

1075.812



PATENT SPECIFICATION

NO DRAWINGS

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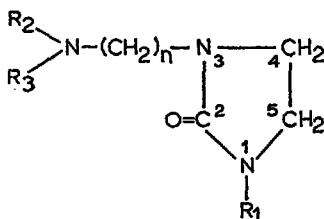
Int. Cl.:—C 07 d 49/34

COMPLETE SPECIFICATION

Basically Substituted Cyclic Ureas and a process for their production

We, ASTA-WERKE AKTIENGESELLSCHAFT CHEMISCHE FABRIK, a body corporate organised under the laws of Germany of 79—91 Bielefelder Strasse, Brackwede/Westf. Germany 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 basically substituted cyclic ureas (imidazolidones) of the general formula



I

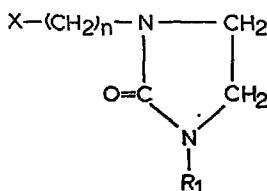
wherein R₁ is a saturated or unsaturated aliphatic hydrocarbon group having from 12 to 18 carbon atoms, n is 2 or 3 and R₂ and R₃, which may be the same or different, represent lower alkyl groups or, together with the nitrogen atom to which they are attached, the piperidino, morpholino and pyrrolidino groups, and salts thereof with non-toxic acids.

In this Specification and the appended claims the term "lower alkyl" refers to alkyl radicals containing one to four carbon atoms.

Preferably, R₂ and R₃ in formula I are ethyl groups.

The hydrochloride is the preferred salt, but any pharmaceutically acceptable non-toxic acid may be used for salt formation, for example, gluconic acid, lactic acid, succinic acid, tartaric acid, citric acid and embonic acid.

The new basically substituted cyclic ureas provided by the invention may be produced by reacting a cyclic urea of the formula II

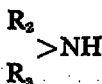


II

[Price 4s. 6d.]

Price 5s. 0d. (25p)

wherein X is a halogen atom, preferably a chlorine atom, and R₁ and n have the same meaning as in the formula I, with a secondary amino compound of formula III



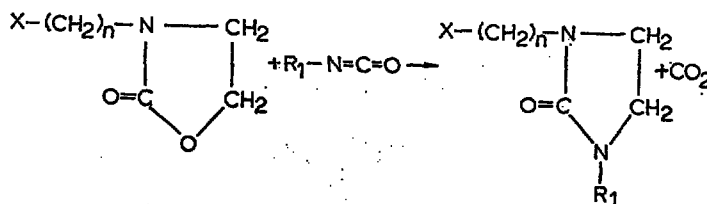
III

wherein R₂ and R₃ have the meaning defined in formula I, in the presence of an acid binding agent at an elevated temperature and, if desired, converting the basically substituted cyclic ureas so obtained into a salt of a non-toxic acid by reaction therewith.

In the process according to the present invention organic bases such as tertiary amines, for example triethylamine or pyridine, or the secondary amine of formula III itself or inorganic bases such as alkali metal carbonates or bicarbonates, for example sodium or potassium carbonate or bicarbonate, may be used as acid binding agents. Preferably, the secondary amine compound of formula III is used in excess.

Preferably, the process according to the invention is carried out in the presence of an inert organic solvent such as dioxane or benzene. The reaction is carried out at the boiling point of the solvent used or in an autoclave at about 120°C. However, the reaction may also be carried out without a solvent.

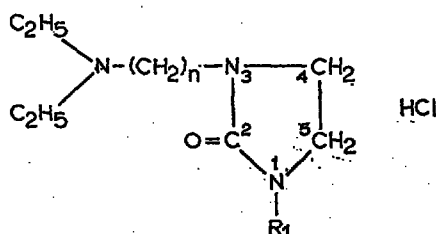
The cyclic ureas of formula II which are used in the process according to the present invention as starting materials may be obtained according to the process which is described in copending British Patent Application 36949/64 (Serial No. 1065295). According to this copending Application the compounds of formula II may be produced by subjecting oxazolidones to reaction with isocyanates according to the following equation:



II

The basically substituted cyclic ureas of formula I according to the present invention exert a strong in vivo and in vitro growth inhibiting effectiveness to certain fungi such as those of the trichophyton group and to *Candida albicans* as shown in the following Table. Furthermore they not only inhibit the growth of the fungi but also kill vegetative formations and spores.

TABLE
Effectiveness of compound of the formula



R ₁	n	complete growth inhibition in the tube dilution test (μg./ml.)	
		Trichophyton mentagrophytes	Candida albicans
n-C ₄ H ₉ —	2	>50	>50
n-C ₁₂ H ₂₅ —	3	8	32
n-C ₁₄ H ₂₉ —	2	2.1	8.4
n-C ₁₆ —H ₃₃ —	2	2.3	9
CH ₃ —(CH ₂) ₇ —CH=CH—(CH ₂) ₈ —	2	2.5	>50
n-C ₁₈ —H ₃₇ —	2	18.8	>50

The present invention is further illustrated by the following Examples:

Illustrative example for the production of the starting materials:

1-*n*-Tetradecyl-3-(β-chloroethyl)-imidazolidone-(2)

0.9 mols (215.5 g.) of *n*-tetradecyl isocyanate and 0.9 mols (134.6 g.) of *N*,β-chloroethyl-oxazolidone-(2) were heated together with 0.2 mols (8.5 g.) of lithium chloride at 160—180°C. After 8 hours the formation of carbon dioxide stopped. The cooled reaction mixture was dissolved in 500 ml. of methylene chloride, the resulting solution washed several times with water and dried over anhydrous sodium sulphate. After the solvent had been distilled off, the residue was recrystallized from 400 ml. of petroleum ether. Thus, 1-*n*-tetradecyl-3-(β-chloroethyl)-imidazolidone-(2) having a melting point at 34—37°C. was obtained in a yield of 222 g. (71.5 % of the theoretical).

The other chloroalkyl imidazolidones used for the production of the compounds according to the present invention can be obtained in an analogous manner.

EXAMPLE 1.

1-*n*-Tetradecyl-3-(β-diethylamino-ethyl)-imidazolidone-(2)

2.5 mols (182.9 g.) of diethylamine (excess) were added to 1.1 mols (379.5 g.) of 1-*n*-tetradecyl-3-(β-chloroethyl)-imidazolidone-(2) dissolved in 500 ml. of dioxane and the mixture was heated to boiling for 6 hours in a round flask equipped with an effective condenser.

The cooled reaction mixture was added to 1.5 litres of water and the resulting mixture extracted once with 600 ml. of methylene chloride and a second time with 400 ml. of methylene chloride. Where necessary, the mixture had to be subjected to centrifugation for a better separation of the two layers. The combined methylene chloride solutions were washed three times each with 1.5 litres of water and then dried over anhydrous sodium sulphate. After distilling off the solvent, 404 g. of the crude base 1-*n*-tetradecyl-3-(β-diethyl-amino-ethyl)-imidazolidone-(2) were obtained.

The hydrochloride of 1-n-tetradecyl-3-(β -diethyl-amino-ethyl)-imidazolidone-(2) was obtained by adding the calculated amount of a solution of hydrogen chloride in anhydrous ether dropwise to a solution of 404.5 g. (1.06 mols) of the crude base in 1600 ml. of anhydrous ether, the addition of the ethereal hydrogen chloride solution however being terminated after the reaction mixture just showed an acid reaction. The precipitated hydrochloride was recrystallized from acetic acid ethyl ester.

M.p.: 79°C. (Kofler bench). Yield: 302 g. (68.1 % of the theoretical).

EXAMPLE 2.

1-Lauryl-3-(γ -diethylaminopropyl)-imidazolidone-(2).

33.1 g. (0.1 mol) of 1-lauryl-3-(γ -chloropropyl)-imidazolidone-(2) were heated together with 16.1 g. (0.22 mols) of diethyl amine in 100 ml. of dioxane to boiling under reflux for 8 hours. When adding water to the cooled reaction mixture an oily product separated. The mixture was extracted with ether, the ethereal solution washed with water and dried over calcined potash. On distilling off the solvent, 34 g. of crude 1-lauryl-3-(γ -diethylamino-propyl)-imidazolidone-(2) were obtained.

The hydrochloride of 1-lauryl-3-(γ -diethylamino-propyl)-imidazolidone-(2) was obtained by dissolving 20 g. of the crude base in anhydrous ether and subjecting this solution to reaction with a saturated solution of hydrogen chloride in anhydrous ether with cooling. The precipitated hydrochloride was recrystallized from a mixture of acetic acid ethyl ester and anhydrous ether. M.p.: 90°C. (kofler bench).

EXAMPLE 3.

1-n-Hexadecyl-3-(β -diethylaminoethyl)-imidazolidone-(2).

This base was produced from 37.3 g. (0.1 mol) of 1-n-hexadecyl-3-(β -chloroethyl)-imidazolidone-(2) and 16.1 g. (0.22 mols) of diethylamine as described in Example 1. Yield: 38 g. of the crude base.

The hydrochloride of 1-n-hexadecyl-3-(β -diethylamino-ethyl)-imidazolidone-(2) is obtained from the crude base as described in Example 1. M.p.: 64°C. (Kofler bench).

EXAMPLE 4.

1-n-Octadecyl-3-(β -diethylaminoethyl)-imidazolidone-(2).

This base was prepared from 16 g. (0.04 mols) of 1-n-octadecyl-3-(β -chloroethyl)-imidazolidone-(2) and 6.6 g. (0.09 mols) of diethylamine as described in Example 1. Yield: 13 g. of the crude base.

The corresponding hydrochloride was prepared from the crude base as described in Example 1. M.p.: 67°C. (Kofler bench).

EXAMPLE 5.

1-Oleyl-3-(β -diethylaminoethyl)-imidazolidone-(2).

This base was prepared from 31.9 g. (0.08 mols) of 1-oleyl-3-(β -chloroethyl)-imidazolidone-(2) and 14.6 g. (0.2 mols) of diethylamine in 100 ml. of dioxane as described in Example 1. Yield: 34 g. of the crude base.

The corresponding hydrochloride of this base was obtained by treating the crude base with an ethereal solution of hydrogen chloride as described in Example 1. M.p.: 84°C. (Kofler bench).

EXAMPLE 6.

1-n-Tetradecyl-3-(β -piperidinoethyl)-imidazolidone-(2).

This base was prepared from 34.5 g. (0.1 mol) of 1-n-tetradecyl-3-(β -chloroethyl)-imidazolidone-(2) and 21.3 g. (0.25 mols) of piperidine in 100 ml. of dioxane as described in Example 2. Yield: 36 g. of the crude base.

The corresponding hydrochloride was obtained by treating the crude base with ethereal hydrogen chloride. After recrystallization from acetic acid ethyl ester, the hydrochloride had a melting point at 143°C. (Kofler bench).

EXAMPLE 7.

1-n-Tetradecyl-3-(β -pyrrolidinoethyl)-imidazolidone-(2).

This base was produced from 34.5 g. (0.1 mol) of 1-n-tetradecyl-3-(β -chloroethyl)-imidazolidone-(2) and 17.8 g. (0.24 mols) of pyrrolidine in 100 ml. of dioxane as described in Example 2. Yield: 35 g. of the crude base.

The corresponding hydrochloride was obtained by treating the crude base with ethereal hydrogen chloride. After recrystallization from acetic acid ethyl ester, it had a melting point at 129°C. (Kofler bench).

The corresponding citrate was obtained by adding a solution of 11.4 g. (0.03 mols) of the above base in 20 ml. of acetone to a solution of 5.8 g. (0.03 mols) of anhydrocitric acid in 60 ml. of acetone at room temperature. The resulting product was recrystallized from acetone. M.p.: 106°C. (Kofler bench).

EXAMPLE 8.

1-n-Tetradecyl-3-(β -morpholinoethyl)imidazolidone-(2).

This base was produced from 34.5 g. (0.1 mols) of 1-n-tetradecyl-3-(β -chloroethyl)imidazolidone-(2) and 21.8 g. (0.25 mols) of morpholine in 100 ml. of dioxane as described in Example 2. Yield: 36 g. of the crude base.

The corresponding hydrochloride may be obtained by treating the crude base with ethereal hydrogen chloride as described in Example 1. It is recrystallized from acetic acid ethyl ester, M.p.: 143°C. (Kofler bench).

The corresponding embonate was obtained in the following way: 11.9 g. (0.03 mols) of the above base and 5.8 g. (0.015 mols) of embonic acid were heated together with 120 ml. of acetone for about 1 hour under reflux until a clear solution was obtained. Thereafter, the acetone was distilled off *in vacuo* and the residue is triturated with petroleum ether. M.p. 62°C. (Kofler bench).

EXAMPLE 9.

1-n-Tetradecyl-3-(β -diethylaminoethyl)-imidazolidone-(2).

69.0 g. (0.2 mols) of 1-n-tetradecyl-3-(β -chloroethyl)imidazolidone-(2), 73.1 g. (1.0 mol) of diethylamine and 50 ml. of benzene were heated in a 500 ml. autoclave for 5 hours at 120°C. The cooled reaction mixture was mixed with 150 ml. of benzene and the resulting mixture was washed several times with water. The benzene layer was dried over anhydrous sodium sulphate, filtered and thereafter the benzene distilled off *in vacuo*. Yield: 69 g. of the crude base.

The crude base may be converted into the corresponding hydrochloride as described in Example 1.

EXAMPLE 10.

1-n-Hexadecyl-3-(β -piperidinoethyl)-imidazolidone-(2).

37.3 g. (0.1 mol) of 1-n-hexadecyl-3-(β -chloroethyl)imidazolidone-(2), 8.5 g. (0.1 mol) of piperidine, 6.9 g. (0.05 mols) of potassium carbonate and 80 ml. of dioxane were heated to boiling under reflux for 8 hours. When adding water to the cooled reaction mixture an oily product separated. The mixture was extracted with methylene chloride, the organic layer is washed several times with water and dried over anhydrous sodium sulphate. On distilling off the solvent, 42 g. of crude 1-n-hexadecyl-3-(β -piperidino-ethyl)-imidazolidone-(2) were obtained.

The corresponding citrate was obtained by dissolving 35.8 g. (0.085 mols) of the crude base in 100 ml. of acetone and adding the solution to a solution of 16.3 g. (0.085 mols) of anhydrocitric acid in 150 ml. of acetone at room temperature.

The salt precipitated shortly thereafter and was recrystallized from acetone. M.p.: 107°C. (Kofler bench).

EXAMPLE 11.

Ointment recipe.

1. W/O-ointment:

1-n-tetradecyl-3-(β -diethylaminoethyl)-imidazolidone-(2) hydrochloride	0.25 g.
demineralized water	49.75 g.
lanoline absorption base	50.00 g.

2. O/W-ointment:

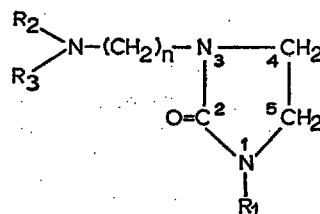
1-n-tetradecyl-3-(β -diethylaminoethyl)-imidazolidone-(2) hydrochloride	0.25 g.
*polyethylene glycol 300 cetyl stearyl ether	12.00 g.
adepts lanæ anhydrous	2.00 g.
isopropyl myristate	3.00 g.
sorbit 70%	10.00 g.
p-hydroxy-benzoic-acid-methyl-ester	0.20 g.
distilled water	78.55 g.

* The figure '300' refers to the polymerisation grade of the polyethylene glycol group. Cetyl and stearyl are present in proportions of 20% and 80% by weight.



WHAT WE CLAIM IS:—

1. Basically substituted cyclic ureas of the general formula I



wherein R_1 is a saturated or unsaturated aliphatic hydrocarbon group having from 12 to 18 carbon atoms, n is 2 or 3 and R_2 and R_3 which may be the same or different, represent lower alkyl groups, or, together with the nitrogen atom to which they are attached, the piperidino, morpholino or pyrrolidino group, and salts thereof with pharmacologically acceptable acids.

2. 1-n-Tetradecyl-3-(β -diethylamino-ethyl)-imidazolidone-(2).

3. 1-Lauryl-3-(γ -diethylaminopropyl)-imidazolidone-(2).

4. 1-n-Hexadecyl-3-(β -diethylaminoethyl)-imidazolidone-(2).

5. 1-n-Octadecyl-3-(β -diethylaminoethyl)-imidazolidone-(2).

6. 1-Oleyl-3-(β -diethylaminoethyl)-imidazolidone-(2).

7. 1-n-Tetradecyl-3-(β -piperidinoethyl)-imidazolidone-(2).

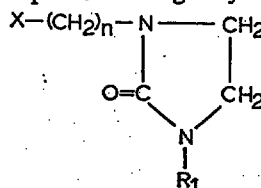
8. 1-n-Tetradecyl-3-(β -pyrrolidinoethyl)-imidazolidone-(2).

9. 1-n-Tetradecyl-3-(β -morpholinoethyl)-imidazolidone-(2).

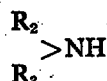
10. 1-n-Tetradecyl-3-(β -diethylaminoethyl)-imidazolidone-(2).

11. 1-n-Hexadecyl-3-(β -piperidinoethyl)-imidazolidone-(2).

12. A process for the production of basically substituted cyclic ureas as claimed in Claim 1 which comprises reacting a cyclic urea of the general formula II



wherein X is a halogen atom and R_1 and n have the meaning defined in Claim 1, with a secondary amine of the general formula III



wherein R_2 and R_3 have the meaning defined in Claim 1 in the presence of an acid binding agent at an elevated temperature and, if desired, converting the resulting basically substituted cyclic urea into the salts with pharmacologically acceptable acids.

13. A process as claimed in Claim 12 wherein 1 mol of the cyclic urea of the general formula II is reacted with 2 mols of the secondary amine of the general formula III.

14. A process as claimed in Claim 12 or 13 wherein the reaction is carried out in dioxane as solvent at the boiling temperature of the reaction mixture.

15. A process for the production of basically substituted cyclic ureas of the general formula I defined in Claim 1 substantially as described with reference to any of the Examples.

16. Basically substituted cyclic ureas of the general formula I defined in Claim 1 when produced by the process claimed in any of the preceding claims.

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