

1117:782



PATENT SPECIFICATION

NO DRAWINGS

1117:782

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Date of filing Complete Specification: 2 July, 1965.

Application Date: 6 July, 1964.

No. 27788/64.

Complete Specification Published: 26 June, 1968.

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Index at acceptance:—C2 C(2B6A3, 2B6G1B, 2B6G10, 2B6J, 3A7V2A3, 3A7V2E1, 3A7V2J1, 3A7V4A3, 3A7V4E1, 3A7V4G1, LD20Y, LD29X, LD29Y, LD32Y, LD36Y, LD321, LD322, LD323, LD360, LD361, LD437, LD730, LD732)

Int. Cl.:—C 07 c 65/14, C 07 c 69/74

COMPLETE SPECIFICATION

Nopinic Acid Derivatives, their preparation and Pharmaceutical Compositions containing them

We, PHARMATIC INC., a body corporate organised under the laws of the State of Delaware, United States of America, of 205, East 42nd Street, New York 17, New York, United

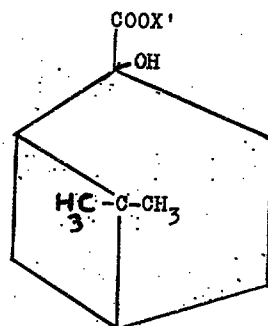
5 States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

10 This invention relates to certain new nopinic acid derivatives, to processes for the preparation thereof and to new pharmaceutical compositions, in particularly compositions suitable for the prevention and control of

15 ulcers and/or of the pain due to ulcers, particularly ulcers of the digestive tract, such as the ulcers of the gastro-duodenal tract, as well as skin ulcers.

20 Accordingly, this invention provides new compounds represented by the following general formulae (I) and (II):

1)

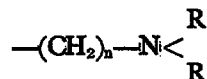


(I)

in which X' represents ammonium, an alkyl radical of 1 to 4 carbon atoms or a group

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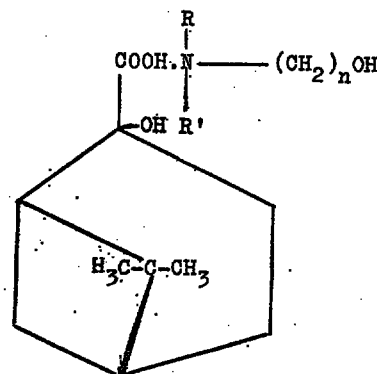
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in which n=1 to 3 inclusive and R and R', which may be the same or different, represent hydrogen or an alkyl radical of 1 to 4 carbon atoms; and

30

2)



(II)

in which n=1 to 3 inclusive, and R and R', which may be the same or different, represent hydrogen or an alkyl radical of 1 to 4 carbon atoms.

35

Among the new compounds of formula (I), the following may be cited as examples:

ammonium nopinate

methyl nopinate (X' = —CH₃)

ethyl nopinate (X' = —C₂H₅)

40

n-propylnopinate (X' = —n—C₃H₇)

isopropyl nopinate (X' = —iso—C₃H₇)

Price 2s 6d

aminoethyl nopinate ($X' = -(\text{CH}_2)_2-\text{NH}_2$)

dimethylaminoethyl nopinate ($X' = -(\text{CH}_2)_2-\text{N} \begin{smallmatrix} \text{CH}_3 \\ < \\ \text{CH}_3 \end{smallmatrix}$)

diethylaminoethyl nopinate ($X' = -(\text{CH}_2)_2-\text{N} \begin{smallmatrix} \text{C}_2\text{H}_5 \\ < \\ \text{C}_2\text{H}_5 \end{smallmatrix}$)

monomethylaminoethyl nopinate ($X' = -(\text{CH}_2)_2-\text{N} \begin{smallmatrix} \text{H} \\ < \\ \text{CH}_3 \end{smallmatrix}$)

5 diisopropylaminoethyl nopinate ($X' = -(\text{CH}_2)_2-\text{N} \begin{smallmatrix} \text{iso}-\text{C}_3\text{H}_7 \\ < \\ \text{iso}-\text{C}_3\text{H}_7 \end{smallmatrix}$)

di-n-butylaminoethyl nopinate ($X' = -(\text{CH}_2)_2-\text{N} \begin{smallmatrix} \text{n}-\text{C}_4\text{H}_9 \\ < \\ \text{n}-\text{C}_4\text{H}_9 \end{smallmatrix}$)

dimethylaminopropyl nopinate ($X' = -(\text{CH}_2)_3-\text{N} \begin{smallmatrix} \text{CH}_3 \\ < \\ \text{CH}_3 \end{smallmatrix}$)

Among the new compounds of formula II, the following may be cited:

- 10 aminoethanol salt of nopinic acid
($\text{R}=\text{R}'=\text{H}$; $n=2$)
dimethylaminoethanol salt of nopinic acid
($\text{R}=\text{R}'=\text{CH}_3$; $n=2$)
15 diethylaminoethanol salt of nopinic acid
($\text{R}=\text{R}'=\text{C}_2\text{H}_5$; $n=2$)
monomethylaminoethanol salt of nopinic acid
($\text{R}=\text{H}$; $\text{R}'=\text{CH}_3$; $n=2$)
diisopropylaminoethanol salt of nopinic acid
($\text{R}=\text{R}'=\text{iso}-\text{C}_3\text{H}_7$; $n=2$)
20 di-n-butylaminoethanol salt of nopinic acid
($\text{R}=\text{R}'=\text{n}-\text{C}_4\text{H}_9$; $n=2$)
dimethylaminopropanol salt of nopinic acid
($\text{R}=\text{R}'=\text{CH}_3$; $n=3$).

25 This invention includes as new compounds the esters and salts of nopinic acid of the formulae (I) and (II), as well as the acid addition salts thereof, such as the hydrochlorides of the compounds of the formula I.

30 The invention also covers pharmaceutical compositions containing as active ingredients the new compounds according to the present invention. The compositions are generally intended for peroral, topical or parenteral administration. Therapeutical compositions to be administered perorally may, for example, be in the form of tablets, dragees or capsules, in which at least one of the novel compounds according to the invention is mixed with a solid, pharmaceutically acceptable vehicle or excipient.

40 The therapeutical compositions may also be used in the form of ointments or creams for the treatment of skin ulcers, the ointments or creams containing at least one of the novel

compounds (I) or (II) mixed with a conventional pharmaceutical cream or ointment base. 45

The therapeutical compositions can also be used in the form of liquid preparations for oral administration, especially syrups, elixirs, aqueous dispersions or solutions. 50

The therapeutical compositions according to the present invention can also be used in the form of solutions to be administered parenterally. Solutions or suspensions for injection purpose can be prepared by using, for example, distilled water or sterile, apyrogenic water, in which at least one compound of the aforementioned formula I or II is dissolved or suspended, if desired in the presence of a dissolving or stabilizing agent, such as propylene glycol. 55 60

Finally, it is possible for a compound of the formula I or II to be administered rectally, by incorporating it in a composition for suppositories, for example, in cocoa butter. 65

Compounds of the general formulae (I) and (II) can be administered in varying doses, depending on the particular compound being used, the condition of the patient and the method of administration. 70

Thus, the compounds in question can be administered in doses of from 50 to 600 mg per day, in the form of several doses taken throughout the day.

75 The invention relates also to processes for the preparation of the new compounds represented by the formulae (I) and (II).

The alkyl esters as well as the aminoalkyl esters of nopinic acid of the formula (I) may be prepared by the usual esterification methods, such as: 80

1°) Heating of nopinic acid in the suitable esterification alcohol, possibly in the presence

of a catalyst such as hydrochloric acid or *p*-toluene sulphonic acid, with or without azeotropic removal of the formed water;

- 2°) Transesterification; or
 5 3°) Reaction of an alkali metal salt of nopinic acid with an appropriate alkyl halide or aminoalkyl halide.

- 10 The aminoalkanol salts of nopinic acid of the formula II may be prepared by dissolving nopinic acid in an anhydrous organic solvent, by neutralising the solution with a stoichiometric quantity of the suitable aminoalcohol dissolved in the same solvent and by concentrating to dryness.

- 15 Examples of methods for the preparation of the compounds used in the pharmaceutical compositions according to this invention, as well as several examples of pharmaceutical compositions are given below for illustrative purposes.

EXAMPLE 1.—

Preparation of the ammonium salt of nopinic acid.—

- 25 1.8 g of pure nopinic acid are dissolved in 20 ml of methanol and the alcoholic solution is exactly neutralised with a titrated solution of gaseous ammonia in methanol. The methanol is removed under vacuum. The ammonium nopinate obtained is soluble in water.

EXAMPLE 2.—

Preparation of methyl nopinate.—

- 30 10 g of sodium nopinate are refluxed during 18 hours with 20 g of methyl iodide dissolved in 100 ml of methanol. The mixture is then concentrated to dryness. 25 ml of water are added to the residue and the aqueous solution is extracted several times with 20 ml of methylene chloride. The combined extracts are dried on anhydrous sodium sulphate and the methylene chloride is evaporated. The methyl nopinate is distilled under reduced pressure. Yield: 76%. This product is a liquid which is not miscible with water, but may be dissolved in organic solvents.

EXAMPLE 3.—

- 45 Preparation of the dimethylaminoethyl ester of nopinic acid and the hydrochloride thereof.—

- 50 7 g of methyl nopinate prepared as described in example 2 are heated during 12 hours at 100°C. in the presence of 50 ml of dimethylaminoethanol and 1 g of sodium. The excess of dimethylaminoethanol is removed by concentration to dryness. The solid residue is suspended in 100 ml of ether. 50 ml of water are added, whereafter methanol is added in a sufficient quantity for dissolving again the precipitate. The organic (ether) phase is collected and the aqueous phase is extracted three times with 50 ml of ether. The ether extracts are combined and washed 5 times with 25 ml of

water. The ether solutions are dried on anhydrous magnesium sulphate. After distillation of the ether, a solid residue of dimethylaminoethyl nopinate is obtained.

For obtaining the hydrochloride of this base gaseous hydrochloric acid is bubbled into an ether solution of said base until saturation is reached. The hydrochloride precipitates; M.P. 226°C. This salt may be recrystallised from a mixture (1:3) of methanol and isopropanol. Fine white needles melting at 230—231°C are obtained. This product is soluble in water and methanol, insoluble in ether, benzene and hexane.

EXAMPLE 4.—

Preparation of the aminoethyl ester of nopinic acid and the hydrochloride thereof.—

This compound and the hydrochloride thereof is prepared as described in example 3 from methyl nopinate, aminoethanol and sodium.

The hydrochloride melts at 146°C.

EXAMPLE 5.—

Preparation of the monomethylaminoethyl ester of nopinic acid and the hydrochloride thereof.—

These compounds are prepared by the process described in example 3 from methyl nopinate, monomethylaminoethanol and sodium.

The ester melts at 144—145°C. The hydrochloride melts at 141—143°C. after recrystallisation from acetone.

EXAMPLE 6.—

Preparation of the diisopropylaminoethyl ester of nopinic acid and the hydrochloride thereof.—

These compounds are prepared by the process described in example 3 from methyl nopinate, diisopropylaminoethanol and sodium. The hydrochloride melts at 179—180°C after recrystallisation from a mixture of benzene and acetone.

EXAMPLE 7.—

Preparation of the di-*n*-butylaminoethyl ester of nopinic acid and the hydrochloride thereof.—

These compounds are prepared by the process described in example 3 from methyl nopinate, di-*n*-butylaminoethanol and sodium. The hydrochloride cannot be crystallised.

EXAMPLE 8.—

Preparation of the dimethylaminopropyl ester of nopinic acid and the hydrochloride thereof.—

These compounds are prepared by the process described in example 3 from methyl nopinate, dimethylaminopropanol and sodium. The hydrochloride melts at 90—91°C.

EXAMPLE 9.—

Preparation of the dimethylaminoethanol salt of nopinic acid.—

- 18.4 g of nopinic acid are dissolved in 100 ml of methylene chloride and 8.9 g of dimethylaminoethanol are added. The mixture is refluxed during 30 minutes and then concentrated to incipient crystallization. After crystallization during one night, the suspension is filtered and the crystals are washed with anhydrous ether. The obtained product melts at 62—63°C.; $[\alpha]_D^{20} = -17^\circ$ (methanol, 10%). The product is soluble in water, methanol, ethanol, acetone, benzene and liquid chlorinated hydrocarbons and insoluble in ether, pentane and hexane.

EXAMPLE 10.—

Preparation of the aminoethanol salt of nopinic acid.—

- This compound is prepared as described in example 9 from nopinic acid and aminoethanol. After recrystallization from a mixture of ethanol and benzene, the compound melts at 155°C.

EXAMPLE 12.—

Preparation of the monomethylaminoethanol salt of nopinic acid.—

- This compound is prepared as described in example 9 from nopinic acid and monoethylaminoethanol. This compound melts at 99—100°C. after recrystallization from benzene.

EXAMPLE 12.—

Preparation of the diethylaminoethanol salt of nopinic acid.—

- This compound is prepared as described in example 9 from nopinic acid and diethylaminoethanol. This compound melts at 66—67°C. (benzene).

EXAMPLE 13.—

- Preparation of the diisopropylaminoethanol salt of nopinic acid.

- This compound is prepared as described in example 9 from nopinic acid and diisopropylaminoethanol. The compound melts at 72—73°C. after recrystallisation from ethanol.

EXAMPLE 14.—

Preparation of the di-*n*-butylaminoethanol salt of nopinic acid.—

- This compound is prepared as described in example 9 from nopinic acid and di-*n*-butylaminoethanol. The white glassy compound cannot be recrystallized.

EXAMPLE 15.—

- Preparation of the dimethylaminopropanol salt of nopinic acid.—

- This compound is prepared as described in example 9 from nopinic acid and dimethylaminopropanol. The pasty white product obtained by this process cannot be recrystallized.

EXAMPLE 16.—

Tablets of nopinic acid derivative.—

Nopinic acid derivative	100 mg
Starch	100 mg
Talc	50 mg
Magnesium stearate	5 mg

EXAMPLE 17.—

Viale for intramuscular injection.—

Nopinic acid derivative	100 mg
Buffering phosphate to pH	7.5
Apyrogenic water q.s.ad.	1 ml

EXAMPLE 18.—

Suppositories

Nopinic acid derivative	100 mg
Cocoa butter q.s. ad.	1 suppository

EXAMPLE 19

Ointment

Nopinic acid derivative	10 g
Ointment base (sodium lauryl sulfate, cetyl alcohol, petrolatum)	90 g

In examples 16, 17, 18 and 19, the nopinic acid derivative is preferably the dimethylaminoethanol salt of nopinic acid or the hydrochloride of dimethylaminoethyl nopinate.

Many pharmacological tests have been made with the nopinic acid derivatives of formulae I and II, particularly with the dimethylaminoethanol salt of nopinic acid (S.N.D.).

Tests made on rats in order to determine the preventive anti-ulcer action of the compounds of formulae I and II have shown that these compounds prevent the gastric ulcer caused by intermittent electrization of rats.

Extensive tests have also shown that said compounds have cicatrizing effect on ulcers, such as haemorrhagic gastric ulcers and skin ulcers.

It has also been found that these compounds possess a strong antispasmodic and anticholinergic activity which is very useful in the therapy of the prevention and control of ulcers.

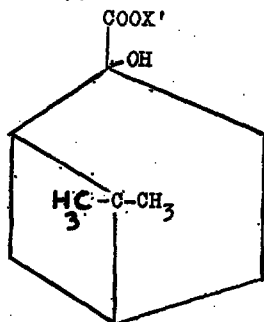
Other tests have also shown that the compounds reduce the gastric secretion and diminish the acidity of the gastric juice, these effects being favourable to ulcer therapy.

All the esters and salts of nopinic acid of the formulae I and II are especially active, the compounds wherein R and R' represent identical methyl, ethyl, or propyl groups being the most active compounds. The best compound seems to be the dimethylaminoethanol salt of nopinic acid (called S.N.D.).

Clinical tests have also been made and have shown that SND has a very strong and consistent antalgic activity on the gastro-duodenal ulcer, when the patients receive 300 to 400 mg of SND per day (6 × 50 or 8 × 50 mg). In several cases, a curative effect on the ulcer itself has been found.

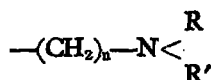
WHAT WE CLAIM IS:—

1. A pharmaceutical composition which contains, as an active ingredient, a compound of the formula (I):



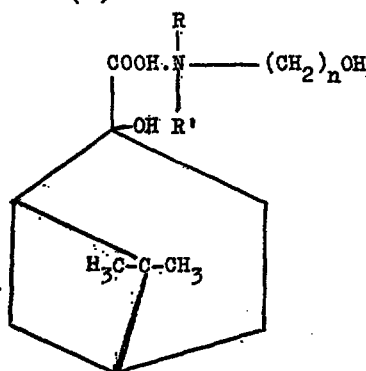
(I)

in which X' represents ammonium, an alkyl radical of 1 to 4 carbon atoms or a group of the formula:



- 10 in which n=1 to 3, inclusive and R and R', which may be identical or different, represent hydrogen or an alkyl radical of 1 to 4 carbon atoms, or a non-toxic acid addition salt of a compound of the formula I, together with a
15 non-toxic, pharmaceutically acceptable carrier or diluent.

2. A pharmaceutical composition which contains, as an active ingredient, a compound of the formula (II):



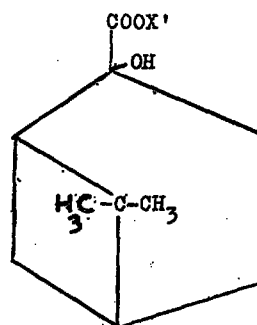
(II)

- in which n=1 to 3 inclusive, and R and R', which may be identical or different, represent hydrogen or an alkyl radical of 1 to 4 carbon atoms, together with a non-toxic, pharmaceutically acceptable carrier or diluent.
25

3. A pharmaceutical composition as claimed in claim 2, in which the active ingredient is the dimethylaminoethanol salt of nopinic acid.

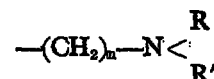
4. A pharmaceutical composition as claimed in any one of claims 1 to 3 in the form of a preparation for peroral, topical or parenteral use.
30

5. Compounds of the general formula (I):



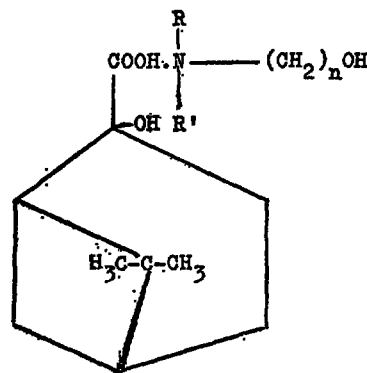
(I)

in which X' represents ammonium, an alkyl radical of 1 to 4 carbon atoms or a group of the formula:



in which n=1 to 3 inclusive whereas R and R', which may be identical or different, represent hydrogen or an alkyl radical of 1 to 4 carbon atoms, as well as the acid addition salts of said compounds of formula IV.
40

6. Methyl nopinate.
7. Ethyl nopinate.
8. n-propyl nopinate.
9. Isopropyl nopinate.
10. Aminoethyl nopinate and the acid addition salts thereof.
11. Dimethylaminoethyl nopinate and the acid addition salts thereof.
12. Diethylaminoethyl nopinate and the acid addition salts thereof.
13. Monomethylaminoethyl nopinate and the acid addition salts thereof.
14. Diisopropylaminoethyl nopinate and the acid addition salts thereof.
15. Di-n-butylaminoethyl nopinate and the acid addition salts thereof.
16. Dimethylaminopropyl nopinate and the acid addition salts thereof.
17. Compounds of the general formula:
45
50
55
60



(II)



- in which $n=1$ to 3 inclusive, whereas R and R', which may be identical or different, represent hydrogen or an alkyl radical of 1 to 4 carbon atoms.
- 5 18. Aminoethanol salt of nopinic acid.
19. Dimethylaminoethanol salt of nopinic acid.
20. Diethylaminoethanol salt of nopinic acid.
10 21. Monomethylaminoethanol salt of nopinic acid.
22. Diisopropylaminoethanol salt of nopinic acid.
23. Di-n-butylaminoethanol salt of nopinic acid.
15 24. Dimethylaminopropanol salt of nopinic acid.
25. Pharmaceutical compositions for the prevention and control of ulcers and/or of the pain due to ulcers substantially as described in examples 16, 17, 18 and 19. 20
26. Compounds of the general formulae (I) and (II) and processes for the preparation thereof substantially as described in examples 1 to 15. 25
27. Pharmaceutical compositions for the treatment of ulcers containing, as an active ingredient a compound as claimed in any of claims 5 to 24 and 26, together with a non-toxic pharmaceutically acceptable carrier or diluent. 30

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1968.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2. from which
copies may be obtained.



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