PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 :		(11) International Publication Number:
C07D 233/64, A61K 31/415	A1	WO 89/10360
		(43) International Publication Date: 2 November 1989 (02.11.89)

(21) International Application Number: PCT/NL89/00019

(22) International Filing Date: 5 April 1989 (05.04.89)

(30) Priority data:
8800998 18 April 1988 (18.04.88) NL

(71) Applicant *(for all designated States except US):* CEDONA PHARMACEUTICALS B.V. [NL/NL]; Oudeweg 147, NL-2031 CC Haarlem (NL).

(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* ERIKS, John, Charles [NL/NL]; Driehuizerkerkweg 92, NL-1985 HC Driehuis (NL). VAN DER GOOT, Henderikus [NL/NL]; Grote Belt 193, NL-2133 GW Hoofddorp (NL). TIMMERMAN, Hendrik [NL/NL]; De Savorin Lohmanplantsoen 3, NL-2253 VM Voorschoten (NL). KOPER, Jan, Gijsbert [NL/NL]; Waardijnstraat 9, NL-1383 CG Weesp (NL).

(74) Agent: KOOY, L., W.; Octrooibureau Vriesendorp & Gaade, P.O. Box 266, NL-2501 AW The Hague (NL).

(81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), CF (OAPI patent), CG (OAPI patent), CH (European patent), CM (OAPI patent), DE (European patent), DK, FI, FR (European patent), GA (OAPI patent), GB (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, RO, SD, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.

Published
With international search report.

(54) Title: PROCESS FOR PREPARING A SUBSTITUTED OR AN UNSUBSTITUTED 4(5)-(ω-AMINOALKYL)IMIDAZOLE

(57) Abstract

A process for preparing a substituted or unsubstituted 4(5)-(ω-aminoalkyl)imidazole of formula (5), wherein n is 1 to 6, R_1 is hydrogen or a linear, branched or cyclic, saturated or unsaturated alkyl group having 1-6 C-atoms or a phenyl ring being unsubstituted, or mono- or di-substituted with groups such as lower alkyl, halogen, alkoxy, methylendioxy or a combination thereof, and R_2 is hydrogen or methyl, by brominating an ω-phthalimidoalkan-2-one with bromine in anhydrous methanol to a 1- or 3-bromo-ω-phthalimido-alkan-2-one, subjecting said derivative to ring closure with an amidine in N.N-dimethylformamide with potassium carbonate under mild conditions followed by hydrolytic separation of the phthalic residue.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**FR**	France	**ML**	Mali
AU	Australia	**GA**	Gabon	**MR**	Mauritania
BB	Barbados	**GB**	United Kingdom	**MW**	Malawi
BE	Belgium	**HU**	Hungary	**NL**	Netherlands
BG	Bulgaria	**IT**	Italy	**NO**	Norway
BJ	Benin	**JP**	Japan	**RO**	Romania
BR	Brazil	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SN**	Senegal
CH	Switzerland	**LI**	Liechtenstein	**SU**	Soviet Union
CM	Cameroon	**LK**	Sri Lanka	**TD**	Chad
DE	Germany, Federal Republic of	**LU**	Luxembourg	**TG**	Togo
DK	Denmark	**MC**	Monaco	**US**	United States of America
FI	Finland	**MG**	Madagascar		

Process for preparing a substituted or an unsubstituted 4(5)-(ω-aminoalkyl)imidazole.

The invention relates to a process for preparing a substituted or an unsubstituted 4(5)-(ω-aminoalkyl)-imidazole, by brominating an ω-phthalimidoalkan-2-one to a 1- or 3-bromo-ω-phthalimido-alkan-2-one, subjecting said derivative to ring closure with an amidine, followed by hydrolytic separation of the phthalic residue.
Such a process is already known from S.Elz and W.Schunack, Z.Naturforsch., 42b, 238-242 (1987).

Histamine H_2-receptor agonists, like Impromidine(1) described in Proc. VIIIth Internat. Symp.Med. Chem., Uppsala, pages 202-203 (1985), editors R. Dahlblom and J.L.G. Nilson, SK&E 91486 (2) described by M.E. Parsons et al., Agents and Actions. 5, 464 (1975) and N-(ω-substituted alkyl)-N'-{(imidazole-4-yl)-alkyl)} guanidines, described in Dutch patent application 86 01585 and indicated therein with formula 1, all contain under physiological conditions a protonated "substituted" N-{ω-(imidazole-4-yl)alkyl}guanidine fragment which is essential for the biological activity of this type of compounds.

For the preparation of these and other H_1 and H_2-receptor active compounds the 4(5)-(2-aminoethyl)imidazole or histamine (3) and 4(5)-(3-aminopropyl)imidazole(4), in general the substituted 4(5)-(ω-aminoalkyl)imidazoles (5) are of crucial importance as starting materials for the preparation of the above mentioned H_1 and H_2-receptor active compounds, so that in the field of pharmaceutical industry they are highly interested in the preparation of this kind of compounds, in view of pharmaceutical composition for the treatment of heart failures and allergic conditions.

Tedious syntheses of 4(5)-(3-aminopropyl)imidazole (4) starting from one of the two difficult obtainable compounds 4(5)-(2-bromoethyl)imidazolium bromide and 4(5)-(2-choloethyl)imidazolium chloride as described by W.Bloemhoff and K.E.T. Kerling, Rec.Trav.Chim., 89, 1181-1184 (1970), followed by chain extension with sodium cyanide or potassium cyanide and by reduction of the obtained nitrile with hydrogen and Raney Nickel catalyst as described in German Offenlegungsschrift 2 053 175, results in almost unacceptable low overall yields of the desired 4(5)-(3-aminopropyl)imidazole (4).

In the process described by S. Elz and W. Schunack Z.Naturforsch., 42b, 238-242 (1987) in the preamble, the bromination of 5-phthalimidopentane-2-one to 1-bromo-5-phthalimidopentane-2-one (6) is carried out in a b-butanol/methanol mixture with an equivalent bromo/dioxane complex which results in a yield of only 22%. The following ring closure in liquid NH_3 under elevated pressure, followed by isolation of the desired imidazole via the dipicrate is impracticable in large scale syntheses.

Preparation of the corresponding halogen compounds from the corresponding diazoketones as described by J.Michalsky, J. Borkovec and J.Hádacek, Chem.Listy Vedu Prum.49, 1979 (1955), cf. Chem.Abstr.50, 5681d (1956) does not lend itself for large scale syntheses, and the bromination as described by E.W. Garbisch Jr., J.Org.Chem. 30, 2109 (1965) for the 3-phthalimidopropan-2-one, according to M.Gall and B.V. Kamdar, J.Org.Chem.46, 1575-1585 (1981) does not lend itself for scale enlargement.

Alternatively the ring closure of a 1-bromo-ω-phthalimidoalkan-2-one with an amidine as mentioned for the preparation of 2-methylhistamine under the reaction conditions reported by Durant et al., J.Med.Chem., 19(7), 923-928 (1976) is not very advantageous due to low yields obtained in this procedure.

It was now found that with the process as described in the preamble a much higher yield can be reached than disclosed in the state of the art, when certain reaction conditions are taken into account towards bromination and the ring closure. In this process the bromination proceeds with great selectively, which enhances the yield highly, in addition the process is suitable for large scale application. The process is practical for a large number of compounds, among which histamine and its analogues, some of which even being novel.

The invention has the characterizing features that in a process as described in the preamble a substituted or unsubstituted 4(5)-(ω-aminoalkyl)imidazole of the formula 5 is prepared, wherein n is 1 to 6, R_1 is hydrogen or a linear, branched or cyclic, saturated or unsaturated alkyl group having 1-6 C-atoms or a phenyl ring being unsubstituted, mono- or di substituted with groups such as lower alkyl, nitro and/or amino, if any halogen, alkoxy, methylenedioxy or a combination thereof, and R_2 is hydrogen or methyl and the bromination with bromine is carried out in anhydrous methanol and the ring closure is carried in N.N-dimethylformamide with potassium carbonate under mild conditions.

The invention also relates to a pharmaceutical composition that contains a compound obtained according to the just described process.

The invention also relates to the use of said compound or pharmaceutical composition as obtained by the earlier mentioned method for the treatment of heart and vasculer diseases or allergic affections.

The present synthetic proceeds according to the annexed reaction scheme.

As starting materials serve in the above mentioned reaction scheme ω-phthalimido-2-alkanones (7) which can be prepared according to known literature methods.

The bromination of these ketones is performed according to the method for the selective bromination of 2-alkanones as mentioned by M. Gaudry and A.Marquet, Tetrahedron, 26, 5611-5615 (1970) which method gives significantly higher yields of the desired primary bromo compounds (10) in comparison with the method described by S. Elz and W. Schunack, Z.Natur.forsch.42b, 238-242 (1987).

Depending on the nature of the starting materials the intermediate bromo dimethyl acetals (8) and (9) are isolated and purified before hudrolysis, or the total reaction mixture is hydrolysed and the bromo ketones (10) and (11) are separated by fractional crystallization.

Although the secundary bromo ketones (11) are produced with low yields, they have been isolated from the reaction mixture to serve as starting material for the ring closure to 4-(ω-phthalimidoalkyl)-5-methylimidazoles (13) and alternatively they can be obtained in much higher yields by bromination in solvents like acetic acid.

The ring closure of the bromo ketones (10) and (11) together with lower alkane amidines or substituted benzamidines leading to the formation of 4(5)-(ω-phthalimidoalkyl)imidazoles (12) and corresponding methyl derivatives (13) is performed in N.N-dimethylformamide with potassium carbonate as proton acceptor under mild conditions.

Hydrolysis of the compounds (12) and (13) with diluted hydrochloric acid as described in U.S.patent specification 3 736 331, or hydrazinolysis with hydrazine hydrate as described by M.Gall and B.V.Kamdar, J.Org. Chem. 46, 1575-1585 (1981) provides 4(5)-(ω-aminoalkyl) imidazoles (5).

The invention is illustrated by the following examples.

All chemicals and solvents are commercially available unless otherwise stated.

Melting points were determined with a Mettler FP 52 melting point apparatus.

^{1}H-NMR-spectra were measured with a Bruker WH-90 spectrophotometer and chemical shifts δ (in ppm) are given relative to tetramethylsilane.

Mass spectra are recorded on a Varian Mat CH_5 spectrometer.

Example I

a. 4-Phthalimidobutan-2-one (7a)

The 4-phthalimidobutan-2-one is prepared according to a modified procedure as mentioned by H.Irai et al., Kogyo Kagaku Zasshi., 62, 82-85 (1959); cf. Chem.Abstr., 58, 5659b (1963).

To a well stirred suspension of 147 g (1 mole) of phthalimide and 70 g (1 mole) of methyl vinyl ketone in 1000 ml ethyl acetate is added under nitrogen a freshly prepared solution of 2.7 g (0.05 mole) of sodium methoxide in 250 ml anhydrous methanol.

After stirring for two hours at room temperature the mixture is heated until reflux remperature and refluxed until an almost clear solution is obtained and refluxing is continued for an additional two hours.

The solution is allowed to cool down and concentrated in vacuum and the residue is recrystallized from hot 96% ethanol.

Yield 90%.

Melting point 108.5-110.0°C (Lit: H.Irai et al., 111-113°C).

^{1}H-NMR ($CDCl_3$): 2.22 ppm., singlet, 3 H; 2.96 ppm.,triplet (J = 7 Hz),2 H; 3.96 ppm., triplet (J = 7 Hz), 2 H; 7.62-7.96 ppm., multiplet, 4 H.

b. 1-Bromo-4-phthalimidobutan-2-one (10a)

To a suspension of 130 g (0.6 mole) of 4-phthalimido butan-2-one (7a) in 1000 ml of absolute methanol is added 96 g (0.6 mole) of bromine and the reaction mixture is stirred for 24 hours at room temperature.

The precipitate, N-(4-bromo-3.3-dimethoxybutyl) phthalimide (8a) is filtered off, suspended in methanol and 30 ml of 10 N sulfuric acid is added, after which the reaction mixture is heated until a clear solution is obtained.

After cooling down the precipitate is collected and recrystallized from hot methanol.

Yield 60%.

Melting point: 120-122°C (lit: R.G.Jones et al., J.Am. Chem.Soc., 72, 4526-4529 (1950), 119-120°C).
^{1}H-NMR ($CDCl_3$): 3.13 ppm.,triplet, 2 H (J = 7.2 Hz); 3.92 ppm., singlet, 2 H; 4.04 ppm., triplet (J = 7.2 Hz), 2 H; 7.60-7.96 ppm., multiplet, 4 H.

c. 4(5)-(2-phthalimidoethyl)imidazole (12a)

A mixture of 29.6 g (0.1 mole) of 1-bromo-4-phthalimido- butan-2-one (10a), 10.4 g (0.1 mole) formamidine acetate, 27.6 g (0.2 mole) of carefully grounded anhydrous potassium carbonate and 150 ml of anhydrous N.N-dimethylformamide is slowly heated in a shaking autoclave for about 24 hours to 80°C.

After cooling down the solid inorganic materials are filtered off and the filtrate is concentrated in vacuum. To the residue 50 ml of xylene is added and again concentrated in vacuum to remove traces of N.N-dimethylformamide, after which the residue is taken up in 200 ml of ethyl acetate and extracted three times with 50 ml of demineralized water.

The organic layer is dried on anhydrous sodium sulfate, filtered and concentrated in vacuum.

The residue is taken up in aceton and a saturated solution of oxalic acid in aceton is added until no more precipitation occurs.

The precipitate is filtered off, washed with three portions of warm aceton and dried in vacuum.

Yield 60%.

Melting point: the oxalate decomposes on heating.
^{1}H-NMR*| ($CDCl_3$/d_6-DMSO): 2.91 ppm., triplet (J = 7.2 Hz), 2 H; 3.96 ppm., triplet (J = 7.2 Hz), 2 H; 6.84 ppm., singlet, 1 H; 7.63 ppm., singlet, 1 H; 7.74 ppm., broad singlet, 4 H; 8.12 ppm., broad singlet, 1 H. *| free base

d. 4(5)-(2-Aminoethyl)imidazoledihydrochloride (histaminedihydrochloride) (5a)

The 4(5)-(2-aminoethyl)imidazole dihydrochloride is prepared by hydrolysis of 4(5)-(2-phthalimidoethyl) imidazole (12a) according to U.S. patent specification 3 736 331.

A solution of 16.55 g (0.05 mole) of 4(5)-(2-phthalimidoethyl)imidazole (12a) oxalate is dissolved in 200 ml of distilled water and brought on pH = 12 with a diluted sodium hydroxide solution. The base is extracted with ethyl acetate, and the organic layer is dried on anhydrous sodium sulfate, filtered and concentrated in vacuum.

The residue is hydrolysed by refluxing with 5 N hydrochloric acid and after cooling down the volume is reduced in vacuum, the phthalic acid is filtered off and the filtrate is concentrated to dryness, after which the residue is recrystallized from hot ethanol.

Yield 85%.

Melting point 249-252°C.

^{1}H-NMR (D_2O): 3.38-3.80 ppm.,multiplet, 4 H; 7.72 ppm., doublet (J = 0.6 Hz), 1 H; 8.98 ppm., doublet (J = 1 Hz), 1 H.

Example II

a. 5-Phthalimido pentan-2-one (7b)

5-Phthalimidopentan-2-one is prepared according to a modified procedure as mentioned by M.Sletzinger et al., Chem. & Ind. (London),1957, 1215.

A mixture of 294 g (2 moles) of phthalimide, 241 g (2 moles) of 5-chloropentan-2-one and 198 g (2 moles) of carefully grounded anhydrous potassium carbonate in

1000 ml of anhydrous N.N-dimethylformamide was heated while stirring for a period of 12 hours at 110°C.

After cooling down the inorganic solids were filtered off and the filtrate was concentrated in vacuum.

The residue was dissolved in 500 ml ethyl acetate and after standing overnight at 0°C the unreacted phthalimide was filtered off, the filtrate was concentrated in vacuum and the residue was recrystallize from hot methanol.

Yield 53%.

Melting point: 72-74 °C (Lit: M. Sletzinger et al., 75-77°C; S. Elz and W.Schunack, Z.Natur.Forsch., 42b, 238-242 (1987), 71-72°C).

^{1}H-NMR ($CDCl_3$): 1.89-2.12 ppm., multiplet, 2 H; 2.15 ppm., singlet, 3 H; 2.51 ppm., triplet (J = 7.2 Hz), 2 H; 3.72 ppm., triplet (J = 6.6 Hz), 2 H; 7.67-7.92 ppm., multiplet, 4 H.

b. 1-Bromo-5-phtalimidopentan-2-one (10b)

To a solution of 231 g (1 mole) of 5-phtalimidopentan-2-one (7b) in 1350 ml of anhydrous methanol was added at 0°C in one portion 160 g (1 mole) of bromine.

While stirring, the mixture was allowed to warm up to ambient temperature and stirring was continued for an additional 24 hours.

To the clear solution 200 ml of 10 N sulfuric acid was added and the reaction mixture was left overnight.

The precipitate was collected, suspended in 500 ml of methanol and refluxed for 15 minutes and the

crystalline material was filtered off while hot, washed with two portions of 100 ml of hot methanol and dried in vacuum.

Yield 52%.

Melting point: 131-133.4°C (Lit: S.Elz and W.Schunack, Z.Natur.forsch. 42b, 238-242 (1987), 122-125°C, J. Michalksky et al., Chem.Listy, 49, 1379-1384 (1955), cf. Chem.Abstr. 50, 5681 d (1956), 139°C.

^{1}H-NMR ($CDCl_3$): 1.82-2.24 ppm., multiplet, 2 H; 2.74 ppm., triplet (J = 7.2 Hz), 2 H; 3.74 ppm.,triplet (J = 7.2 Hz), 2 H; 3.94 ppm., singlet, 2 H; 7.64-7.88 ppm., multiplet, 4 H.

c. 4(5)-(3-Phthalimidopropyl)imidazole (12b)

A mixture of 114.0 g (0.37 mole) of 1-bromo-5-phthalimidopentan-2-one (10b), 38.3 g (0.37 mole) of formamidine acetate, 101.5 g (0.74 mole) of carefully grounded anhydrous potassium carbonate and 500 ml of anhydrous N.N-dimethylformamide is slowly heated in a shaking autoclave for 24 hours at 80°C. After cooling down the solid inorganic materials are filtered off and the filtrate is concentrated in vacuum. To the residue 200 ml of xylene is added and it is again concentrated in vacuum to remove traces of N.N-dimethylformamide,after which the residue is taken up in 750 ml of ethyl acetate and is extracted three times with 100 ml of demineralized water.

The organic layer is dried on anhydrous sodium sulfate, filtered and concentrated in vacuum.

The residue is taken up in aceton and a saturated solution of oxalic acid in aceton is added until no more

precipitation occurs.

The precipitate is filtered off, washed with warm aceton and dried in vacuum.

Yield 55%.

Melting point: the oxalate decomposes on heating. ^{1}H-NMR* ($CDCl_3$): 1.80-2.12 ppm., quintet (J = 7.2 Hz), 2 H; 2.60 ppm., triplet (J = 7.2 Hz), 2 H; 3.68 ppm., triplet (J = 7.2 Hz), 2 H; 6.81 ppm., singlet, 1 H; 7.54 ppm., singlet, 1 H; 7.54-7.85 ppm., multiplet, 4 H. Position of NH-proton strongly depends on concentration.

* free base.

d. 4(5)-(3-Aminopropyl)imidazole dihydrochloride (5b)

4(5)-(3-aminopropyl)imidazole (5b) dihydrochloride is prepared by hydrolysis of 4(5)-3-phthalimidopropyl)-imidazole (12b) according to U.S.patent specification 3 736 331.

A solution of 17.25 g (0.05 mole) of 4(5)-(3-phthalimidopropyl)imidazole (12b) oxalate is prepared in 200 ml of distillated water and brought on pH = 12 with a diluted sodium Hydroxide solution. The base is extracted with ethyl acetate and the organic layer is dried on anhydrous sodium sulfate, filtered and concentrated in vacuum.

The residue is hydrolysed by refluxing with 5 N hydrochloric acid and after cooling down the volume is reduced in vacuum, the phthalic acid is filtered off and the filtrate is concentrated to dryness, after which the residue is recrystallized from ethanol/ether.

Yield 92%.

Melting point: 154-155°C (Lit: J.W. Black et al, U.S. patent specification 3 736 331, 156°-158°C).
^{1}H-NMR (d_6-DMSO): 1.80-2.13 ppm.,multiplet, 2 H: 2.80 ppm., broad triplet (J = 7.2 Hz), 4 H; 2.8 H; 7.52 ppm., doublet (J = 0.6 Hz), 1 H; 8.30 ppm., broad singlet, 2.6 H, 9.14 ppm., doublet (J = 1 Hz), 1 H.

Example III

3-Bromo-4-phthalimidobutan-2-one (11b)

The filtrate obtained after the removal of N-(4-bromo-3.3-dimethoxybutyl)phthalimide (8a) in example Ib is treated with diluted sulfuric acid and worked up as mentioned for the preparation of 1-bromo-4-phthalimido-butan-2-one (10a) in the same example.

Yield 30%.

Melting point: 104°-105°C.
^{1}H-NMR ($CDCl_3$): 2.46 ppm., singlet, 3 H; 4.16-4.28 ppm., double doublet, 2 H; 4.76-4.92 ppm., broad triplet, 1 H; 7.71-7.95 ppm., multiplet, 4 H.

Example IV

a. 3-Bromo-5-phthalimidopentan-2-one (11b)

The mother liquor obtained after the filtration of the 1-bromo-5-phthalimidopentan-2-one (10b) in example IIb was concentrated to approximately half of its original volume and the precipitate was filtered off and recrystallized from hot methanol.

Yield 35%.

Melting point 99.0°-100.7°C.
^{1}H-NMR ($CDCl_3$): 2.22-2.70 ppm., multiplet, 2 H; 2.42 ppm.,

singlet, 3 H; 3.80 ppm., triplet (J = 6.6 Hz), 2 H; 4.34 ppm., triplet (J = 7.2 Hz), 1 H; 7.66-7.90 ppm., multiplet, 4 H.

Mass spectrum M/Z (% rel., fragm.): 267(20) 230(99), 188(47), 174(52), 161(94), 160(100), 148(23), 133(20), 104(43).

M^+ = M/Z 309.0006 calculated $C_{13}H_{12}BrNO_3$ 309.0001

b. 4-methyl-5(2-phthalimidoethyl)imidazol

A mixture of 31.0 g (0.1 mole) of 3-bromo-5-phthalimidopentan-2-one (11b), 10.4 g (0.1 mole) of formamidine acetate, 27.6 g (0.2 mole) of carefully grounded anhydrous potassium carbonate and 150 ml of anhydrous N.N-dimethylformamide is heated in a shaking autoclave at 80°C for 24 hours.

After cooling down the solid inorganic materials are filtered off and the filtrate is concentrated in vacuum. To the residue 50 ml of xylene is added and it is again concentrated in vacuum to remove traces of N.N-dimethylformamide, after which the residue is taken up in 200 ml of ethyl acetate and extracted three times with 50 ml of demineralized water.

The organic layer is dried on anhydrous sodium sulfate, filtered and concentrated in vacuum.

The residue is taken up in aceton and the mixture is allowed to crystallize.

The precipitate is filtered off, washed with 3 portions of warm aceton and dried in vacuum.

Yield 70%.

Melting point: 197.0°-198.5°C.

^{1}H-NMR ($CDCl_3/d_6$-DMSO): 2.10 ppm., singlet, 3 H; 2.90 ppm., triplet (J = 7.2 Hz), 2 H; 3.90 ppm., triplet

(J = 7.2 Hz), 2 H; 7.40 ppm, singlet, 1 H; 7.43 ppm., singlet, 0.7 H; 7.64-7.85 ppm., multiplet, 4 H.
Mass spectrum M/Z (% rel., fragm.): 255(37), 230(5), 174(52), 160(33), 108(100), 95(92).
M^+ = M/Z 255.1021 calculated $C_{14}H_{13}N_3O_2$ 255.1008.

c. 4-(2-Aminoethyl)-5-methylimidazole dihydrochloride (5c)

4-2-Aminoethyl)-5-methylimidazole dihydrochloride is prepared by hydrolysis of 4-methyl-5(2-phthalimidoethyl) imidazole (13a) according to U.S. patent specification 3 736 331.

A solution of 15.3 g (0.06 mole) 4-(2-phthalimidoethyl)-5-methylimidazole (13a) in 150 ml 5N hydrochloric acid is heated under reflux for 5 hours and after cooling down the volume is reduced in vacuum, the phthalic acid is filtered off and the filtrate is concentrated to dryness, after which the residue is recrystallized from ethanol/ether.

Yield 86%.
Melting point: hydrochloride decomposes on heating.
^{1}H-NMR (D_2O/DMSO) : 2.15 ppm., singlet, 3 H; 3.25-3.70 ppm., broad singlet, 4 H; 7,40 ppm., singlet, 1 H.

Example V

a. 2.5-dimethyl 4-(2-phthalimidoethyl) imidazole (13b)

A mixture of 31.0 g (0.1 mole) of 3-bromo-5-phthalimidopentan-2-one (11b), 11.8 g (0.1 mole) of acetamidine acetate, 27.6 g (0.2 mole) of carefully grounded anhydrous potassium carbonate and 150 ml of anhydrous N.N-dimethylformamide is heated in a shaking autoclave at 80°C for 24 hours.

After cooling down the solid organic materials are filtered off and the filtrate is concentrated in vacuum. To the residue 50 ml of xylene is added and it is again concentrated in vacuum to remove traces of N.N-dimethylformamide, after which the residue is taken up in 200 ml of ethyl acetate and extracted three times with 50 ml of demineralized water.

The organic layer is dried on anhydrous sodium sulfate, filtered and concentrated in vacuum.

The residue is taken up in aceton and a saturated solution of oxalic acid in aceton is added until no more precipitation occurs.

The precipitate is filtered off, washed with three portions of warm aceton and dried in vacuum.

Yield 40%.

Melting point: the oxalate decomposes on heating.

^{1}H-NMR* ($CDCl_3$/d_6-DMSO): 2.10 ppm., singlet, 3 H; 2.25 ppm., singlet, 3 H; 2.90 ppm., triplet (J = 7.2 Hz), 2 H; 3.90 ppm., triplet (J = 7.2 Hz), 2 H; 7.43 ppm., singlet, 0.7 H; 7.64-7.85 ppm., multiplet, 4 H.

*free base

b. 4-(2-Aminoethyl)-2.5-dimethylimidazole dihydrochloride (5d).

4-(2-Aminoethyl)-5-methylimidazole dihydrochloride (5d) is prepared by hydrolysis of 2.5-dimethyl 4-(2-phthalimidoethyl)-imidazole (13b) according to U.S.patent specification 3 736 331.

A solution of 9.4 g (0.035 mole) 2.5-dimethyl 4(2-phthalimidoethyl)-imidazole (13b) oxalate in 200 ml distilled water is brought on pH = 12 with diluted sodium hydroxide solution. The base is extracted with ethyl acetate and

the organic layer is dried on anhydrous sodium sulfate, filtered and concentrated in vacuum.

The residue is hydrolysed by refluxing with 5 N hydrochloric acid and after cooling down the volume is reduced in vacuum, the phtalic acid is filtered off and the filtrate is concentrated to dryness, after which the residue is recrystallized from ethanol/ether.

Yield 91%.

Melting point: the hydrochloride decomposes on heating.

^{1}H-NMR (D_2O/DMSO): 2.10 ppm., singlet, 3 H; 2.38 ppm, singlet, 3 H; 3.23-3.65 ppm., broad singlet, 4 H.

Example VI

a. 2-Phenyl-4(5)-(2-phthalimidoethyl)imidazole-hydrochloride (13c)

A mixture of 12.0 g (0.1 mole) benzamidine, 29.6 g (o.1) mole 1-bromo-4-phthalimidobutan-2-one (10a), 27.6 g (0.2 mole) of carefully grounded anhydrous potassium carbonate and 125 ml of anhydrous N.N-dimethylformamide is heated under stirring at 35°C for 24 hours, after which it is subsequently heated at 50°C for 2 hours.

After cooling down the reaction mixture is concentrated in vacuum, after which to the residue demineralized water is added. Subsequently it is extracted 3 times with 50 ml ethyl acetate, the combined organic phases are collected, dried on anhydrous sodium sulfate, filtered and concentrated in vacuum.

To the residue a circa 3% -hydrochloric acid-solution is added and under stirring carefully heated to 40°C. After cooling down the precipitate is filtered off and dried in vacuum, after which it is crystallized from

methanol.

Yield 40%.

Melting point: 222.0-225.0°C (dec.)

^{1}H-NMR (d_6-DMSO): 3.23 ppm., triplet (J = 7.5 Hz), 2 H, 4.13 ppm., triplet (J = 7.5 Hz), 2 H; 7.60-7.87 ppm., multiplet, 4 H; 8.00 ppm., singlet, 4 H; 8.20-8.40 ppm., multiplet, 2 H; 15.17 ppm., broad singlet, 1.4 H.

b. 4(5)-(2-aminoethyl)2-phenyl-imidozole-dihydro chloride (5e)

A solution of 12.4 g (0.035 mole) 2-phenyl-4(5)-(2-phthalimidoethyl)imidoethyl)imidazole hydrochloride (13c) and 8.8 g (0.175 mole) hydrazine hydrate in 150 ml absolute ethanol is heated under reflux for 5 hours.

After cooling down and after standing overnight the crystalline material is filtered off, after which the filtrate is concentrated in vacuum.

The residue was taken up in 50 ml of absolute ethanol and by means of a concentrated hydrochloric acid solution acidified to acid reaction, after which the precipitate is filtered off.

Subsequently the precipitate is recrystallized from ethanol/water.

Yield 85%.

Melting point: 268.9-271.0°C (dec.)

^{1}H-NMR(d_6-DMSO): 3.00-3.50 ppm., multiplet, 4 H; 7.50-7.75 ppm., multiplet, 4 H; 8.00-8.55 ppm., multiplet, 5 H; 15.16 ppm., broad singlet, 2 H.

Example VII

a. 2-(4-chlorophenyl)-4(5)-(2-phthalimidoethyl)-imidazole hydrochloride (13d)

A mixture of 15.4 g (0.1 mole) of 4-chlorobenzamidine, 29.6 g (0.1 mole) of 1-bromo-4-phthalimidobutan-2-one (10a), 27.6 g (0.2 mole) of carefully grounded anhydrous potassium carbonate and 125 ml anhydrous N.N-dimethyl formamide is heated while stirring at 35°C for 24 hours, after which heating at 50° is continued for 2 hours.

After cooling down the reaction mixture is concentrated in vacuum, after which demineralized water is added to the residue.

Subsequently there is extracted three times with 50 ml of ethyl acetate, the combined organic phases are collected, dried on anhydrous sodium sulfate, filtered and concentrated in vacuum.

To the residue a circa 3% -hydrochloric acid-solution is added and while stirring carefully heated to 40°C.

After cooling down the precipitate is filtered off and dried in vacuum, after which it is crystallized from an ethanol/ether mixture.

Yield 54%.

Melting point: 250°C (dec.)

^{1}H-NMR (d_6-DMSO): 3.15 ppm., triplet (J = 7.5 Hz), 2 H; 4.00 ppm., triplet (J = 7.5 Hz), 2 H; 7.70-8.20 ppm., multiplet, 9 H; 14.50 ppm., broad singlet, 2 H.

b. 4(5)-(2-Aminoethyl)-2-(4-chlorophenyl)-imidazole dihydrochloride (5f)

A solution of 19.4 g (0.050 mole) of 2-(4-chlorophenyl)-4(5)-(2-phthalimidoethyl)imidazole hydrochloride (13d) and 12.5 g (0.0250 mole) of hydrazine hydrate in 150 ml of absolute ethanol is heated under reflux for

5 hours.

After cooling down and after standing overnight the crystalline material is filtered off, after which the filtrate is concentrated in vacuum.

The residue is subsequently taken up in 50 ml of absolute ethanol and by means of concentrated hydrochloric acid solution acidified to acid reaction, after which the precipitate is filtered off.

Thereafter recrystallisation takes place from an ethanol/water mixture.

Yield 92%

Melting point: 191.3-195.6°C (dec.)

^{1}H-NMR (d_6-DMSO): 2.90-3.60 ppm., multiplet, 4 H; 7.50 ppm., singlet, 1 H; 7.80 ppm., doublet (J = 9.0 Hz), 2 H; 7.90-8.20 ppm., broad multiplet, 5 H; 15.10 ppm., broad singlet, 2 H.

Example VIII

a. 2-(4-methoxyphenyl)4(5)-(2-phthalimidoethyl)-imidazole hydrochloride (13e)

A mixture of 15.0 g (0.1 mole) of 4-methoxybenzamidine, 29.6 g (0.1 mole) of 1-bromo-4-phthalimidobutan-2-one (10a), 27.6 g, (0.2 mole) of carefully grounded anhydrous potassium carbonate and 125 ml of anhydrous N.N-dimethyl formamide is heated while stirring at 35°C for 24 hours, after which the heating is continued at 50°C for 2 hours.

After cooling down the reaction mixture is concentrated in vacuum, after which to the residue demineralized water is added.

There is extracted three times with 50 ml ethyl acetate, the combined organic phases are collected, dried

SUBSTITUTE SHEET

on anhydrous sodium sulfate, filtered and concentrated in vacuum. To the residue a circa 3% - hydrochloric acid solution is added and carefully heated while stirring to 40°C. After cooling down the precipitate is filtered off and dried in vacuum, after which it is crystallized from an ethanol/ether mixture.

Yield 50%

Melting point: 191.3 - 195.6°C (dec.)

^{1}H-NMR (d_6-DMSO): 2.90-3.60 ppm., multiplet, 4 H; 7.50 ppm., singlet, 1 H; 7.80 ppm., doublet (J = 9.0 Hz), 2 H; 7.90 - 8.20 ppm., broad multiplet, 5 H; 15.10 ppm., broad singlet, 2 H.

Example VIII

4(5)-2-Aminoethyl)-2-(4-methoxyphenyl) imidazole dihydrochloride (5g)

A solution of 17.3 g (0.0045 mole) of 4(5)-2-(4-methoxyphenyl)-(2-phthalimidoethyl)imidazole hydrochloride (13e) and 11.3 g (0.225 mole) of hydrazine hydrate in 150 ml of absolute ethanol is heated under reflux for 5 hours.

After cooling down and after standing overnight the crystalline material is filtered off, after which the filtrate is concentrated in vacuum.

The residue is taken up in 50 ml of absolute ethanol and acidified by means of a concentrated hydrochloric acid solution to acid reaction, after which the precipitate is filtered off. Thereafter there is crystallized from an ethanol/water mixture.

Yield 80%.

Melting point: 219.0 - 221.5°C

^{1}H-NMR (d_6-DMSO): 3.06 - 3.57 ppm., broad triplet, 4 H; 4.00 ppm., singlet, 3 H; 7.32 ppm., doublet (J = 9.0 Hz) 2 H; 7.67 ppm., singlet, 1 H; 8.19 - 8.63 ppm., broad singlet, 3 H; 8.35 ppm., doublet (J = 9.0 Hz), 2 H; 15.06 ppm., broad doublet, 2 H.

Example IX

a. 2-(3.4-methylene-dioxyphenyl)4(5)-(2-phthal-imidoethyl)-imidazole hydrochloride (13f)

A mixture of 16.4 g (0.1 mole) of 3.4-methylene-dioxybenzamidine, 29.6 g (0.1 mole) of 1-bromo-4-phthal-imidobutan-2-one (10a), 27.6 g(0.2 mole) of carefully grounded anhydrous potassium carbonate and 125 ml of anhydrous N.N-dimethyl formamide is heated while stirring at 35°C for 24 hours, after which the heating is continued at 50°C for 2 hours.

After cooling down the reaction mixture is concentrated in vacuum, after which to the residue demineralized water is added. The residue is extracted three times with 50 ml of ethyl acetate, the combined organic phases are collected, dried on anhydrous sodium sulfate, filtered and concentrated in vacuum.

To the residue a circa 3% - hydrochloric acid solution is added, while stirring it is carefully heated to 40°C.

After cooling down the precipitate is filtered off and dried in vacuum. after which it is crystallized from an ethanol/ether mixture.

Yield 55%.

Melting point 241.8-245.9°C (dec.).

^{1}H-NMR (d_6-DMSO): 3.12 ppm., triplet (J = 7.5 Hz), 2 H; 4.05 ppm., triplet (J = 7.5 Hz), 2 H; 6.27 ppm., singlet, 2 H; 7.28 ppm., doublet (J = 9.0 Hz), 1 H; 7.60 ppm., singlet, 1 H; 7.66 ppm., multiplet, 3 H; 7.93 ppm., singlet, 4 H; 14.85 ppm., broad singlet, 2 H.

b. 4(5)-(2-Aminoethyl)-2-(3.4-methylenedioxy-phenyl)imidazole dihydrochloride (5h)

A solution of 19.9 g (0.050 mole) or 2-(3.4-methylene dioxyphenyl)4(5)-(2-phthalimidoethyl) imidazole hydrochloride (13f) and 12.5 g (0.025 mole) of hydrazinehydrate in 150 ml of absolute ethanol is heated under reflux for 5 hours.

After cooling down and after standing overnight the crystalline material is filtered off, after which the filtrate is concentrated in vacuum.

The residue is taken up in 50 ml of absolute ethanol and acidified with the aid of a concentrated hydrochloric acid solution to acid reaction, after which the precipitate is filtered off.

Then the residue is recrystallized from an ethanol/water mixture.

Yield 90%

Melting point: 250.0 - 255.0°C (dec.)

^{1}H-NMR (d_6-DMSO): 2.86 - 3.60 ppm., multiplet, 4 H; 6.16 ppm., singlet, 2 H; 7.16 ppm., doublet (J = 9.0 Hz), 1 H; 7.50 ppm., singlet, 1 H; 7.88 ppm., doublet (J = 9.0 Hz), 1 H; 8.00 ppm., singlet, 1 H; 8.40 ppm., broad singlet, 3 H; 15.27 ppm., broad singlet, 1 H.

Example X

a. 2-(3,4-dimethoxy-phenyl)imidazole 4(5)-(2-phthalimidoethyl) hydrochloride (13g)

A mixture of 18.0 g (0.1 mole) of 3.4-dimethoxy-benzamidine, 29.6 g (0.1 mole) of 1-bromo-4-phthal-imidobutan-2-one (10a), 27.6 g (0.2 mole) of carefully grounded anhydrous carbonate and 125 ml of

SUBSTITUTE SHEET

of anhydrous N.N-dimethylformamide is heated while stirring at 35°C for 24 hours, after which the heating is continued at 50°C for 2 hours.

After cooling down the reaction mixture is concentrated in vacuum, after which to the residue demineralized water is added.

The residue is extracted three times with 50 ml ethyl acetate. the combined organic phases are collected, dried on anhydrous sodium sulfate, filtered and concentrated in vacuum.

To the residue a circa 3% - hydrochloric acid solution is added and carefully heated while stirring to 40°C.

After cooling down the precipitate is filtered off and dried in vacuum, after which it is crystallized from an ethanol/ether mixture.

Yield 52%

Melting point: 208.5-211.9°C (dec.)

^{1}H-NMR (d_6-DMSO): 3.14 ppm., triplet (J = 7.5 Hz), 2 H; 3.50-4.40 ppm., broad multiplet, 8 H; 7.20-8.20 ppm., multiplet, 7 H; 15.00 ppm., broad singlet, 2 H.

b. 4(5)-(2-Aminoethyl)-2-(3.4-dimethoxyphenyl)-imidazole dihydrochloride (5i)

A solution of 20.7 g (0.050 mole) 2-(3.4-dimethoxyphenyl)4(5)-(2-phthalimidoethyl) imidazole hydrochloride (13 g) and 12.5 g (0.25 mole) hydrazine hydrate in 150 ml of absolute ethanol is heated under reflux for 5 hours.

After cooling down and after standing overnight the crystalline material is filtered off, after which the filtrate is concentrated in vacuum.

The residue is taken up in 50 ml of absolute ethanol and with a concentrated hydrochloric acid solution acidified to acid reaction, after which the precipitate is filtered off.

Then the residue is recrystallized from an ethanol/water mixture.

Yield 85%.

Melting point: 264.8°-265.8°C (dec.)

^{1}H-NMR (d_6-DMSO): 2.90-3.51 ppm., broad triplet, 4 H; 3.88 ppm., singlet, 3 H; 3.92 ppm., singlet, 3 H; 7.20 ppm., doublet (J = 9.0 Hz, 1 H; 7.53 ppm., singlet, 1 H; 7.87 ppm., doublet (J = 9.0 Hz), 1 H; 8.05 ppm., singlet, 1 H; 8.25 ppm., broad singlet, 3 H; 15.00 ppm., broad doublet, 2 H.

Example XI

a. 2-(4-methylphenyl)-4(5)-(2-phthalimidoethyl) imidazole hydrochloride (13h).

A mixture of 13.4 g (0.1 mole) 4-methyl benzamidine, 29.6 g (0.1 mole) 1-bromo-4-phthalimido-butan-2-one (10a), 27.6 g (0.2 mole) of carefully grounded anhydrous potassium carbonate and 125 ml of anhydrous N.N-dimethylformamide is heated while stirring at 35°C for 24 hours, after which the heating is continued at 50°C for 2 hours.

After cooling down the reaction mixture is concentrated in vacuum, after which demineralized water is added to the residue.

The residue is three times extracted with 50 ml ethyl acetate, the combined organic phases are collected, dried on anhydrous sodium sulfate, filtered and concentrated in vacuum.

To the residue a circa 3% -hydrochloric acid solution is added and carefully heated under stirring to

40°C.

After cooling down the precipitate is filtered off and dried in vacuum, after which it is crystallized from an ethanol/ether mixture.

Yield 60%.

Melting point: 238°C (dec.)

^{1}H-NMR (d_6-DMSO): 2.40 ppm., singlet, 3 H; 3.23 ppm., triplet, (J = 7.5 Hz), 2 H; 4.15 ppm., triplet (J = 7.5 Hz), 2 H; 7.49 ppm., doublet (J = 9.0 Hz), 2 H; 7.71 ppm., doublet (J = 9.0 Hz), 2 H; 7.80-8.10 ppm., broad singlet, 5 H; 15.15 ppm., broad singlet, 2 H.

b. 4(5)-(2-Aminoethyl)2-(4-methylphenyl) imidazole dihydrochloride (5j)

A solution of 18.4 g (0.050 mole) 2-(4-methylphenyl) 4(5)-(2-phthalimidoethyl) imidazole hydrochloride (13h) and 12.5 g (0.25 mole) of hydrazine hydrate in 150 ml of absolute ethanol is heated under reflux for 5 hours.

After cooling down and after standing overnight the crystalline material is filtered off, after which the filtrate is concentrated in vacuum.

The residue is taken up in 50 ml of absolute ethanol and with a concentrated hydrochloric acid solution acidified to acid reaction, after which the precipitate is filtered off.

Then the precipitate is recrystallized from an ethanol/water mixture.

Yield 80%.

Melting point: 232.2-236.5°C (dec.)

^{1}H-NMR (D_2O): 2.42 ppm., singlet, 3 H; 3.04-3.54 ppm., multiplet, 4 H; 7.38 ppm., singlet, 1 H; 7.47 ppm., doublet (J = 9.0 Hz), 2 H; 7.76 ppm., doublet (J = 9.0 Hz), 2 H.

CLAIMS

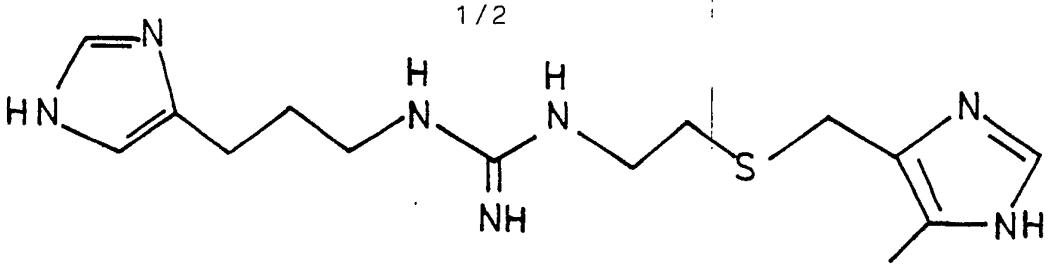
1. A process for preparing a substituted or an unsubstituted 4(5)-(ω-aminoalkyl)imidazole, by brominating an ω-phthalimidoalkan-2-one to a 1- or 3-bromo-ω-phthalimido-alkan-2-one, subjecting said derivative to ring closure with an amidine, followed by hydrolytic separation of the phthalic residue, characterized in that a substituted or unsubstituted 4(5)-(ω-aminoalkyl)imidazole of the formula 5 is prepared, wherein n is 1 to 6, R_1 is hydrogen or a linear, branched or cyclic, saturated or unsaturated alkyl group having 1-6 C-atoms or a phenyl ring being unsubstituted, mono- or di-substituted with groups such as lower alkyl, halogen, alkoxy, methylenedioxy or a combination thereof, and R_2 is hydrogen or methyl and the bromination with bromine is carried out in anhydrous methanol and the ring closure is carried our in N.N-dimethylformamide with potassium carbonate under mild conditions.

2. New compounds of the formula 5 as defined in claim 1, which may be produced according to the process of claim 1.

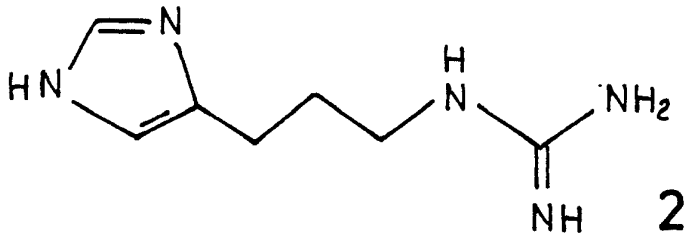
3. Pharmaceutical composition, characterized in that it contains a new compound according to claim 2.

4. Pharmaceutical composition, characterized in that it contains a compound as obtained according to the process of claim 1.

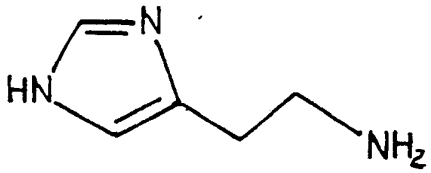
5. Use of a compound or pharmaceutical composition according to any of the preceding claims, for the treatment of heart failures or allergic conditions.



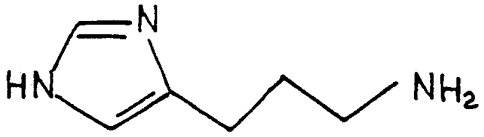
1



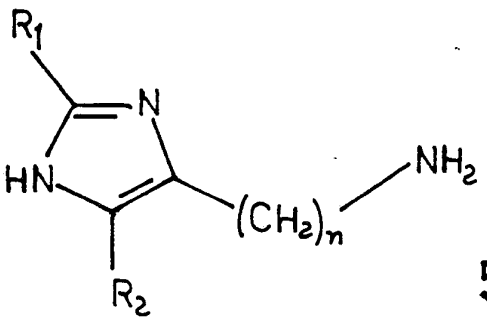
2



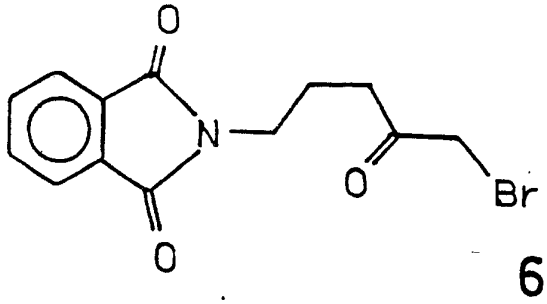
3



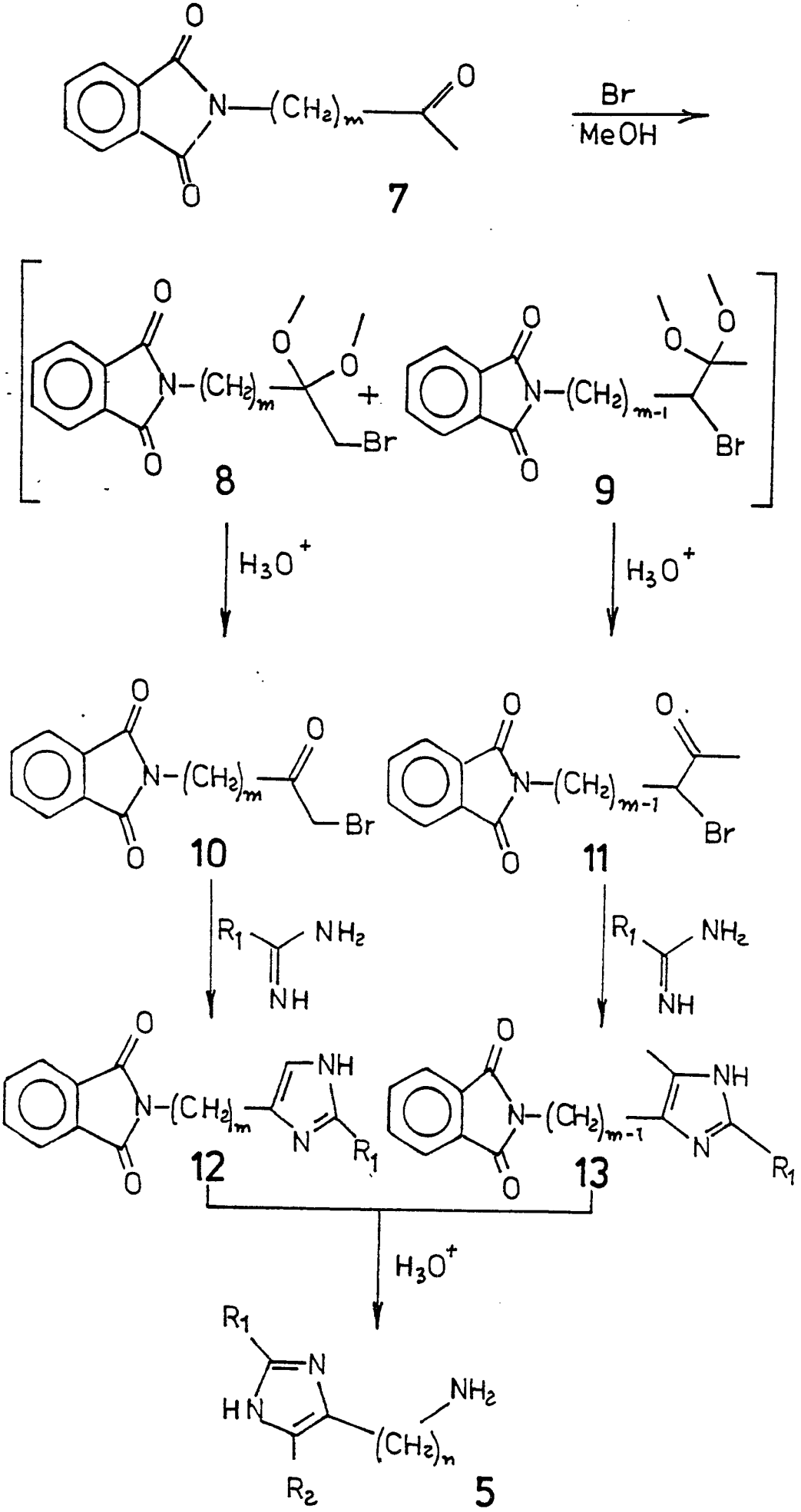
4



5



6


Br
MeOH
7
8
9
H_3O^+
H_3O^+
10
11
R_1 NH_2 NH
R_1 NH_2 NH
12
13
H_3O^+
R_1 N HN NH_2 $(CH_2)_n$ R_2
5

INTERNATIONAL SEARCH REPORT

International Application No PCT/NL 89/00019

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 D 233/64, A 61 K 31/415

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	C 07 D 233/00, A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	Zeitschrift für Naturforschung B, vol. 42, no. 2, 1 February 1987, Verlag der Zeitschrift für Naturforschung (Tübingen, DE), Sigurd Elz: "Eine alternative Synthese von Homohistamin und strukturverwandten (Imidazol-4-yl)alkylaminen", pages 238-242, see the whole article cited in the application --	
A	Tetrahedron, vol. 26, no. 23, 1 December 1970, Pergamon Press (Oxford, GB), M. Gaudry et al.: "Enolisation des cetones dissymétriques-III. Accès facile aux bromométhylcétones par bromation en présence de méthanol", pages 5611-5615, see the whole article cited in the application --	

./.

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
5th July 1989	03. 08. 89
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. VAN MOL

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	US, A, 3736331 (SMITH KLINE & FRENCH LABORATORIES) 29 May 1973 cited in the application	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. NL 8900019 SA 27990

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 28/07/89
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 3736331	29-05-73	US-A- 3881015	29-04-75
		BE-A- 758146	28-04-71
		CA-A- 954522	10-09-74
		CA-A- 945171	09-04-74
		CA-A- 983853	17-02-76
		CH-A- 529751	31-10-72
		CH-A- 544087	28-12-73
		DE-A- 2053175	08-07-71
		FR-A,B 2070178	10-09-71
		GB-A- 1305546	07-02-73
		NL-A- 7015660	04-05-71
		SE-B- 390967	31-01-77
		SE-B- 376613	02-06-75
		US-A- 3868457	25-02-75
		US-A- 3881016	29-04-75
		US-A- 3968216	06-07-76
		US-A- 4048319	13-09-77
		US-A- 4088769	09-05-78