PATENT SPECIFICATION

NO DRAWINGS

1,155,937

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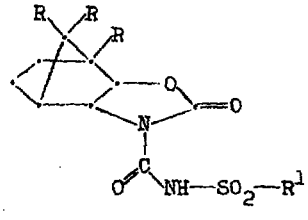
COMPLETE SPECIFICATION

Novel Oxazolidinones

We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

The present invention relates to novel oxazolidinones. More particularly, the invention is concerned with novel N - substituted - oxazolidinones, a process for the manufacture thereof and pharmaceutical preparations containing same. The invention is also concerned with novel N - unsubstituted - oxazolidinones useful in said process.

The novel N - substituted - oxazolidinones provided by the invention may be generically formulated thus:



(I)

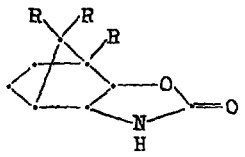
wherein R stands for a hydrogen atom or a methyl group and R^1 stands for a phenyl group which may be substituted by halogen, lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino, a benzamidoethylphenyl group which is substituted by lower-alkoxy and/or halogen or a 5-membered or 6-membered nitrogen-containing heterocyclic group linked through a nitrogen atom.

It will be appreciated that the term "lower alkyl" is used in the foregoing description and in the accompanying claims to mean a straight-chain or branched-chain alkyl group containing from 1 to 7 carbon atoms (e.g. methyl, ethyl, propyl, *iso*propyl, butyl, pentyl and hexyl). The term "lower alkoxy" is used to mean lower-alkyl ether groups in which the lower-alkyl moiety has the foregoing meaning. The term "halogen" denotes bromine, iodine and chlorine with chlorine being preferred. The term "acylamino" denotes an aliphatic or aromatic acyl residue such as actamino or benzoylamino. The term "diacylamino" denotes, for example, phthalimido. A preferred substituted - benzamido - ethylphenyl group is an alkoxy - halo - benzamidoethylphenyl group, especially the β - (2 - methoxy - 5 - chloro - benzamido) - ethylphenyl group. The term "aryl" denotes a group such as phenyl or tolyl. Examples of 5- or 6-membered nitrogen-containing heterocyclic groups linked through nitrogen are piperidino and pyrrolidino.

An interesting class of novel N-substituted-oxazolidinones provided by the invention comprises those in which R^1 stands for a phenyl group which may be substituted by a halogen atom of a lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino group. The preferred novel N-substituted-oxazolidinones provided by the invention are those in which R stands for a methyl group.

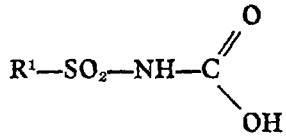
According to the process provided by the invention the novel N - substituted - oxazolidinones aforesaid are manufactured by reacting an N-unsubstituted-oxazolidinone of the general formula

[*Price* 4*s*. 6*d*.]



(II)

wherein R has the significance given earlier, with a reactive derivative of a sulphonylcarbamic acid of the general formula



(III)

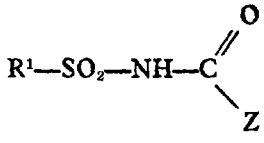
wherein R^1 has the significance given earlier, or with a sulphonylisocyanate of the general formula

$$R^1—SO_2—N=C=O \qquad (IV)$$

wherein R^1 has the significance given earlier.

The N - unsubstituted - oxazolidinone starting materials of formula II, which also form part of this invention, can be prepared from the corresponding amino alcohols (for example, from amino-borneol or amino-norborneol) using phosgene in the presence of an acid-binding agent.

In accordance with the present process, the novel N - substituted - oxazolidinones are manufactured by reacting an N - unsub - stituted - oxazolidinone of formula II with a reactive derivative of a sulphonylcarbamic acid of formula III or a sulphonylisocyanate of formula IV. The preferred reactive derivatives of a sulphonylcarbamic acid which can be used are those having the general formula



(IIIa)

wherein R^1 has the significance given earlier and Z stands for a lower-alkoxy, aryloxy, lower-alkylthio, arylthio, imidazolyl - (1) or 3, 5 - di(lower alkyl) - pyrazolyl - (1) group. A preferred 3, 5 - di(lower alkyl) - pyrazolyl - (1) group is the 3, 5 - dimethyl - pyrazolyl - (1) group. Further, the substituent R^1 in the reactive derivative of the sulphonyl carbamic acid or the sulphonylisocyanate is suitably a phenyl group which may be substituted by a halogen atom or a lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino group.

According to one aspect of the present process, a reactive derivative of formula IIIa in which Z stands for the imidazolyl - (1) group (prepared *in situ*) is reacted with an N - unsubstituted - oxazolidinone of formula II. Conveniently the corresponding sulphonamide or preferably an alkali-metal salt thereof is reacted with carbonyl-diimidazole in a suitable anhydrous organic solvent which is inert towards carbonyl compounds and which does not contain hydroxy groups and the sulphonylcarbamic acid imidazolide which is formed is then allowed to react *in situ* with an N - unsubstituted - oxazolidinone of formula II. Suitable organic solvents for this reaction are, for example, N, N - dimethyl - formamide, hydrocarbons such as benzene and halogenated hydrocarbons such as chloroform.

The novel N - substituted - oxazolidinones of formula I are distinguished by their blood-sugar depressant activity on oral administration. Thus, they are useful as hypoglycaemic agents or as anti-diabetic agents and can be used as medicaments in the form of pharmaceutical preparations (e.g. tablets, capsules or dragées) which contain them in association with a compatible pharmaceutical carrier. The orally administerable pharmaceutical preparations can contain organic or inorganic carrier materials such as, for example, lactose, starch, talc and magnesium stearate. The pharmaceutical preparations can also contain other active ingredients, including other hypoglycaemic agents.

In addition to being useful as hypoglycaemic agents or as anti-diabetic agents, the novel N-substituted-oxazolidinones of formula I are useful as starting materials in the manufacture of the sulphonyl - urea derivatives which form the subject of our copending Application for Letters Patent No. 48920/67 (now Serial No. 1155936).

The following Examples illustrate the process provided by the invention:

Example 1

A) The preparation of the starting material:

280 ml of a 20% solution of phosgene in toluene are slowly added dropwise with stirring to a suspension of 70 g of 3 - endo - amino - *D* - borneol and 140 g of lead carbonate in 200 ml of toluene. Upon completion of the reaction, the mixture is stirred for an additional hour, then filtered. The filtrate is washed with hot toluene. The filtrate is evaporated and the residue recrystallized from acetone/(petroleum ether) to yield endo - *D* - bornano[3′, 2′:4, 5] - oxazolidinone - (2) which decomposes at 168° C; $[\alpha]_D=87°$ (in alcohol, c=3).

B) The process:

A suspension of 20 g of endo - *D* - bornano [3′, 2′:4, 5] - oxazolidinone - (2) in 100 ml of absolute xylene is heated at reflux with 24 ml of *para*toluenesulphonyl isocyanate for

a period of 3 hours. The xylene is then evaporated off, and the residue is extracted several times with a total of 200 ml of ether and thereafter recrystallized to yield N - (*para*toluenesulphonyl - carbamoyl) - endo - D - bornano[3', 2':4, 5]oxazolidinone - (2) having a decomposition point of 155° C [from acetone/(petroleum ether)]; $[\alpha]_D =$ 155° (in chloroform, c=3).

EXAMPLE 2

A) The preparation of the starting material:

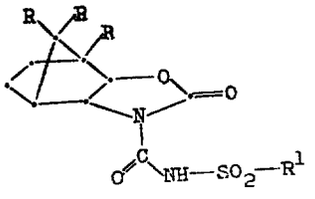
A solution of 6 g of 3 - amino - *D, L* - norborneol hydrochloride in 200 ml of water is made alkaline with sodium hydroxide solution. The released base is taken up in benzene. The benzene is evaporated off and the residue is dissolved in 40 ml of toluene. The resulting solution is reacted with 19 g of lead carbonate and then, over a period of 0.75 hour, with 30 ml of a 20% solution of phosgene in toluene. The resulting mixture is stirred at 20° C for 2 hours, then filtered. The precipitate is boiled twice with 70 ml of ethyl acetate. The combined filtrates are evaporated and crystallized to yield endo - *D, L* - norbonano - [3', 2':4, 5]oxazolidi - none - (2) of melting point 137°—139° C [from acetone/(petroleum ether)].

B) The process:

3 g of endo - *D, L* - norbornano[3', 2': 4, 5] - oxazolidinone - (2) are boiled with 4.3 g of paratoluene-sulphonyl isocyanate in 30 ml of toluene for a period of 3 hours. The resulting mixture is evaporated and the residue is crystallized from ether/(petroleum ether) to yield N - (*para*toluenesulphonyl - carbamoyl) - endo - *D, L* - norbornano[3', 2':4, 5]oxazolidinone - (2) of melting point 140°—142° C [from acetone/(petroleum ether)].

WHAT WE CLAIM IS:—

1) An N - substituted - oxazolidinone of the general formula



wherein R stands for a hydrogen atom or a methyl group and R^1 stands for a phenyl group which may be substituted by halogen, lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino, a benzamidoethylphenyl group which is substituted by lower-alkoxy and/or halogen or a 5-membered or 6-membered nitrogen-containing heterocyclic group linked through a nitrogen atom.

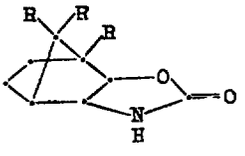
2) An N - substituted - oxazolidinone as formulated in claim 1, wherein R^1 represents a phenyl group which may be substituted by a halogen atom or a lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino group.

3) A compound as formulated in claim 1 or as set forth in claim 2, wherein R stands for a methyl group.

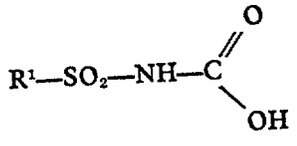
4) N - (*Para*toluenesulphonyl - carbamoyl) - endo - D - bornano[3', 2:4, 5]oxazolidinone - (2).

5) N - (*Para*toluenesulphonyl - carb - amoyl) - endo - *D, L* - norbornano[3', 2': 4, 5]oxazolidinone - (2).

6) A process for the manufacture of the N - substituted - oxazolidinones claimed in claim 1, which process comprises reacting an N-unsubstituted-oxazolidinone of the general formula



wherein R has the significance given in claim 1, with a reactive derivative of a sulphonyl-carbamic acid of the general formula



wherein R^1 has the significance given in claim 1, or with a sulphonylisocyanate of the general formula

$$R^1—SO_2—N=C=O$$

wherein R^1 has the significance given in claim 1.

7) A process as set forth in claim 6, wherein R^1 in said reactive derivative or sulphonyl-isocyanate stands for a phenyl group which may be substituteed by a halogen atom or a lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino group.

8) A process as set forth in claim 6 or claim 7, wherein said reactive derivative is a compound of the general formula

a period of 3 hours. The xylene is then evaporated off, and the residue is extracted several times with a total of 200 ml of ether and thereafter recrystallized to yield N - (*para*toluenesulphonyl - carbamoyl) - endo - D - bornano[3', 2':4, 5]oxazolidinone - (2) having a decomposition point of 155° C [from acetone/(petroleum ether)]; $[\alpha]_D$= 155° (in chloroform, c=3).

EXAMPLE 2

A) The preparation of the starting material:

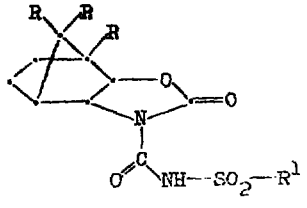
A solution of 6 g of 3 - amino - *D, L* - norborneol hydrochloride in 200 ml of water is made alkaline with sodium hydroxide solution. The released base is taken up in benzene. The benzene is evaporated off and the residue is dissolved in 40 ml of toluene. The resulting solution is reacted with 19 g of lead carbonate and then, over a period of 0.75 hour, with 30 ml of a 20% solution of phosgene in toluene. The resulting mixture is stirred at 20° C for 2 hours, then filtered. The precipitate is boiled twice with 70 ml of ethyl acetate. The combined filtrates are evaporated and crystallized to yield endo - *D, L* - norbonano - [3', 2':4, 5]oxazolidi - none - (2) of melting point 137°—139° C [from acetone/(petroleum ether)].

B) The process:

3 g of endo - *D, L* - norbornano[3', 2': 4, 5] - oxazolidinone - (2) are boiled with 4.3 g of paratoluene-sulphonyl isocyanate in 30 ml of toluene for a period of 3 hours. The resulting mixture is evaporated and the residue is crystallized from ether/(petroleum ether) to yield N - (*para*toluenesulphonyl - carbamoyl) - endo - *D, L* - norbornano[3', 2':4, 5]oxazolidinone - (2) of melting point 140°—142° C [from acetone/(petroleum ether)].

WHAT WE CLAIM IS:—

1) An N - substituted - oxazolidinone of the general formula



wherein R stands for a hydrogen atom or a methyl group and R^1 stands for a phenyl group which may be substituted by halogen, lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino, a benzamidoethylphenyl group which is substituted by lower-alkoxy and/or halogen or a 5-membered or 6-membered nitrogen-containing heterocyclic group linked through a nitrogen atom.

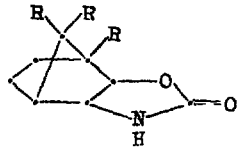
2) An N - substituted - oxazolidinone as formulated in claim 1, wherein R^1 represents a phenyl group which may be substituted by a halogen atom or a lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino group.

3) A compound as formulated in claim 1 or as set forth in claim 2, wherein R stands for a methyl group.

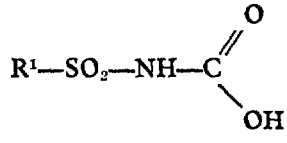
4) N - (*Para*toluenesulphonyl - carbamoyl) - endo - D - bornano[3', 2:4, 5]oxazolidinone - (2).

5) N - (*Para*toluenesulphonyl - carb - amoyl) - endo - *D, L* - norbornano[3', 2': 4, 5]oxazolidinone - (2).

6) A process for the manufacture of the N - substituted - oxazolidinones claimed in claim 1, which process comprises reacting an N-unsubstituted-oxazolidinone of the general formula



wherein R has the significance given in claim 1, with a reactive derivative of a sulphonylcarbamic acid of the general formula



wherein R^1 has the significance given in claim 1, or with a sulphonylisocyanate of the general formula

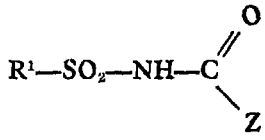
$$R^1—SO_2—N=C=O$$

wherein R^1 has the significance given in claim 1.

7) A process as set forth in claim 6, wherein R^1 in said reactive derivative or sulphonylisocyanate stands for a phenyl group which may be substituteed by a halogen atom or a lower-alkyl, lower-alkoxy, lower-alkylthio, amino, acetyl, acylamino or diacylamino group.

8) A process as set forth in claim 6 or claim 7, wherein said reactive derivative is a compound of the general formula

* C L M S *



wherein R^1 has the significance given in claim 1 and Z stands for a lower-alkoxy, aryloxy, lower-alkylthio, arylthio, imidazolyl-(1) or 3, 5 - di(lower alkyl) - pyrazolyl - (1) group.

9) A process as set forth in claim 8 insofar as said reactive derivative is an imidazolide, wherein same is reacted with the N-unsubstituted-oxazolidinone without isolating said imidazolide from the medium in which it is prepared.

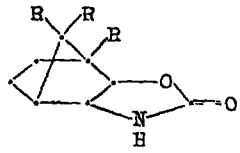
10) A process as set forth in any one of claims 6 to 9 inclusive, wherein said N-unsubstituted - oxazolidinone is endo - *D* - bornano[3′, 2′:4, 5]oxazolidinone - (2) or endo - *D, L* - norbornano[3′, 2′:4, 5]oxa - zolidinone - (2).

11) A process for the manufacture of the N - substituted - oxazolidinones claimed in claim 1, substantially as described with reference to the Examples.

12) N - substituted - oxazolidinones as claimed in claim 1, when manufactured by the process claimed in any one of claims 6 to 11 inclusive.

13) A pharmaceutical preparation comprising an N - substituted - oxazolidinone as set forth in claim 1 in association with a compatible pharmaceutical carrier.

14) An N - unsubstituted - oxazolidinone of the general formula



wherein R has the significance given in claim 1.

15) Endo - *D* - bornano[3′, 2′:4, 5] oxazolidinone - (2).

16) Endo - D, L - norbornano[3′, 2′:4, 5] oxazolidinone - (2).

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