-aziridine-acetate.
58. 3-(2-Cyano-aziridin-l-yl)-acrolein.
59. Dimethyl 3-(2-cyanoaziridin-l-yl)-fumarate.
60. Ethyl 3-(2-cyanoaziridin-l-yl)-acrylate.
61. 1-Phenyl-l-(2-cyanoaziridin-l-yl)-2-cyanoethylene.
62. 1-(2-Carbamoylaziridin-l-yl)-l-(*p*-methoxycarbonyl-phenyl)-ethylene.
63. 1-Phenyl-l-(2-carbamoylaziridin-l-yl)-ethylene.
64. 1-Phenyl-l-(2-carbamoylaziridin-l-yl)-2-cyanoethylene.
65. 1-(2-Carbamoyl-aziridin-l-yl)-2-carebethoxy-cyclohex-l-ene.
66. 4-(2-Carbamoylaziridin-l-yl)-1-methyl-3,4-dehydropiperidine.
67. 1-Allyl-2-cyano-3-methylaziridine.
68. Ethyl 1-allylaziridine-2-carboxylate.
69. 2-Cyano-l-(2-methylthiobenzyl)-aziridine.
70. 2-Cyano-l-(3,4-dimethoxybenzyl)-aziridine.
71. 2-Cyano-l-(4-methylbenzyl)-aziridine.
72. 1-(2-Cyanoaziridin-l-yl)-2-carebethoxy-cyclohex-l-ene.
73. Process for the preparation of compounds according to claim 7, wherein either

a) a compound of the general formula:-



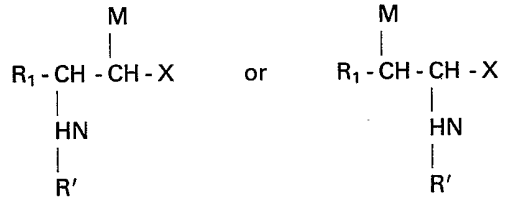
(II)

in which R_1 and X have the same meanings as in Claim 7, Hal_1 and Hal_2 are chlorine or bromine atoms, L is a hydrogen atom or Hal_1 and L together represent a valency bond, is reacted with an amine of the general formula:-

$$R' - NH_2 \qquad \text{(III)}$$

in which R′ has the same meaning as in claim 7; or

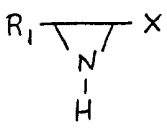
b) a compound of the general formula:-



(IV)

in which X, R_1 and R′ have the same meanings as in claim 7 and M is a chlorine or bromine atom or an A-Z grouping, A being an oxygen or sulphur atom and Z being a hydrogen atom or a grouping which, together with oxygen or sulphur, is easily eliminated, or of a salt thereof, is treated with a reagent which splits off M-H; or

c) a compound of the general formula:-



(V)

in which R_1 and X have the same meanings as in claim 7, is reacted with a compound of the general formula:-

$$R' - Y \qquad (VI)$$

in which R' has the same meaning as in claim 7 and Y is Hal or an $-O-SO_2-OR$ radical, Hal being a chlorine, bromine or iodine atom; or

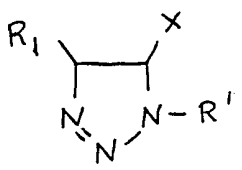
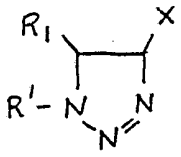
d) an azide of the general formula:-

$$R' - N_3 \qquad (VII)$$

in which R' has the same meaning as in claim 7, is reacted with a compound of the general formula:-

$$R_1\text{-}CH{=}CH\text{-}X \qquad (VIII)$$

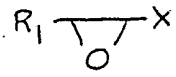
in which R_1 and X have the same meanings as in claim 7, to give a compound of general formula (I), whereby, as intermediate, there canbe formed a triazoline of the general formula:-

(IX)

in which R', R_1 and X have the same meanings as in claim 7, which, by thermolysis or photolysis, can be converted, with the splitting off of nitrogen, into a compound of general formula (I); or

e) an epoxide of the general formula:-



(X)

in which R_1 and X have the same meanings as in claim 7, is reacted with an amine of general formula (III); or

f) a compound of the general formula (V) is reacted with a compound of the general formula:-

$$T\text{-}C{=}\text{-}U \qquad (XI)$$

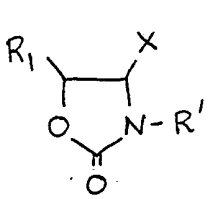
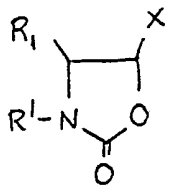
in which T is a hydrogen atom or an alkyl or carboxylic acid ester group and U is an aldehyde or carboxylic acid ester group; or

g) a compound of the general formula (V) is reacted with a compound of the general formula:-

(XII),

in which B is an optionally substituted alkyl or phenyl radical, D is an optionally substituted alkyl radical or B and D together can represent a ring which is optionally interrupted by hetero atoms; or

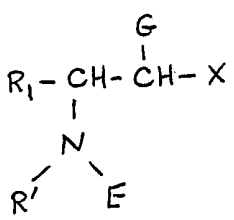
h) an oxazolidinone of the general formula:-

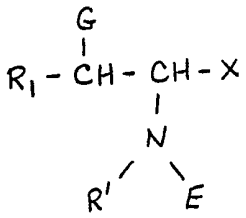



(XIII),

in which R', R_1 and X have the same meanings as in claim 7, as subjected tothermolysis; or

i) a compound of the general formula:-





or (XIV)

in which R', R_1 and X have the same meanings as in claim 7, and G is a hydrogen atom or Hal and E is Hal or a trialkylamino or arylsulphonic acid ester radical, Hal being a chlorine or bromine atom, is treated with a reagent splitting off E-G;

whereafter, if desired, a compound obtained of general formula (I) is subsequently converted into another compound of general formula (I) and, if desired, a compound obtained of general formula (I) is converted into a pharmacologically-acceptable salt.

74. Process for the preparation of compounds according to claim 7, substantially as hereinbefore described and exemplified.

75. Compounds according to claim 7, whenever prepared by the process according to claim 73 or 74.

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