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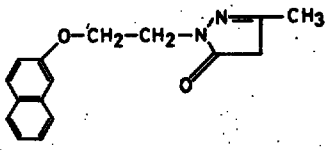
(54) AN ETHER OF 1-(2-HYDROXYETHYL)-3-METHYL-PYRAZOLIN-5-ONE PROCESSES FOR ITS PREPARATION AND ITS USE AS AN ANTITHROMBOTIC AGENT

(71) We, BAYER AKTIENGESELLSCHAFT, a body corporate organised under the laws of Germany, of Leverkusen, 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 the new compound 1-(2-(β-naphthyloxy)-ethyl)-3-methyl-pyrazolin-5-one, several processes for its preparation and its use as a medicament, especially as an antithrombotic agent and thrombolytic agent.

It has already been disclosed that 3-methylpyrazolin-5-ones can be used as antipyretics, analgesics and antiphlogistics (see G. Ehrhardt and H. Ruschig, "Arzneimittel", volume 1, page 148 (1972)). However, their use as antithrombotic agents is new and has not previously been described.

According to the present invention we provide a 1-(2-(β-naphthyloxy)-ethyl)-3-methylpyrazolin-5-one which may be represented by the formula (I)



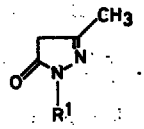
(I)

and salts thereof. The compounds of the invention (i.e. the compound of the formula (I) and its salts) exhibit powerful antithrombotic properties. Amongst these compounds of the invention that are salts therefore, those that are pharmaceutically acceptable and particularly important and preferred, for example the sodium and potassium salts.

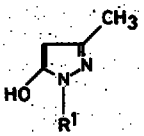
The compound according to the invention can exist in any one of the following tautomeric forms, or as a mixture of such tautomeric forms,

wherein

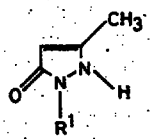
R^1 denotes the above-mentioned naphthyl-(2)-oxyethyl radical.



1a



1b



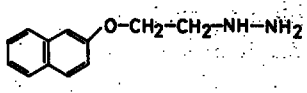
1c

For convenience, throughout the specification and claims the above name and formula (I) will be used to represent the compounds of the invention. However

this name and formula is to be construed as including all tautomeric forms of the compounds.

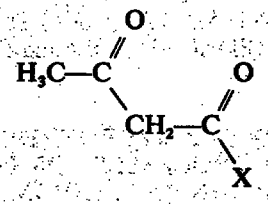
1-(2-(β-Naphthyloxy)-ethyl)-3-methylpyrazolin-5-one of the formula (I) is obtained when

(A) 2-(β-naphthyloxy)-ethylhydrazine of the formula (II)



(II)

is reacted with an acetoacetic acid derivative of the formula (III)



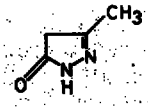
(III)

in which

X represents an alkoxy, aralkoxy, amino or alkylamino radical,

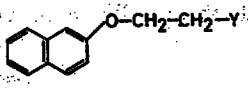
if appropriate in the presence of inert solvents and basic or acid catalysts, preferably at a temperature of from 10 to 200°C, or when

(B) 3-methylpyrazolin-5-one of the formula (IV)



(IV)

is reacted with a 2-(β-naphthyloxy)-ethyl derivative of the formula (V)



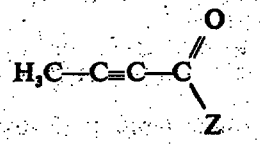
(V)

in which

Y represents a radical which is removed, such as halogen, or the dialkyloxonium, dialkylsulphonium or trialkylammonium radical or the arylsulphonic, alkylsulphonic or trifluoromethylsulphonic acid radical,

if appropriate in the presence of inert solvents and inorganic or organic bases, preferably at a temperature of from 10 to 200°C, or when

(C) a tetrolic acid derivative of the formula (VI)



(VI)

in which

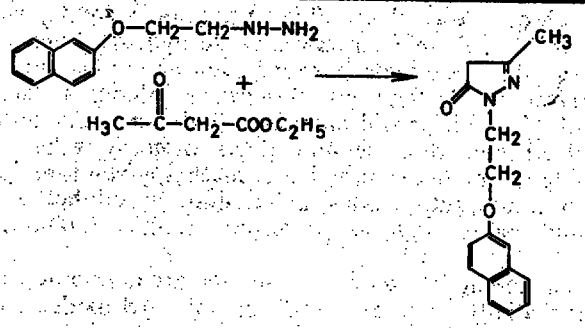
Z represents an hydroxyl, alkoxy, aralkoxy, amino or alkylamino radical,

is reacted with a 2-(β-naphthyloxy)-ethylhydrazine of the formula (II), if appropriate in the presence of inert solvents and inorganic or organic bases, preferably at a temperature of from 50 to 200°C.

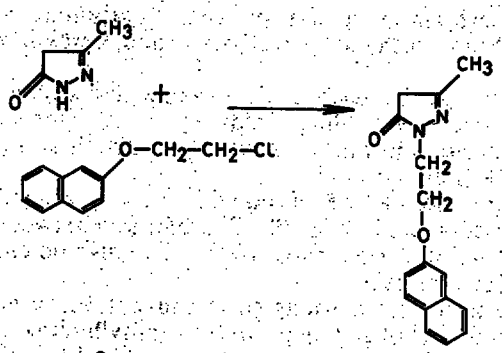
It is surprising that the compounds according to the invention exhibit a powerful antithrombotic action because known pyrazolin-5-one derivatives have not hitherto been shown to have antithrombotic effects.

Depending on the nature of the starting materials used, the synthesis of the compound according to the invention can be represented by the following illustrative equations:

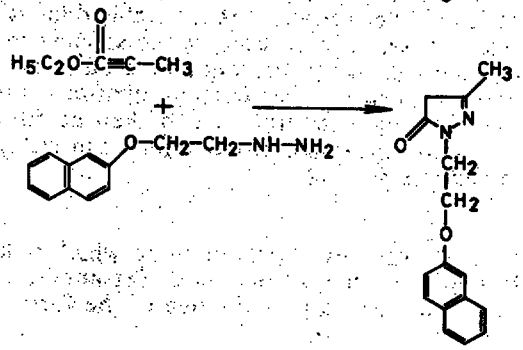
(A)



(B)

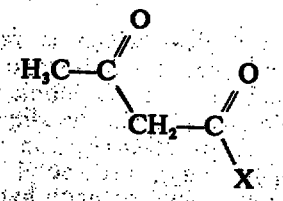


(C)



Process variant A

According to process A, the known 2-(β-naphthyloxy)-ethylhydrazine is reacted with an acetoacetic acid derivative of the formula (III)



(III)

In the formula (III)

X preferably represents an optionally substituted alkoxy group with 1 to 6, especially with 1 to 4, carbon atoms, a benzyloxy group, an amino group, or an alkylamino or dialkylamino group each with 1 to 4 carbon atoms per alkyl group.

The acetoacetic acid derivatives used as starting materials according to formula (III) are known from the literature or can be prepared according to processes known from the literature (see D. Borrmann in Houben-Weyl, Methoden der Organischen Chemie (methods of Organic Chemistry), volume VII/4, page 229 *et seq.* (1968)).

The following may be mentioned as examples: acetoacetic acid ethyl ester, aceto-acetic acid n-butyl ester, acetoacetic acid propyl ester, acetoacetic acid tert.-butyl ester, acetoacetic acid benzyl ester, acetoacetic acid amide, aceto-acetic acid methylamide, acetoacetic acid n-butylamide and acetoacetic acid diethylamide.

Diluents which can be used are all inert organic solvents, where appropriate diluted with water. These preferentially include hydrocarbons such as benzene, toluene and xylene, halogenohydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and chlorobenzene, alcohols such as methanol, ethanol, propanol, butanol, benzyl alcohol and glycol monomethyl ether, ethers such as tetrahydrofurane, dioxane and glycol dimethyl ether, amides such as dimethylformamide, dimethylacetamide, N-methylpyrrolidone and hexamethylphosphoric acid triamide, sulphoxides such as dimethylsulphoxide, sulphones such as sulpholane and bases such as pyridine, picoline, collidine, lutidine and quinoline.

Basic condensation agents which can be used are inorganic and organic bases. These preferentially include alkali metal hydroxides such as sodium hydroxide, alkali metal carbonates, such as potassium carbonate, and alkali metal alcoholates such as sodium methylate or ethylate and potassium methylate or ethylate.

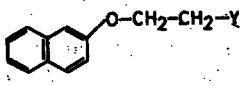
Acid catalysts which can be used are inorganic and organic acids. These preferentially include hydrogen halide acids such as hydrochloric acid or hydrobromic acid, sulphuric acid and sulphonic acids such as toluenesulphonic acid and trifluoromethylsulphonic acid.

The reaction temperatures can be varied within a wide range. In general, the reaction is carried out at between 10 and 200°C, preferably between 20 and 100°C. It is usually carried out under normal pressure but can also be carried out under elevated pressure in closed vessels.

In carrying out the process according to the invention, in accordance with equation A, preferably one mol of 2-(β-naphthyloxy)-ethylhydrazine (II) is reacted per mol of the acetoacetic acid derivative III in a suitable diluent. Either the free hydrazine or its acid addition salt can be used as the starting material, and the reaction can also be carried out in the presence of a basic catalyst. After the exothermic initial reaction has ceased, the reaction mixture is preferably stirred for two to five hours at elevated temperature and then acidified slightly. The compound according to the invention thereby obtained can easily be purified by recrystallisation from a suitable solvent.

Process variant B

According to process B, 3-methylpyrazolin-5-one which is known from the literature and has the formula (IV) (see R. Jones et al. Tetrahedron *19*, 1497 (1963)) is reacted with a 2-(β-naphthyloxy)-ethyl derivative of the formula (V)



(V)

In the formula (V)

Y preferably represents a radical which is removed, such as halogen, especially chlorine or bromine, or a dialkyloxonium, dialkylsulphonium or trialkylammonium radical, or an arylsulphonic acid, alkylsulphonic acid or trifluoromethylsulphonic acid radical, the alkyl groups mentioned in each case containing 1 to 4 carbon atoms and in particular denoting methyl, ethyl, propyl, iso-propyl, butyl, tert.-butyl or iso-butyl, and aryl in particular denoting phenyl, toluyl or naphthyl.

The β-naphthyl compounds of the formula (V) used as starting materials are known or can be prepared according to known processes (Kirner et al.; J. am. chem. Soc. 51, 3417).

Diluents which can be used are all inert solvents. These preferentially include hydrocarbons such as benzene, toluene and xylene, alcohols such as methanol, ethanol, propanol, butanol, benzyl alcohol and glycol monomethyl ether, ethers such as tetrahydrofurane, dioxane and glycol dimethyl ether, amides such as dimethylformamide, dimethylacetamide, N-methylpyrrolidone and hexamethylphosphoric acid triamide, sulphoxides such as dimethylsulphoxide and sulphones such as sulpholane (tetrahydrothiophene-1,1-dioxide).

Bases which can be used are inorganic and organic bases. These preferentially include alkali metal hydroxides and alkali metal carbonates such as sodium hydroxide and carbonate or potassium hydroxide, alkali metal alcoholates such as sodium ethylate, and alkali metal hydrides and amides such as sodium hydride or sodium amide.

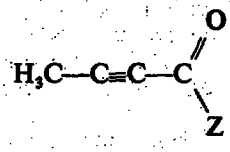
The reaction temperatures can be varied between 10 and 200°C. Preferably, the reaction is carried out at between 20 and 120°C. It is carried usually out under normal pressure but can also be carried out under elevated pressure in closed vessels.

In carrying out the process according to the invention, in accordance with reaction B, preferably one mol of the salt of 3-methylpyrazolin-5-one is reacted per mol of the compound (V) in a suitable solvent.

The compound according to the invention is preferably isolated by distilling off the solvent *in vacuo*, taking up the residue in water and slightly acidifying the aqueous mixture. The compound according to the invention obtained by this method can be purified by recrystallisation.

Process variant C

According to process C, the known 2-(β-naphthyloxy)-ethylhydrazine of the formula (II) is reacted with a tetrolic acid derivative of the formula (VI)



(VI)

In the formula

Z preferably represents hydroxyl, an optionally substituted alkoxy group with 1 to 6, especially with 1 to 2, carbon atoms, a benzyloxy group, an amino group or an alkylamino or dialkylamino group each with 1 to 4 carbon atoms per alkyl group.

The tetrolic acid derivatives of the formula (VI) used as starting materials are known or can be prepared according to methods known from the literature (see, for example, Beilsteins "Handbuch der Organischen Chemie" *2*, 480 (1920); ibid. *2*, III 1,447 et seq. (1961)).

The following may be mentioned as examples: tetrolic acid methyl ester, tetrolic acid ethyl ester, tetrolic acid n-butyl ester, tetrolic acid isopropyl ester, tetrolic acid tert.-butyl ester, tetrolic acid benzyl ester, tetrolic acid amide, tetrolic acid methylamide, tetrolic acid n-butylamide, tetrolic acid dimethylamide and tetrolic acid diethylamide.

Diluents which can be used are all inert organic solvents, where appropriate diluted with water. These preferentially include hydrocarbons such as benzene, toluene, and xylene, halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and chlorobenzene, alcohols such as methanol, ethanol, propanol, butanol, benzyl alcohol and glycol monomethyl ether, ethers such as tetrahydrofurane, dioxane and glycol dimethyl ether, amides such as dimethylformamide, dimethylacetamide, N-methylpyrrolidone and hexamethylphosphoric acid triamide, sulphoxides such as dimethylsulphoxide, sulphones such as sulpholane and bases such as pyridine, picoline, collidine, lutidine and quinoline.

Inorganic and organic bases can be used as the basic condensation agents. These preferentially include alkali metal hydroxides such as sodium hydroxide, alkali metal carbonates, such as potassium carbonate, and alkali metal alcoholates such as sodium methylate, ethylate or butylate and potassium methylate, ethylate or butylate.

The reaction temperatures can be varied within a wide range. In general, the reaction is carried out at a temperature of from 50 and 200°C, preferably between 70 and 150°C. It is usually carried out under normal pressure but can also be carried out under elevated pressure in closed vessels.

In carrying out the process according to the invention in accordance with reaction C, preferably one mol of the tetrolic acid derivative (VI) is reacted per mol of 2-(β-naphthyloxy)-ethylhydrazine in a suitable diluent. The compound according to the invention, obtained in a crystalline form after evaporating off the diluent, can easily be purified by recrystallisation.

As stated above, the invention also relates to the use in human and veterinary medicine of the compounds of the invention.

The present invention provides a pharmaceutical composition containing as active ingredient a compound of the invention in admixture with a solid or liquefied gaseous diluent, or in admixture with a liquid diluent other than a solvent

of a molecular weight less than 200 (preferably less than 350) except in the presence of a surface active agent.

The invention further provides a pharmaceutical composition containing as active ingredient a compound of the invention in the form of a sterile or isotonic aqueous solution.

The invention also provides a medicament in dosage unit form comprising a compound of the invention either alone or in admixture with a diluent.

The invention also provides a medicament in the form of tablets (including lozenges and granules), dragees, capsules, pills, ampoules or suppositories comprising a compound of the invention either alone or in admixture with the diluent.

"Medicament" as used in this Specification means physically discrete coherent portions suitable for medical administration. "Medicament in dosage unit form" as used in this Specification means physically discrete coherent portions suitable for medical administration each containing a daily dose or a multiple (up to four times) or sub-multiple (down to a fortieth) of a daily dose of the compound of the invention. Whether the medicament contains a daily dose or, for example, a half, a third, or a quarter of a daily dose will depend on whether the medicament is to be administered once or, for example, twice, three times or four times a day respectively.

The pharmaceutical compositions according to the invention may, for example, take the form of suspensions, solutions and emulsions of the active ingredient in aqueous or non-aqueous diluents, syrups, granules or powders.

The diluents to be used in pharmaceutical compositions (e.g. granulates) adapted to be formed into tablets, dragees, capsules and pills include the following:
(a) fillers and extenders, e.g. starch, sugars, mannitol, and silicic acid; (b) binding agents, e.g. carboxymethyl cellulose and other cellulose derivatives, alginates, gelatine and polyvinyl pyrrolidone; (c) moisturizing agents, e.g. glycerol; (d) disintegrating agents, e.g. agar-agar, calcium carbonate and sodium bicarbonate; (e) agents for retarding dissolution e.g. paraffin; (f) resorption accelerators, e.g. quaternary ammonium compounds; (g) surface active agents, e.g. cetyl alcohol, glycerol monostearate; (h) adsorptive carriers, e.g. kaolin and bentonite; (i) lubricants, e.g. talc, calcium and magnesium stearate and solid polyethylene glycols.

The tablets, dragees, capsules and pills formed from the pharmaceutical compositions of the invention can have the customary coatings, envelopes and protective matrices, which may contain opacifiers. They can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes and protective matrices may be made, for example, of polymeric substances or waxes.

The ingredient can also be made up in microencapsulated form together with one or several of the above-mentioned diluents.

The diluents to be used in pharmaceutical compositions adapted to be formed into suppositories can, for example, be the usual water-soluble or water-insoluble diluents, such as polyethylene glycols and fats (e.g. cocoa oil and high esters [e.g. C_{14}-alcohol with C_{16}-fatty acid]) or mixtures of these diluents.

The pharmaceutical compositions which are powders can, for example, contain the usual diluents, e.g. lactose, talc, silicic acid, aluminium hydroxide, calcium silicate, and polyamide powder or mixtures of these substances.

The pharmaceutical compositions which are solutions and emulsions can, for example, contain the customary diluents (with, of course, the above-mentioned exclusion of solvents having a molecular weight below 200 except in the presence of a surface-active agent), such as solvents, dissolving agents and emulsifiers; specific examples of such diluents are water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butyleneglycol, dimethylformamide, oils [for example ground nut oil], glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitol or mixtures thereof.

For parenteral administration, the solutions and emulsions should be sterile, and, if appropriate, blood-isotonic.

It is advantageous to formulate the compounds of the invention with an equimolar amount of a non-toxic organic or inorganic base, if necessary in a suitable solvent, for parenteral administration. Sodium hydroxide solution, potassium hydroxide solution, ethanolamine, diethanolamine, triethanolamine,

amino-tris-hydroxymethyl-methane glucosamine and N-methylglucosamine may be mentioned as examples of suitable bases.

The pharmaceutical compositions which are suspensions can contain the usual diluents, such as liquid diluents, e.g. water, ethyl alcohol, propylene glycol, surface-active agents (e.g. ethoxylated isostearyl alcohols, polyoxyethylene sorbite and sorbitane esters), microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragancth or mixtures thereof.

All the pharmaceutical compositions according to the invention can also contain colouring agents and preservatives as well as perfumes and flavouring additions (e.g. peppermint oil and eucalyptus oil) and sweetening agents (e.g. saccharin).

The pharmaceutical compositions according to the invention preferably contain from 0.1 to 99.5, more preferably from 0.5 to 95% of the active ingredient by weight of the total composition.

In addition to a compound of the invention, the pharmaceutical compositions and medicaments according to the invention can also contain other pharmaceutically active compounds. They may also contain a plurality of compounds of the invention.

Any diluent in the medicaments of the present invention may be any of those mentioned above in relation to the pharmaceutical compositions of the present invention. Such medicaments may include solvents of molecular weight less than 200 as sole diluent.

The discrete coherent portions constituting the medicament according to the invention (whether in dosage unit form or not) may be, for example, any of the following: tablets, (including lozenges and granules), pills, dragees, capsules, suppositories and ampoules. Some of these forms may be made up for delayed release of the active ingredient. Some, such as capsules, include a protective envelope which renders the portions of the medicament physically discrete and coherent.

The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

This invention further provides a method of combatting (including prevention, relief and cure of) thrombembolic diseases in non-human animals, which comprises administering to the animals a compound of the invention alone or in admixture with a diluent or in the form of a medicament according to the invention.

It is envisaged that these active compounds will be adminstered perorally, parenterally (for example intramuscularly, intraperitoneally or intravenously) or rectally, preferably orally or parenterally. Preferred pharmaceutical compositions and medicaments are therefore those adapted for oral and parenteral administration.

In the case of parenteral use, it is particularly advantageous to combine compounds according to the invention in a suitable solvent with an equimolar amount of a non-toxic inorganic or organic base. Sodium hydroxide solution, potassium hydroxide solution, ethanolamine, diethanolamine, triethanolamine, amino-tris-hydroxymethyl-methane, glucosamine and N-methylglucosamine may be mentioned as examples.

Such salts can also be of increased importance for oral use of the compounds according to the invention, in that they accelerate or delay the resportion, as desired. In addition to the salts already mentioned above, the following may be named as examples: the magnesium salt, calcium salts, the aluminium salt and iron salts.

In general it has proved advantageous, in the case of parenteral administration, to administer amounts of from 0.01 to 50 mg/kg of body weight, preferably from 0.1 to 10 mg/kg of body weight, per day, in order to achieve effective results, whilst in the case of oral administration the dosage is from 0.1 to 500 mg/kg of body weight, preferably 0.5 mg to 100 mg/kg of body weight, per day.

Nevertheless it can at times be necessary to deviate from the amounts mentioned, and in particular to do so in accordance with the body weight of the test animal or the nature of the method of administration, and also because of the species of animal and its individual behaviour towards the medicament, or the type of formulation of the medicament and the time of interval at which it is

administered. Thus it may suffice in some cases to use less than the above-mentioned minimum amount whilst in other cases the upper limit mentioned must be exceeded. Where major amounts are administered it can be advisable to divide these into several individual administrations over the course of the day.

The examples which follow are intended to illustrate the formulation procedure:

(a) 500 g of 1-(2-(β-naphthyloxy)-ethyl)-3-methyl-pyrazolin-5-one are comminuted to a powder, mixed with 300 g of lactose and 200 g of potato starch, moistened with an aqueous gelatine solution and then granulated by passing through a sieve. After drying, 60 g of talc and 5 g of sodium lauryl-sulphate are added and the mixture is pressed to form 10,000 tablets each containing 50 mg of active compound.

(b) 50 g of the sodium salt of 1-(2-(β-naphthyloxy)-ethyl)-3-methyl-pyrazolin-5-one are dissolved in 1,000 ml of propylene glycol and the solution is made up to 2,000 ml with water. This solution is filled, under aseptic conditions, into sterile ampoules each of 5 ml capacity and each containing 50 mg of active compound.

To demonstrate the antithrombotic action of the compound according to the invention, the substance as administered to rats.

The left jugular veins of rats weighing 170—180 g were exposed under ether narcosis and supercooled to −12°C for 2 minutes to stimulate thrombus formation. 4 hours later, the thrombus was isolated from the vein and weighed. The test animals were given the test preparation in tragacanth mucilage immediately before supercooling the wall of the vein. Accordingly, the protective antithrombotic activity was tested within the first 4 hours after stimulating thrombus formation.

The results of the investigations with the compound according to the invention are shown in the table which follows:

TABLE 1

	Control on animals without active compound	Animals treated with the compound according to the invention (100 mg/kg administered orally)
Size of thrombus in μg Average value	115 ± 12	53 ± 10
Number of experiments	18	16

The experiments show that the compound according to the invention significantly inhibits the formation of venous thrombi.

After a treatment period of 4 hours, the size of the thrombi is reduced by 54%.

The product of the process can therefore be used for the prophylaxis of thrombembolic diseases.

In addition to the inhibiting effect on the formation of thrombi, the compound according to the invention is also distinguished by a very powerful thrombolytic effect. Thrombolytic depositions already formed are redissolved under the influence of the compound. Hitherto corresponding thrombolytic effects were only achievable by repeated intravenous administeration of toxic fibrinolytics such as streptokinase and urokinase, whilst the compound according to the invention is administered orally and only once per day.

To demonstrate the thrombolytic effect, narcotised male rats are used. The left jugular vein is exposed and briefly cooled to −12°C. This damages the wall of the vein so that a thrombus is produced, which grows to its maximum size over the course of 4 hours.

The compound according to the invention is administered orally 24 hours and 26 hours after producing the thrombosis. In contrast, the streptokinase used for comparison can only be administered intravenously since it is completely inactive after oral administration. 4 hours after the first administration, the thrombi are removed from the vein and weighed. The thrombolytic effect is detected by

comparison with a control group to which the solvents, without active compounds, were administered in the same way. The results are shown in Table 2.

After intravenous injection of twice 10,000 U/kg, streptokinase, which is fibrinolytically active, reduces the thrombus weight over the course of 4 hours from 351±53 to 194±64 μg, that is to say by 45%. The compound according to the invention has the same effect after oral administration of twice 10 mg/kg. The thrombus weight is reduced from 288±26 to 147±16 μg, that is to say by 49%.

TABLE 2

Thrombolytic effect/rats

	Number of animals	Thrombus weight, μg	Difference and significance, relative to control
Control, administered orally	93	288 ± 26	–
Compound according to the invention	84	147 ± 16	-49%
2 × 10 mg/kg, administered orally			
Control, administered intravenously	23	351 ± 53	–
Streptokinase, administered intravenously	21	194 ± 64	-45%
2 × 10,000 U/kg i.v.			
Streptokinase, administered orally			no effect

Example 1 (variant A).

13 g (0.1 mol) of ethyl acetoacetate in 20 ml of absolute ethanol were added to 20.2 g (0.1 mol) of 2-(β-naphthyloxy)-ethylhydrazine in a little absolute ethanol. After the exothermic initial reaction had ceased, the reaction mixture was heated for 2 hours under reflux.

On cooling, the crude product crystallised out. It was purified by recrystallisation from an ethanol-dimethylformamide mixture (10:1).

Yield: 82% of theory.

Melting point: 162—164°C.

Example 2 (variant A).

Analogously to Example 1, tert.-butyl acetoacetate and 2-(β-naphthyloxy)-ethylhydrazine gave 1-(β-naphthyloxy)-ethyl)-3-methylpyrazolin-5-one according to the invention.

Example 3 (variant A).

The compound according to the invention was obtained in approx. 75% yield from benzyl acetoacetate and 2-(β-naphthyloxy)-ethylhydrazine under the reaction conditions of Example 1.

Example 4 (variant B).

19.6 g of 3-methyl-pyrazolin-5-one were added in portions to a suspension of 10.0 g of sodium hydride in 200 ml of absolute dimethylformamide.

After the evolution of H_2 had ceased, 41.2 g of 2-(β-naphthyloxy)-ethyl chloride were added dropwise to the reaction solution. The mixture was then stirred for 2 hours at 60°C, the solvent was distilled off *in vacuo*, the residue was

taken up in water and the solution was acidified with dilute acetic acid.

The crude product thereby obtained was recrystallised from an ethanol/dimethylformamide mixture.

Yield: 28% of theory.

Melting point: 162—164°C.

Example 5 (variant B).

9.8 g of 3-methylpyrazolin-5-one and 25.1 g of 2-(naphthyloxy)-ethyl bromide were thoroughly triturated and slowly heated to 110°C in a reaction vessel. The melt thereby produced was heated for a further 4 hours at approx. 110°C. The crystal paste obtained after cooling was dissolved in a hot mixture of dimethylformamide and ethanol. The crystals obtained after the solution had crystallised out were purified by a further recrystallisation.

Yield: 38%.

Melting point: 162—164°C.

Example 6 (variant C).

8.3 g (0.074 mol) of tetrolic acid ethyl ester and 14.8 g of 2-(β-naphthyloxy)-ethylhydrazine in 70 ml of n-butanol were heated for 8 hours under reflux.

The reaction solution was then concentrated and the solid residue was twice recrystallised from an ethanol/dimethylformamide mixture (10:1).

Yield: 45% of theory.

Melting point: 162—164°C.

Example 7 (variant C).

The compound according to the invention was obtained analogously to Example 4 from tetrolic acid methyl ester and 2-(β-naphthyloxy)-ethylhydrazine.

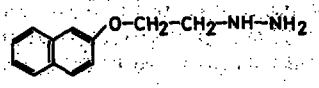
Example 8 (variant C).

On reacting tetrolic acid benzyl ester and 2-(β-naphthyloxy)-ethylhydrazine, the compound according to the invention was obtained in approx. 40% yield if the reaction was carried out in accordance with the conditions of Example 4.

WHAT WE CLAIM IS:—

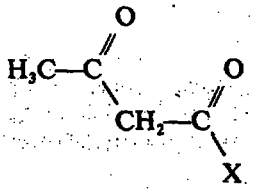
1. 1-(2-(β-Naphthyloxy)-ethyl)-3-methylpyrazolin-5-one or a salt thereof.
2. A compound according to claim 1 in the form of the sodium salt.
3. Any compound according to claim 1 specifically mentioned herein.
4. A process for the preparation of a compound according to claim 1 wherein

(A) 2-(β-naphthyloxy)-ethylhydrazine of the formula (II)



(II)

is reacted with an acetoacetic acid derivative of the formula (III)

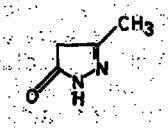


(III)

in which

X represents an alkoxy, aralkoxy, amino or alkylamino radical,

if appropriate in the presence of inert solvents and basic or acid catalysts, or (B) 3-methylpyrazolin-5-one of the formula (IV)



(IV)

taken up in water and the solution was acidified with dilute acetic acid.

The crude product thereby obtained was recrystallised from an ethanol/dimethylformamide mixture.

Yield: 28% of theory.

Melting point: 162—164°C.

Example 5 (variant B).

9.8 g of 3-methylpyrazolin-5-one and 25.1 g of 2-(naphthyloxy)-ethyl bromide were thoroughly triturated and slowly heated to 110°C in a reaction vessel. The melt thereby produced was heated for a further 4 hours at approx. 110°C. The crystal paste obtained after cooling was dissolved in a hot mixture of dimethylformamide and ethanol. The crystals obtained after the solution had crystallised out were purified by a further recrystallisation.

Yield: 38%.

Melting point: 162—164°C.

Example 6 (variant C).

8.3 g (0.074 mol) of tetrolic acid ethyl ester and 14.8 g of 2-(β-naphthyloxy)-ethylhydrazine in 70 ml of n-butanol were heated for 8 hours under reflux.

The reaction solution was then concentrated and the solid residue was twice recrystallised from an ethanol/dimethylformamide mixture (10:1).

Yield: 45% of theory.

Melting point: 162—164°C.

Example 7 (variant C).

The compound according to the invention was obtained analogously to Example 4 from tetrolic acid methyl ester and 2-(β-naphthyloxy)-ethylhydrazine.

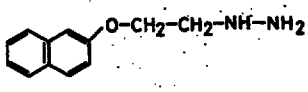
Example 8 (variant C).

On reacting tetrolic acid benzyl ester and 2-(β-naphthyloxy)-ethylhydrazine, the compound according to the invention was obtained in approx. 40% yield if the reaction was carried out in accordance with the conditions of Example 4.

WHAT WE CLAIM IS:—

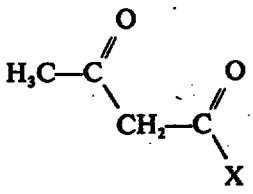
1. 1-(2-(β-Naphthyloxy)-ethyl)-3-methylpyrazolin-5-one or a salt thereof.
2. A compound according to claim 1 in the form of the sodium salt.
3. Any compound according to claim 1 specifically mentioned herein.
4. A process for the preparation of a compound according to claim 1 wherein

(A) 2-(β-naphthyloxy)-ethylhydrazine of the formula (II)



(II)

is reacted with an acetoacetic acid derivative of the formula (III)

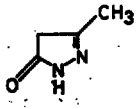


(III)

in which

X represents an alkoxy, aralkoxy, amino or alkylamino radical,

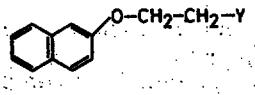
if appropriate in the presence of inert solvents and basic or acid catalysts, or (B) 3-methylpyrazolin-5-one of the formula (IV)



(IV)

* C L M S *

is reacted with a 2-(β-naphthyloxy)-ethyl derivative of the formula (V)

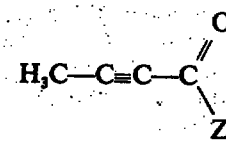


(V)

in which

Y represents a radical which is removed, such as halogen, or the dialkyloxonium, dialkylsulphonium or trialkylammonium radical or the arylsulphonic, alkylsulphonic or trifluoromethylsulphonic acid radical,

if appropriate in the presence of inert solvents and inorganic or organic bases, or (C) a tetrolic acid derivative of the formula (VI)



(VI)

in which

Z represents a hydroxyl, alkoxy, aralkoxy, amino or alkylamino radical, is reacted with 2-(β-naphthyloxy)-ethylhydrazine of the formula (II), if appropriate in the presence of inert solvents and inorganic or organic bases.

5. A process according to claim 4 wherein the reaction (A) is carried out at a temperature from 10 to 200°C.

6. A process according to claim 4 or claim 5 wherein X is an optionally substituted alkoxy group of from 1 to 4 carbon atoms, a benzyloxy group, an amino group or an alkylamino or dialkylamino group containing from 1 to 4 carbon atoms per alkyl group.

7. A process according to any one of claims 4 to 6 wherein the compound of the formula (II) and the compound of the formula (III) are reacted in equimolar quantities.

8. A process according to claim 4 wherein the reaction (B) is carried out at a temperature of from 10 to 200°C.

9. A process according to claim 4 or claim 8 wherein Y represents a chlorine or bromine atom or a dialkyloxonium, dialkylsulphonium or trialkylammonium radical in which the alkyl groups each contain from 1 to 4 carbon atoms.

10. A process according to any one of claims 4, 8 and 9 wherein the compound of the formula (IV) and the compound of the formula (V) are reacted in equimolar quantities.

11. A process according to claim 4 wherein the reaction (C) is carried out at a temperature of from 50 to 200°C.

12. A process according to claim 4 or claim 11 wherein Z represents an optionally substituted alkoxy radical of from 1 to 6 carbon atoms, a benzyloxy group or a mono- or dialkylamino group in which the or each alkyl group contains from 1 to 4 carbon atoms.

13. A process according to any one of claims 4, 11 and 12 wherein the compound of the formula (VI) and the compound of the formula (II) are reacted in equimolar quantities.

14. A process according to any one of claims 4 to 13 wherein the reaction is effected in an inert solvent.

15. A process according to any one of claims 4 to 14 wherein the said base is an alkali metal hydroxide, an alkali metal carbonate or an alkali metal alcoholate.

16. A process according to any one of claims 4 to 7 wherein the acidic catalyst is a hydrogen halide, sulphuric acid or a sulphonic acid.

17. A process for the production of a compound according to claim 1 substantially as hereinbefore described in any one of Examples 1 to 8.

18. Compounds according to claim 1 whenever prepared by a process according to any of claims 4 to 17.

19. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 3 and 18 in admixture with a solid or liquefied gaseous diluent or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 except in the presence of a surface-active agent.

20. A pharmaceutical composition containing as an active ingredient a

compound according to any one of claims 1 to 3 and 18 in the form of a sterile or isotonic aqueous solution.

21. A composition according to claim 19 or 20 containing from 0.5 to 95% by weight of the said active ingredient.

22. A medicament in dosage unit form comprising a compound according to any one of claims 1 to 3 and 18 either alone or in admixture with a diluent.

23. A medicament in the form of tablets, pills, dragees, capsules, ampoules, or suppositories comprising a compound according to any one of claims 1 to 3 and 18, either alone or in admixture with a diluent.

24. A method of combatting thrombembolic diseases in non-human animals which comprises administering to the animals an active compound according to any one of claims 1 to 3 and 18 either alone or in admixture with a diluent or in the form of a medicament according to claim 22 or 23.

25. A method according to claim 24 in which the active compound is administered in an amount of from 0.01 to 500 mg per kg body weight per day.

26. A method according to claim 24 or claim 25 in which the active compound is administered orally or parenterally.

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