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(54) **METHOD FOR STABILIZING ARYLCARBOXYLIC ACID, STABILIZER THEREOF AND AQUEOUS SOLUTION CONTAINING STABILIZED ARYLCARBOXYLIC ACID**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(52) **U.S. Cl.** **514/291**; 514/230.5; 514/253.04; 514/253.08; 514/264; 514/300; 514/312; 514/352; 514/365; 514/420; 514/567; 514/226.2

(58) **Field of Search** 546/89, 311, 204, 546/500, 501; 544/38; 514/291, 226.2, 352, 365, 420, 567, 264, 300, 253.08, 312, 230.5, 253.04

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(57) **ABSTRACT**

A method for stabilizing an arylcarboxylic acid, which comprises adding a heterocyclic base to the arylcarboxylic acid or a pharmacologically acceptable salt thereof, a stabilizer thereof and an aqueous solution containing a stabilized arylcarboxylic acid. According to the stabilization method of the present invention, arylcarboxylic acid and pharmacologically acceptable salts thereof, particularly pranoprofen, can be stabilized at every temperature range, particularly at lower temperatures, thereby making the production of an aqueous solution to be used as an eye drop, nasal drop, ear drop and the like possible.

7 Claims, No Drawings

METHOD FOR STABILIZING ARYLCARBOXYLIC ACID, STABILIZER THEREOF AND AQUEOUS SOLUTION CONTAINING STABILIZED ARYLCARBOXYLIC ACID

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a method for stabilizing arylcarboxylic acid, which is an acidic compound and which has an antiinflammatory activity, or a pharmacologically acceptable salt thereof, a stabilizer thereof and an aqueous solution containing a stabilized arylcarboxylic acid.

BACKGROUND OF THE INVENTION

Arylcarboxylic acid and pharmacologically acceptable salts thereof have been known to be extremely superior antiinflammatory agents. However, said arylcarboxylic acids, particularly pranoprofen, diclofenac and bromfenac, are associated with a problem that they become unstable in an aqueous solution.

Arylcarboxylic acid and pharmacologically acceptable salts thereof have been also known to be stabilized by adding an antioxidant, by adjusting the pH, concentration and ionic strength thereof, by shutting out the light, and the like. These methods, nevertheless, cannot provide sufficient stability at lower temperatures.

Thus, an aqueous solution has not been provided which contains an arylcarboxylic acid or a pharmacologically acceptable salt thereof, particularly pranoprofen, dicrofenac or bromfenac, and which has sufficient stability at lower temperatures.

While WO9632941 A1 discloses pranoprofen combined with an organic amine, it does not disclose the heterocyclic base to be used in the present invention.

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide a method for stabilizing an arylcarboxylic acid and a pharmacologically acceptable salt thereof.

Another object of the present invention is to provide a stabilizer of an arylcarboxylic acid and a pharmacologically acceptable salt thereof, which contains a heterocyclic base.

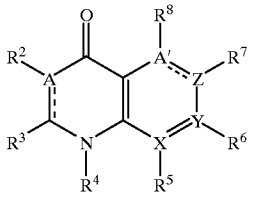
Yet another object of the present invention is to provide an aqueous solution containing a solubilized arylcarboxylic acid and a heterocyclic base.

According to the present invention, it has now been found that the addition of a heterocyclic base to an arylcarboxylic acid or a pharmacologically acceptable salt thereof leads to successful stabilization thereof, particularly pranoprofen, at every temperature range, particularly at low temperatures.

Thus, the present invention provides the following.

(1) A method for stabilizing an arylcarboxylic acid or a pharmacologically acceptable salt thereof, which comprises adding a heteroryclic base of the formula (II):

(II)



wherein

A and A' are each a carbon atom or a nitrogen atom;

X is a carbon atom or a nitrogen atom;

Y and Z are each a carbon atom or Y and Z may combinedly form CH;

R^2, R^3, R^4, R^5, R^6, R^7 and R^8 may be the same or different and each is a hydrogen atom, a halogen, a carboxyl group, an optionally substituted lower alkyl group, an optionally substituted cycloalkyl group, an optionally substituted acyl group, an optionally substituted aryl group or an optionally substituted heterocyclic group,

wherein R^4 and R^5 may form a 4- to 6-membered heterocyclic group with the adjacent nitrogen atom and X, and R^6 and R^7 may form a 4- to 6-membered heterocyclic group with the adjacent Y and Z, provided that when X is a nitrogen atom, R^5 is void; and

====is a single bond or a double bond, provided that when A is a carbon atom, Y and Z are each CH and ====is a double bond, and when A is a nitrogen atom, Y and Z combinedly form CH and ====is a single bond,

to an arylcarboxylic acid of the formula (I):

$$L^1—R^1\ COOH \qquad (I)$$

wherein

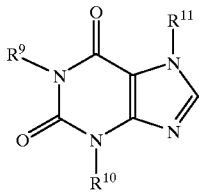
L^1 is an optionally substituted heterocyclic group or aryl group having not more than 14 carbon atoms; and

R^1 is an optionally substituted alkyl group having not more than 4 carbon atoms or a single bond,

or a pharmacologically acceptable salt thereof.

(2) The method of (1) above, wherein the heterocyclic base is a purine base of the formula (III):

(III)



wherein

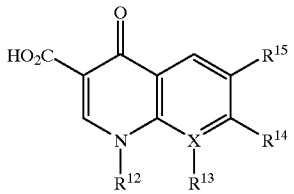
R^9, R^{10} and R^{11} may be the same or different and each is a hydrogen atom or an optionally substituted alkyl group,

or a pharmacologically acceptable salt thereof.

(3) The method of (2) above, wherein the purine base is at least one compound selected from the group consisting of caffeine, theobromine and theophylline.

(4) The method of (1) above, wherein the heterocyclic base is a pyridonecarboxylic acid of the formula (IV):

(IV)



wherein

X is as defined above; and

R^{12}, R^{13}, R^{14} and R^{15} may be the same or different and each is a hydrogen atom, a halogen, a carboxyl group, an optionally substituted lower alkyl group, an optionally substituted cycloalkyl group, an optionally substituted acyl group, an optionally substituted aryl group or an optionally substituted heterocyclic group;

wherein R^{12} and R^{13} may form a 4- to 6-membered heterocyclic group with the adjacent nitrogen atom and X, and R^{14} and R^{15} may form a 4- to 6-membered heterocyclic group with the adjacent carbon atom, provided that when X is a nitrogen atom, R^{13} is void,

or a pharmacologically acceptable salt thereof.

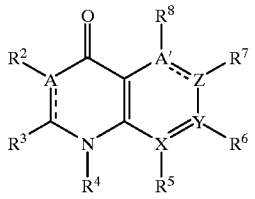
(5) The method of (4) above, wherein the pyridonecarboxylic acid is at least one compound selected from the group consisting of lomefloxacin, norfloxacin, ofloxacin, enoxacin, ciprofloxacin and tosufloxacin.

(6) The method of (1) above, wherein the arylcarboxylic acid is at least one compound selected from the group consisting of ibuprofen, diclofenac, 2-naphthoic acid, 2-naphthylacetic acid, 2-naphthoxyacetic acid, bromfenac, pranoprofen, salicylic acid, aspirin, flufenisal, ibufenac, alclofenac, flurbiprofen, ketoprofen, naproxen, mefenamic acid, niflumic acid, metiazinic acid, protizinic acid, clonixin, indomethacin and fenclozic acid.

(7) The method of (1) above, wherein the heterocyclic base is added in a proportion of 0.001–5 parts by weight per 100 parts by weight of the arylcarboxylic acid.

(8) A stabilizer of an arylcarboxylic acid or a pharmacologically acceptable salt thereof, which comprises, as an active ingredient, a heterocyclic base of the formula (II):

(II)



wherein

A and A' are each a carbon atom or a nitrogen atom;

X is a carbon atom or a nitrogen atom;

Y and Z are each a carbon atom or Y and Z may combinedly form CH;

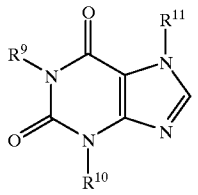
R^2, R^3, R^4, R^5, R^6, R^7 and R^8 may be the same or different and each is a hydrogen atom, a halogen, a carboxyl group, an optionally substituted lower alkyl group, an optionally substituted cycloalkyl group, an optionally substituted acyl group, an optionally substituted aryl group or an optionally substituted heterocyclic group,

wherein R^4 and R^5 may form a 4- to 6-membered heterocyclic group with the adjacent nitrogen atom and X, and R^6 and R^7 may form a 4- to 6-membered heterocyclic group with the adjacent Y and Z, provided that when X is a nitrogen atom, R^5 is void; and

====is a single bond or a double bond, provided that when A is a carbon atom, Y and Z are each CH. and ====is a double bond, and when A is a nitrogen atom, Y and Z combinedly form CH and ====is a single bond.

(9) The stabilizer of (8) above, wherein the heterocyclic base is a purine base of the formula (III):

(III)



wherein

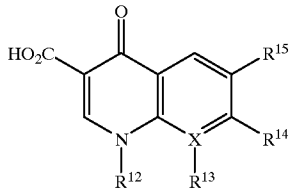
R^9, R^{10} and R^{11} may be the same or different and each is a hydrogen atom or an optionally substituted alkyl group,

or a pharmacologically acceptable salt thereof.

(10) The stabilizer of (9) above, wherein the purine base is at least one compound selected from the group consisting of caffeine, theobromine and theophylline.

(11) The stabilizer of (8) above, wherein the heterocyclic base is a pyridonecarboxylic acid of the formula (IV):

(IV)



wherein

X is as defined above; and

R^{12}, R^{13}, R^{14} and R^{15} may be the same or different and each is a hydrogen atom, a halogen, a carboxyl group, an optionally substituted lower alkyl group, an optionally substituted cycloalkyl group, an optionally substituted acyl group, an optionally substituted aryl group or an optionally substituted heterocyclic group;

wherein R^{12} and R^{13} may form a 4- to 6-membered heterocyclic group with the adjacent nitrogen atom and X, and R^{14} and R^{15} may form a 4- to 6-membered heterocyclic group with the adjacent carbon atom, provided that when X is a nitrogen atom, R^{13} is void,

or a pharmacologically acceptable salt thereof.

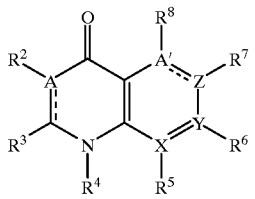
(12) The stabilizer of (11) above, wherein the pyridonecarboxylic acid is at least one compound selected from the group consisting of lomefloxacin, norfloxacin, ofloxacin, enoxacin, ciprofloxacin and tosufloxacin.

(13) The stabilizer of (8) above, wherein the arylcarboxylic acid is at least one compound selected from the group consisting of ibuprofen, diclofenac, 2-naphthoic acid, 2-naphthylacetic acid, 2-naphthoxyacetic acid, bromfenac, pranoprofen, salicylic acid, aspirin, flufenisal, ibufenac, aldlofenac, flurbiprofen, ketoprofen, naproxen, mefenamic acid, niflumic acid, metiazinic acid, protizinic acid, clonixin, indomethacin and fenclozic acid.

(14) The stabilizer of (8) above, wherein the heterocyclic base is contained in a proportion of 0.001–5 parts by weight per 100 parts by weight of the arylcarboxylic acid.

(15) An aqueous solution containing an arylcarboxylic acid or a pharmacologically acceptable salt thereof stabilized by the method of (1) above and a heterocyclic base of the formula (II):

(II)



wherein

A and A' are each a carbon atom or a nitrogen atom;

X is a carbon atom or a nitrogen atom;

Y and Z are each a carbon atom or Y and Z may combinedly form CH;

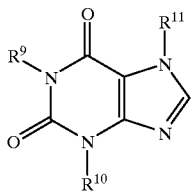
R^2, R^3, R^4, R^5, R^6, R^7 and R^8 may be the same or different and each is a hydrogen atom, a halogen, a carboxyl group, an optionally substituted lower alkyl group, an optionally substituted cycloalkyl group, an optionally substituted acyl group, an optionally substituted aryl group or an optionally substituted heterocyclic group,

wherein R^4 and R^5 may form a 4- to 6-membered heterocyclic group with the adjacent nitrogen atom and X, and R^6 and R^7 may form a 4- to 6-membered heterocyclic group with the adjacent Y and Z, provided that when X is a nitrogen atom, R^5 is void; and

====is a single bond or a double bond, provided that when A is a carbon atom, Y and Z are each CH and ====is a double bond, and when A is a nitrogen atom, Y and Z combinedly form CH and ====is a single bond.

(16) The aqueous solution of (15) above, wherein the heterocyclic base is a purine base of the formula (III):

(III)



wherein

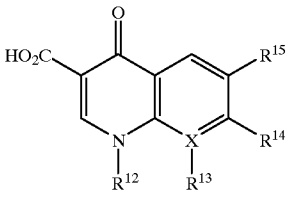
R^9, R^{10} and R^{11} may be the same or different and each is a hydrogen atom or an optionally substituted alkyl group,

or a pharmacologically acceptable salt thereof.

(17) The aqueous solution of (16) above, wherein the purine base is at least one compound selected from the group consisting of caffeine, theobromine and theophylline.

(18) The aqueous solution of (15) above, wherein the heterocyclic base is a pyridonecarboxylic acid of the formula (IV):

(IV)



wherein

X is as defined above; and

R^{12}, R^{13}, R^{14} and R^{15} may be the same or different and each is a hydrogen atom, a halogen, a carboxyl group, an optionally substituted lower alkyl group, an optionally substituted cycloalkyl group, an optionally substituted acyl group, an optionally substituted aryl group or an optionally substituted heterocyclic group;

wherein R^{12} and R^{13} may form a 4- to 6membered heterocyclic group with the adjacent nitrogen atom and X, and R^{14} and R^{15} may form a 4- to 6-membered heterocyclic group with the adjacent carbon atom, provided that when X is a nitrogen atom, R^{13} is void,

or a pharmacologically acceptable salt thereof.

(19) The aqueous solution of (18) above, wherein the pyridonecarboxylic acid is at least one compound selected from the group consisting of lomefloxacin, norfloxacin, ofloxacin, enoxacin, ciprofloxacin and tosufloxacin.

(20) The aqueous solution of (15) above, wherein the arylcarboxylic acid is at least one compound selected from the group consisting of ibuprofen, diclofenac, 2-naphthoic acid, 2-naphthylacetic acid, 2-naphthoxyacetic acid, bromfenac, pranoprofen, salicylic acid, aspirin, flufenisal, ibufenac, alclofenac, flurbiprofen, ketoprofen, naproxen, mefenamic acid, niflumic acid, metiazinic acid, protizinic acid, clonixin, indomethacin and fenclozic acid.

(21) The aqueous solution of any one of the above (15) to (20), which is an eye drop.

(22) The aqueous solution of any one of the above (15) to (20), which is a nasal drop.

(23) The aqueous solution of any one of the above (15) to (20), which is an ear drop.

DETAILED DESCRIPTION OF THE INVENTION

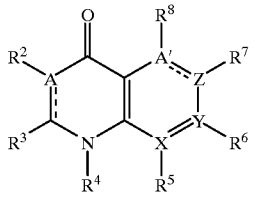
The stabilizing method of the present invention comprises the addition of a stabilizer containing a heterocyclic base as an active ingredient to an arylcarboxylic acid, which is an acidic compound and which has an antiinflammatory activity, or a pharmacologically acceptable salt thereof. For example, a heterocyclic base is added to an arylcarboxylic acid or a pharmacologically acceptable salt thereof.

To be specific, an arylcarboxylic acid and a heterocyclic base are dissolved in water and the pH thereof is adjusted with boric acid, acetic acid, phosphoric acid and the like, which is followed by lyophilization where necessary.

While the pH varies depending on the kind of arylcarboxylic acid, it is generally 5–9, preferably about 6–8.

Said heterocyclic base may be any as long as it has the following formula (II):

(II)



wherein

A and A' are each a carbon atom or a nitrogen atom;

X is a carbon atom or a nitrogen atom;

Y and Z are each a carbon atom or Y and Z may combinedly form CH;

R^2, R^3, R^4, R^5, R^6, R^7 and R^8 may be the same or different and each is a hydrogen atom, a halogen, a carboxyl group, an optionally substituted lower alkyl group, an optionally substituted cycloalkyl group, an optionally substituted acyl group, an optionally substituted aryl group or an optionally substituted heterocyclic group,

wherein R^4 and R^5 may form a 4- to 6-membered heterocyclic group with the adjacent nitrogen atom and X, and R^6 and R^7 may form a 4- to 6-membered heterocyclic group with the adjacent Y and Z, provided that when X is a nitrogen atom, R^5 is void; and

====is a single bond or a double bond, provided that when A is a carbon atom, Y and Z are each CH and ====is a double bond, and when A is a nitrogen atom, Y and Z combinedly form CH and ====is a single bond.

The alkyl of the "optionally substituted lower alkyl group" has 1 to 6 carbon atoms, and may be a linear or branched one, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl, neohexyl and the like.

The cycloalkyl of the "optionally substituted cycloalkyl group" has 3 to 9 carbon atoms, and is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

The substituents of the above-mentioned lower alkyl group and cycloalkyl group include lower alkyl group, halogen and the like.

The lower acyl of the "optionally substituted lower acyl group" may be, for example, formyl group, acetyl group, propionyl group, butyryl group, isobutyryl group, valeryl group, benzoyl group, naphthoyl group, toluoyl group, salicyloyl group and the like.

The above-mentioned acyl may be substituted by suitable substituents which may be the same or different, such as

lower alkyl (e.g., methyl, ethyl, propyl, etc.);

lower alkoxy (e.g., methoxy, ethoxy, propoxy, etc.);

lower alkylthio (e.g., methylthio, ethylthio, etc.);

lower alkylamino (e.g., methylamino, ethylamino, propylamino and the like);

cyclo(lower)alkyl such as cyclo(C_3–C_6)alkyl (e.g., cyclopentyl, cyclohexyl and the like);

cyclo(lower)alkenyl such as cyclo(C_3–C_6)alkenyl (e.g., cycloxenyl, cyclohexadienyl and the like);

halogen (e.g., fluorine, chlorine, bromine and iodine);

amino; amino protecting group; hydroxy; protected hydroxy; cyano; nitro; carboxy; protected carboxy; sulfo; sulfamoyl; imino; oxo;

amino(lower)alkyl (e.g., aminomethyl, aminoethyl and the like), carbamoyloxy, hydroxy(lower)alkyl (e.g., hydroxymethyl, 1- or 2-hydroxyethyl, 1- or 2- or 3-hydroxypropyl and the like); and the like.

The aryl of the "optionally substituted aryl group" is exemplified by phenyl, naphthyl and the like, with preference given to naphthyl.

The heterocyclic group of the optionally substituted heterocyclic group may contain, besides the carbon atom, at least one hetero atom selected from the group consisting of a nitrogen atom, sulfur atom and oxygen atom, as the atom constituting the ring, and may be a saturated or unsaturated, heteromonocyclic or heteropolycyclic group.

The preferable heterocyclic groups are the following:

3- to 6-membered unsaturated heteromonocyclic group having 1 to 4 nitrogen atoms, such as pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl and the like), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl and the like), triazinyl (e.g., 1,2,4-triazinyl and the like), and the like;

3- to 7-membered saturated heteromonocyclic group having 1 to 4 nitrogen atoms, such as pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, homopiperazinyl, and the like;

saturated heteropolycyclic group having 1 to 4 nitrogen atoms, such as quinuclidinyl and the like;

unsaturated heteropolycyclic group having 1 to 5 nitrogen atoms, such as indolyl, isoindolyl, 3H-indolyl, indolizinyl, benzoimidazolyl, quinolyl, isoquinolyl, indazolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl and the like), pteridinyl, carbazolyl, phenanthrinidyl, acridinyl, perimidyl, and the like;

3- to 6-membered unsaturated heteromonocyclic group having 1 to 3 nitrogen atoms and 1 or 2 oxygen atoms, such as oxazolyl, isooxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl and the like), and the like;

3- to 6-membered saturated heteromonocyclic group having 1 to 3 nitrogen atoms and 1 or 2 oxygen atoms, such as morpholinyl, sydnolyl, and the like;

unsaturated condensed heterocyclic group having 1 to 3 nitrogen atoms and 1 or 2 oxygen atoms, such as benzofurazanyl, benzoxazolyl, benzoxazinyl, benzoxadiazolyl, and the like;

3- to 6-membered unsaturated condensed heterocyclic group having 1 to 3 nitrogen atoms and 1 or 2 sulfur atoms, such as thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl and the like), and the like;

3- to 6-membered saturated heteromonocyclic group having 1 to 3 nitrogen atoms and 1 or 2 sulfur atoms, such as thiazolidinyl and the like;

unsaturated condensed heterocyclic group having 1 to 3 nitrogen atoms and 1 or 2 sulfur atoms, such as benzothiazolyl, benzothiadiazolyl, and the like;

3- to 6-membered unsaturated heteromonocyclic group having 1 oxygen atom, such as furyl, pyranyl and the like;

3- to 6-membered unsaturated heteromonocyclic group having 1 or 2 sulfur atoms, such as thienyl, dihydrothienyl, and the like;

unsaturated condensed heterocyclic group having 1 or 2 sulfur atoms, such as benzothienyl and the like; and the like.

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